

Viruses in Periodontitis: Evidence, Mechanisms, Diagnosis and Therapeutic Implications

Dr. Nikita Verma¹, Prof. (Dr.) Anjani Kumar Pathak², Prof. (Dr.) Nand Lal³, Prof. (Dr.) Shalini Kaushal⁴, Prof. (Dr.) Pavitra Rastogi⁵(Dr). Neetu Rani,

¹MDS(pursuing) - Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh

²MDS, FAOI, FISDR, FPFA - Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh

³MDS, FADI, FICD, FPFA, AFILD - Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh

⁴MDS, FPFA, FICD - Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh

⁵MDS, MNAMS, FICD, FPFA, AFILD - Department of Periodontology, Faculty of Dental Sciences, King George's Medical University, Lucknow, Uttar Pradesh

⁶Dr. Neetu Rani, MDS (Periodontology), Assistant Professor, King George's Medical University (KGMU), Lucknow, Uttar Pradesh, India.

DOI: <https://doi.org/10.51244/IJRSI.2026.1308000352>

Received: 07 September 2026; Accepted: 12 September 2026; Published: 26 September 2026

ABSTRACT

Periodontitis is a biofilm-associated, host-mediated inflammatory disease, yet bacterial dysbiosis alone does not fully explain its site-specific and episodic behaviour. This narrative review evaluates human herpesviruses and bacteriophages as context-dependent modifiers of periodontal ecology, with particular attention to methodological uncertainty and clinical translation. Targeted searches of PubMed, PubMed Central and publisher databases were conducted through 31 July 2026. Epstein-Barr virus and human cytomegalovirus are detected more often in many deep or inflamed periodontal sites, but reported prevalence varies markedly with case definition, specimen type, sampling strategy, primer target, assay platform and positivity threshold. Longitudinal evidence is less consistent than cross-sectional association. A central diagnostic distinction is between latent carriage and active viral replication: DNA positivity alone is insufficient, whereas lytic transcripts, viral proteins, tissue localisation and repeated site-level sampling provide stronger evidence of biologically relevant activity. Mechanistic studies support reciprocal viral-bacterial effects on immune surveillance, cytokine signalling, epithelial integrity and osteoclastogenesis, while metagenomic studies suggest that bacteriophages may restructure bacterial communities. Future risk models should test whether viral activity adds incremental value to clinical, bacterial and host-inflammatory markers using externally validated multi-omic frameworks. Mechanical therapy may reduce viral burden indirectly, but controlled evidence for antiviral treatment remains inadequate. Antiviral consideration should therefore remain investigational and restricted to carefully characterised treatment-refractory phenotypes with reproducible evidence of active viral replication. Current evidence supports viruses as conditional cofactors rather than universal causes of periodontitis.

Keywords: periodontitis; oral virome; Epstein-Barr virus; cytomegalovirus; bacteriophage; latent infection; lytic replication; multi-omics; antiviral therapy

INTRODUCTION

Periodontitis is characterised by clinical attachment loss, alveolar bone destruction and periodontal pocket formation. Contemporary classification recognises a multifactorial disease initiated by dysbiotic biofilms and modified by host, behavioural and systemic factors.¹ The polymicrobial synergy and dysbiosis model further proposes that community interactions reprogramme host immunity rather than acting through a single pathogen.² Nevertheless, site-specific progression, episodic activity and relapse after apparently adequate mechanical therapy remain incompletely explained.

The oral cavity contains eukaryotic viruses and bacteriophages in addition to bacteria, fungi and archaea. Interest has centred on Epstein-Barr virus (EBV), human cytomegalovirus (HCMV) and herpes simplex virus because herpesviruses establish latency, reactivate intermittently and alter immune signalling.^{3,4} The relevant question is not simply whether viral nucleic acid can be detected, but whether site-specific viral activity precedes or amplifies tissue destruction and improves prediction beyond conventional periodontal assessment. This review therefore synthesises clinical associations, biological mechanisms, diagnostic limitations and therapeutic implications, while explicitly examining the methodological features that can generate apparently conflicting results.

REVIEW METHODOLOGY

A structured narrative review was undertaken using targeted searches of PubMed, PubMed Central and publisher databases through 31 July 2026. Search concepts combined periodontitis with virus, virome, EBV, HCMV, HSV, bacteriophage, metagenomics, PCR, viral load, latency, lytic replication, longitudinal sampling, biomarkers, multi-omics and antiviral therapy. Priority was given to human clinical studies, longitudinal investigations, meta-analyses, molecular studies, metagenomic analyses and recent reviews. Animal or purely in vitro studies were used only when they addressed a defined biological mechanism relevant to human periodontal tissues. No new quantitative synthesis or formal risk-of-bias instrument was applied because the objective was critical narrative integration rather than systematic effect estimation.

Critical appraisal framework

For the revised evidence synthesis, key studies were appraised across six domains: periodontal case definition; participant-level confounding; specimen type and site selection; assay platform and primer or probe target; distinction between viral carriage and active replication; and ability of the design to address temporality or treatment response. Particular attention was given to whether investigators analysed a single periodontal site or pooled material, whether deep and shallow sites were paired within the same participant, whether viral burden was normalised to sample volume, DNA mass or cell number, and whether the assay detected viral genomic DNA, latent transcripts, lytic transcripts or proteins. These domains are important because a technically sensitive assay can still yield clinically ambiguous results when sampling and biological state are not aligned.

Evidence Synthesis

Human herpesviruses

EBV has the most consistent association with periodontitis. It has been detected in subgingival plaque, gingival crevicular fluid (GCF), saliva and gingival tissue, and several studies report higher detection or copy numbers in deeper periodontal pockets.⁵ Meta-analyses support associations with chronic and aggressive periodontitis, although substantial between-study heterogeneity limits causal interpretation.⁶⁻⁸ The pooled signal is therefore best interpreted as evidence that EBV is enriched in some diseased periodontal environments, not as proof that EBV initiates periodontitis.

HCMV is detected in inflammatory cells and severe lesions in some cohorts and can co-occur with EBV or recognised periodontopathic bacteria. Quantitative studies suggest that combined viral and bacterial burdens may carry more biological information than detection of a single agent.^{9,10} HCMV may alter macrophage function, interferon signalling and local tissue repair. HSV is less consistently associated and appears most

relevant in necrotising, ulcerative or immunocompromised settings. Evidence for human papillomavirus, SARS-CoV-2 and torque teno virus remains insufficient to establish a direct destructive periodontal role.

Biological mechanisms

Herpesviral latency provides a plausible biological framework for episodic disease activity. Local inflammation, systemic illness, tobacco exposure, immunosuppression or bacterial metabolites may favour reactivation. Viral products can reduce antigen presentation, interfere with interferon responses and intensify cytokine-rich inflammation. In experimental models, EBV exposure has increased inflammatory mediator production in gingival fibroblasts and promoted receptor activator of nuclear factor-kappa B ligand-related osteoclast differentiation.^{11,12} These observations support biological plausibility, but they do not by themselves establish that viral reactivation temporally precedes clinical attachment loss.

Viral-bacterial synergy remains the most defensible mechanistic model. Viral immune evasion may permit bacterial expansion, whereas epithelial injury and inflammatory exudate can create ecological niches that favour pathobionts. Conversely, bacterial lipopolysaccharide, proteases and short-chain fatty acids can influence herpesviral lytic programmes.¹⁰ The expected effect is therefore conditional on viral state, bacterial burden, tissue compartment and host susceptibility rather than attributable to a single pathogen. Figure 1 summarises this context-dependent interaction and indicates how future multi-omic models could connect viral activity with bacterial and host-response layers.

Context-dependent viral-bacterial-host model of periodontitis

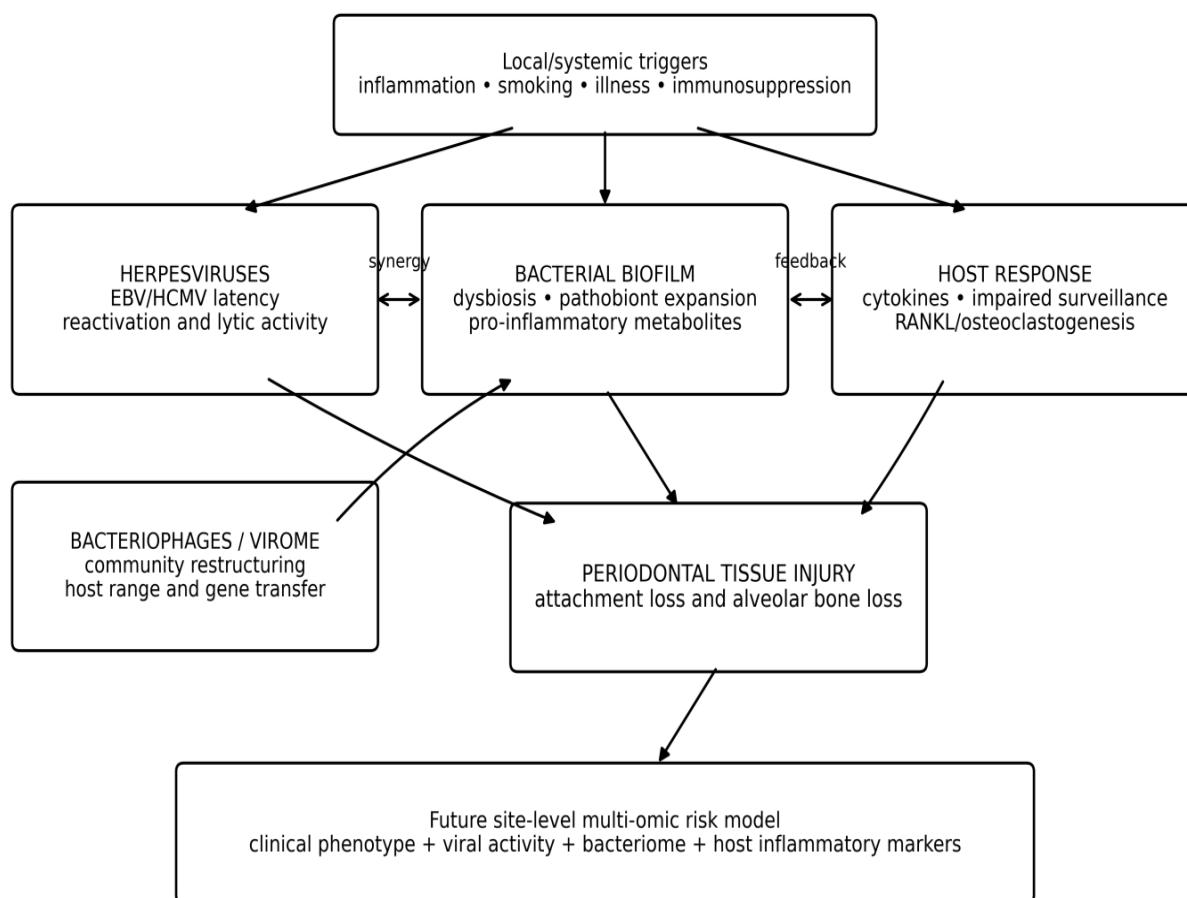


Figure 1. Conceptual model of context-dependent viral-bacterial-host interactions in periodontitis. Local and systemic triggers may promote herpesviral reactivation, bacterial dysbiosis and host inflammation, while bacteriophages can reshape bacterial ecology. The lower panel shows components of a future site-level multi-omic risk model. Author-generated conceptual synthesis.

Bacteriophages and the oral virome

Bacteriophages can alter bacterial abundance, virulence, horizontal gene transfer and biofilm stability. Metagenomic studies have shown periodontal-status-associated changes in oral viral communities.¹³ A 2026 cross-cohort analysis integrated 89 saliva and 86 subgingival plaque metagenomes from six public cohorts and identified 156 periodontitis-associated viral operational taxonomic units; viral-marker models reported area under the receiver operating characteristic curve values of 0.95 for saliva and 0.92 for subgingival plaque.¹⁴ These results are promising, but they remain classification findings derived from retrospectively assembled cohorts rather than proof that phage shifts cause disease. Predicted bacterial hosts and viral functions also require experimental confirmation. The extensive uncharacterised component of the oral virome further complicates annotation and mechanistic inference.¹⁵ Table 1 summarises the current interpretation of major viral groups.

Table 1. Major viral groups considered in periodontitis

Viral group	Representative evidence	Plausible contribution	Current interpretation
Epstein-Barr virus	Higher detection in many deep sites; meta-analytic association	Latency/reactivation, cytokine induction and osteoclastogenesis	Strongest association; causality and clinical thresholds unresolved
Human cytomegalovirus	Detected in inflammatory cells and some severe lesions	Immune evasion, cytokine release and impaired repair	Probable cofactor in a subset; inconsistent across populations
Herpes simplex virus	Occasional detection in necrotising or ulcerative disease	Epithelial injury and local inflammation	Possible modifier; less consistent than EBV or HCMV
Other human viruses	Epidemiological or acute-infection associations	Barrier disruption, immune dysfunction or shared risk factors	Direct periodontal causation unproven
Bacteriophages	Disease-associated community shifts in metagenomic studies	Bacterial killing, host-range effects, gene transfer and biofilm restructuring	Emerging ecological role and possible biomarker source

Abbreviations: EBV, Epstein-Barr virus; HCMV, human cytomegalovirus.

Methodological heterogeneity and critical appraisal of key studies

Table 2 illustrates how study design changes interpretive weight. Kato et al. paired deep and shallow sites and also localised EBER-positive cells, strengthening site specificity, but the cross-sectional nested-PCR design did not establish lytic replication or temporality.⁵ Saygun et al. quantified both herpesviruses and six bacterial species, a notable strength for testing microbial interaction, yet the analysis involved only 15 periodontitis cases and one deepest site per participant.⁹ By contrast, Emecen-Huja et al. repeatedly sampled healthy and diseased sites in 81 participants and directly assessed progression; EBV occurred more often in diseased sites but at low copy number and did not predict progression, whereas bacterial burden did.¹⁶ The 2025 Spanish case-control study found almost no EBV or HCMV despite clear bacterial associations, demonstrating that geography, disease spectrum and assay context can materially change prevalence estimates.¹⁷

The strongest reason for caution is methodological heterogeneity rather than absence of biological plausibility. Sample type changes what is being measured. Saliva captures whole-mouth shedding but is not site-specific; GCF contains inflammatory exudate and leukocytes; subgingival plaque is closer to the diseased ecological niche but is sensitive to contamination, paper-point depth and pooling; and tissue biopsy permits localisation but is invasive and often restricted to surgically treated severe sites.¹⁸ Pooling several pockets can dilute a focal reactivation event, whereas selecting only the deepest site may enrich the sample for inflammation and exaggerate association. Paired deep and shallow sites within the same participant partly reduce between-person confounding and are therefore preferable for mechanistic site-level questions.

Assay selection introduces a second layer of variability. Nested PCR can detect low viral copy numbers but yields binary positivity, increases vulnerability to amplicon contamination and cannot determine biological activity. qPCR improves quantification, yet copy numbers are not directly comparable when studies use different extraction efficiencies, calibration standards, positivity thresholds, units of normalisation or genomic targets. EBV assays have targeted regions including EBNA2, LMP2, EBNA1/BamHI-W and other sequences; repeat-containing targets can generate different apparent copy numbers from single-copy targets, and primer-probe mismatch can alter sensitivity.¹⁸ These differences help explain why meta-analytic associations coexist with negative or low-prevalence studies.^{6,17} Recent periodontal biomarker reviews reach a similar conclusion: high classification performance in selected datasets is not equivalent to validated clinical utility when diagnostic definitions, sampling and laboratory pipelines differ.^{19,20}

Table 2. Critical appraisal of representative studies

Study/design	Methodological strengths	Principal limitations	Interpretive implication
Kato et al., 2013; 85 periodontitis patients plus 20 healthy controls	Paired shallow/deep sites; standardised subgingival sampling; EBV PCR with tissue EBER localisation	Cross-sectional; qualitative nested PCR; no direct lytic marker; single-country population	Supports site enrichment and infected-cell localisation, but not temporal causation
Saygun et al., 2008; 15 periodontitis cases plus 15 healthy controls	Real-time qPCR; simultaneous quantification of EBV, HCMV and six bacterial taxa	Small sample; single deepest site; cross-sectional; viral DNA only	Supports viral-bacterial covariation, but effect estimates are vulnerable to site-selection bias
Maulani et al., 2021; meta-analysis	Pooled evidence with subgroup analyses by population, specimen and assay	Substantial heterogeneity in case definitions, sampling, PCR platforms and thresholds; mainly cross-sectional studies	Association is reproducible at a population level, but certainty for causality is limited
Emecen-Huja et al., 2020; longitudinal, n=81	Repeated healthy/diseased site sampling at 0, 16 and 28 weeks; clinical progression endpoint; qPCR	EBV generally low-copy; HCMV rare; DNA detection did not establish activity; treatment context may modify ecology	High interpretive weight for temporality; did not support EBV/HCMV as predictors of progression
Herrero-Sánchez & Haroyan-Darbinyan, 2025; 24 cases plus 24 controls	Contemporary periodontal assessment; stringent exclusions; bacterial and viral testing in the same samples	Small cohort; Stage I-II disease only; age imbalance; near-zero herpesvirus detection limits viral comparisons	Important negative study showing that herpesvirus prevalence is not universal
Chu et al., 2026; six public cohorts, 175 metagenomes	Cross-cohort virome integration; saliva and plaque analysed; diagnostic models; predicted virus-host interactions	Retrospective cross-sectional datasets; heterogeneous metadata and collection; computational host prediction; prospective validation absent	Strong discovery evidence for viral signatures, but not yet a clinically validated diagnostic model

Diagnostic and Clinical Interpretation

Cross-sectional DNA positivity cannot establish active pathogenic infection. Viral genomes may represent latent carriage, intermittent shedding, salivary contamination or infected leukocytes recruited by pre-existing

inflammation. Longitudinal evidence remains mixed, and some well-designed studies show limited viral detection or no clear association with clinical progression.^{16,17} A clinically useful viral test must therefore do more than distinguish established periodontitis from health; it should identify biologically active infection and improve prediction of future progression or treatment response beyond probing depth, attachment level, bleeding and established risk factors.

Latent carriage versus lytic activity

The distinction between latency and lytic replication is central to diagnostic clarity. EBV genomic DNA establishes that viral material is present, but because EBV persists lifelong in most adults, low-level DNA positivity can have little disease specificity. EBER in situ hybridisation and latent-gene expression can localise or characterise infected cells, yet these markers still do not demonstrate productive replication. Evidence of reactivation is stronger when immediate-early or lytic transcripts such as BZLF1 or BRLF1, downstream lytic proteins, or other replication-associated products are detected at the periodontal site. Similarly, HCMV DNA may reflect carriage in infiltrating cells, whereas immediate-early transcripts/proteins, replication-associated RNA or antigen detection provides stronger evidence of active infection.¹⁸

No single marker is sufficient in every setting. The most persuasive periodontal design would combine site-level quantitative viral burden with an activity marker, localise the signal to periodontal tissue or cells when feasible, and repeat sampling over time. A deep site that is DNA-positive once but lytic-marker-negative should not be interpreted in the same way as a site with reproducibly high viral load, lytic transcripts and concurrent clinical progression. Table 3 summarises this hierarchy.

Table 3. Distinguishing latent carriage from active herpesviral replication

Biological state	Illustrative markers/approaches	What the finding supports	Main caveat
Viral presence/carriage	EBV or HCMV genomic DNA by PCR/qPCR	Presence and approximate burden of viral genomes	Cannot distinguish latent infection, shedding or active replication
EBV latency/localisation	EBER in situ hybridisation; latent-gene transcripts/proteins such as EBNA/LMP markers	Presence of EBV-infected cells and, depending on target, latent transcriptional programme	Latency markers do not demonstrate productive lytic replication
EBV lytic activity	RT-qPCR or protein detection for immediate-early/lytic markers such as BZLF1 or BRLF1, with downstream lytic products	Evidence of reactivation or lytic-cycle activity	RNA is labile; focal activity can be missed; periodontal thresholds are not standardised
HCMV active infection	Immediate-early transcripts/proteins, replication-associated RNA or antigen detection with site-level viral load	Stronger evidence of biologically active HCMV than DNA alone	Assays and thresholds remain insufficiently standardised in periodontal research
High-confidence periodontal attribution	Repeated paired site sampling plus activity marker, tissue localisation and clinical progression	Supports temporality, anatomic relevance and biological activity	More invasive, costly and logistically demanding

Abbreviations: EBNA, Epstein-Barr nuclear antigen; EBER, Epstein-Barr virus-encoded RNA; LMP, latent membrane protein; PCR, polymerase chain reaction; qPCR, quantitative PCR; RT-qPCR, reverse-transcription quantitative PCR.

From viral signals to multi-omic periodontal risk models

A viral biomarker is unlikely to be clinically useful in isolation. A more plausible strategy is a layered site-level model that begins with the clinical phenotype and established risk modifiers, then tests incremental information from the bacteriome, viral activity and host inflammatory response. Candidate viral features could include quantitative EBV/HCMV burden, lytic transcripts and disease-associated phage operational taxonomic units; bacterial features could include abundance or dysbiosis indices; and host features could include inflammatory or tissue-breakdown markers. The model should be trained to predict a prospective endpoint such as site-level attachment loss rather than merely classify existing cases and controls.

Recent studies show both the promise and the validation problem. Cross-cohort bacterial metagenomic models have achieved external area under the curve values around 0.85, demonstrating that microbial signatures can generalise beyond a single dataset.²¹ The 2026 virome analysis reported even higher case-control discrimination for selected viral markers, but its retrospective public-cohort design means that calibration, temporal prediction and clinical added value remain unknown.¹⁴ Multi-omic periodontal studies integrating microbial and metabolic layers also demonstrate coordinated disease-associated changes and partial ecological restoration after therapy.²² The next step is not simply to add more features. Viral variables should be retained only if they improve discrimination, calibration and decision usefulness beyond a pre-specified clinical-bacterial-host baseline in independent cohorts.

For that reason, future models should prespecify the periodontal site as the unit of biological inference, use nested cross-validation during development, report calibration as well as discrimination, and undergo external validation across centres, populations and assay platforms. Comparison with a clinical-only reference model is essential. A statistically impressive area under the curve from a case-control dataset does not establish screening, prognostic or treatment-selection utility.^{19,20} Table 4 summarises minimum methodological requirements for interpretable viral and multi-omic studies.

Table 4. Minimum requirements for interpretable periodontal viral studies

Method or design	Primary output	Essential requirement	Main limitation
Quantitative PCR	Viral copy number	Extraction controls, calibration, normalisation, reported target/primer and validated threshold	DNA does not prove active infection
RT-qPCR or viral protein assay	Lytic activity	Defined transcript/protein targets, RNA quality controls and timing	Lower sensitivity and limited periodontal standardisation
In situ localisation	Virus-containing cells and tissue compartments	Validated probes/antibodies and blinded interpretation	Invasive and technically demanding
Metagenomics/multi-omics	Community-wide viral, bacterial and host profiles	Adequate depth, contamination control, transparent feature selection and external validation	High cost, batch effects and uncertain clinical thresholds
Longitudinal site-level study	Temporality and treatment response	Repeated paired sampling with blinded clinical outcomes	Participant retention and sampling variability

Abbreviations: PCR, polymerase chain reaction; RT-qPCR, reverse-transcription quantitative PCR.

THERAPEUTIC IMPLICATIONS

Scaling and root planing may reduce viral burden indirectly by disrupting biofilm, reducing inflammatory cell influx and changing the local ecological conditions that favour viral reactivation. A post-treatment fall in viral load, however, does not establish that viral replication was the driver of tissue destruction. Evidence for systemic or local antivirals remains limited mainly to case reports, including clinical improvement reported in a patient with severe EBV-positive periodontitis.²³ Umbrella-level appraisal has not identified sufficient controlled

evidence to support routine antiviral prescribing.²⁴ Antiviral exposure also introduces drug-specific adverse effects, interactions, cost and resistance concerns, making empiric use unjustified.

Proposed criteria for a treatment-refractory viral phenotype

The term treatment-refractory phenotype is used here descriptively, not as a formally validated periodontal diagnosis. If antiviral therapy is studied, eligibility should require documented site-level progression or recurrent inflammatory activity despite appropriately delivered periodontal therapy, satisfactory plaque control and management of major modifiable risk factors. Local explanations for persistent disease, including residual calculus, inaccessible anatomy, endodontic-periodontal lesions, root fracture, foreign-body reaction or poor maintenance, should be excluded before a viral mechanism is considered.

A second requirement should be reproducible evidence of active viral biology rather than DNA positivity alone. Ideally, the same progressing site would demonstrate a quantifiable viral burden on repeated samples together with a lytic transcript, replication-associated protein or tissue-localised activity marker. Concordant bacterial and host inflammatory measurements would help determine whether viral activation is part of a broader dysbiotic-inflammatory state. Any antiviral intervention should occur within a research protocol or specialist-led setting with predefined eligibility, safety monitoring, virological endpoints and conventional periodontal outcomes.

These criteria are intentionally stringent because no clinically meaningful viral-load threshold and no treatment-responsive virological phenotype have yet been validated. Before randomised trials are justified, prospective studies should define the distribution and reproducibility of active-infection markers in progressing versus stable sites, identify thresholds associated with future attachment loss, and determine whether a fall in viral activity after standard periodontal therapy predicts improved outcome. Antiviral trials should then enrol only a biomarker-defined subgroup and test adjunctive benefit over optimised periodontal care, rather than compare antivirals with inadequate mechanical treatment.

LIMITATIONS AND RESEARCH PRIORITIES

This review is narrative, was not prospectively registered and did not apply a formal risk-of-bias instrument or certainty-of-evidence framework. Although the revised synthesis explicitly appraises major methodological domains, the underlying evidence remains dominated by cross-sectional designs, heterogeneous periodontal classifications, variable specimen collection, inconsistent assay targets and incomplete control of smoking, diabetes, treatment history and other confounders. Some newer metagenomic datasets were assembled retrospectively from public cohorts and therefore inherit differences in sample processing and clinical metadata.

A useful research sequence is now clearer. First, investigators should standardise site selection, sampling depth, pooling rules, extraction controls, primer/probe reporting, calibration units and minimum metadata. Second, viral DNA measurements should be paired with active-infection markers and, where feasible, tissue or cellular localisation. Third, longitudinal studies should sample the same periodontal sites before clinical progression, during progression and after therapy. Fourth, multi-omic models should test whether viral features add independently validated prognostic value to clinical, bacterial and host-response data rather than simply improve case-control classification.^{15,19-22} Finally, intervention trials should be attempted only after a reproducible virus-associated phenotype, a clinically meaningful threshold and a plausible treatment-responsive endpoint have been defined.

CONCLUSION

Viruses are plausible context-dependent cofactors in periodontitis. EBV and HCMV show the strongest human herpesvirus associations, while bacteriophages may reshape bacterial ecology and provide emerging biomarker signals. The central limitation is not merely inconsistency of prevalence; it is the frequent inability of current studies to separate latent carriage from active site-level infection and to resolve temporality. Stronger inference requires harmonised sampling, transparent primer and assay reporting, lytic or replication-associated markers, tissue localisation where feasible and repeated longitudinal measurements. Viral signatures may ultimately

contribute to multi-omic periodontal risk models, but they must demonstrate incremental predictive value and external validity. Current evidence does not support routine viral testing or antiviral therapy, and antiviral investigation should be restricted to rigorously defined treatment-refractory phenotypes with reproducible evidence of active viral replication.

Patient/Guardian Consent

Not applicable.

Ethical clearance

Not required for this narrative review.

Sources of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest

Declarations of interest: None.

Acknowledgements

None.

Data availability

No new data were generated or analysed in this narrative review.

Declaration Of Generative AI And AI-Assisted Technologies in the Manuscript Preparation Process

During preparation, the authors used ChatGPT (OpenAI) for language editing, structural refinement and journal-format alignment. The authors reviewed and edited the content and take full responsibility for the article.

REFERENCES

1. Papapanou PN, Sanz M, Buduneli N, Dietrich T, Feres M, Fine DH, et al. Periodontitis: consensus report of workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol*. 2018;45 Suppl 20:S162-S170. doi:10.1111/jcpe.12946.
2. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis model of periodontal disease etiology. *Mol Oral Microbiol*. 2012;27(6):409-419. doi:10.1111/j.2041-1014.2012.00663.x.
3. Slots J. Herpesviruses in human periodontal disease. *J Periodontol Res*. 2000;35(1):3-16. doi:10.1034/j.1600-0765.2000.035001003.x.
4. Contreras A, Zadeh HH, Nowzari H, Slots J. Herpesvirus infection of inflammatory cells in human periodontitis. *Oral Microbiol Immunol*. 1999;14(4):206-212. doi:10.1034/j.1399-302X.1999.140402.x.
5. Kato A, Imai K, Ochiai K, Ogata Y. Higher prevalence of Epstein-Barr virus DNA in deeper periodontal pockets of chronic periodontitis in Japanese patients. *PLoS One*. 2013;8(8):e71990. doi:10.1371/journal.pone.0071990.
6. Maulani C, Auerkari EI, Masulili SLC, Soeroso Y, Santoso WD, Kusdhany LS. Association between Epstein-Barr virus and periodontitis: a meta-analysis. *PLoS One*. 2021;16(10):e0258109. doi:10.1371/journal.pone.0258109.

7. Zhu C, Li F, Wong MCM, Feng XP, Lu HX, Xu W. Association between herpesviruses and chronic periodontitis: a meta-analysis based on case-control studies. *PLoS One*. 2015;10(12):e0144319. doi:10.1371/journal.pone.0144319.
8. Li F, Zhu C, Deng FY, Wong MCM, Lu HX, Feng XP. Herpesviruses in etiopathogenesis of aggressive periodontitis: a meta-analysis based on case-control studies. *PLoS One*. 2017;12(10):e0186373. doi:10.1371/journal.pone.0186373.
9. Saygun I, Kubar A, Sahin S, Sener K, Slots J. Quantitative analysis of association between herpesviruses and bacterial pathogens in periodontitis. *J Periodontal Res*. 2008;43(3):352-359. doi:10.1111/j.1600-0765.2007.01043.x.
10. Chen C, Feng P, Slots J. Herpesvirus-bacteria synergistic interaction in periodontitis. *Periodontol* 2000. 2020;82(1):42-64. doi:10.1111/prd.12311.
11. Zeng W, Liu G, Luan Q, Yang C, Luo X, Zhu Z, Yu X. Epstein-Barr virus promotes inflammatory cytokine production in human gingival fibroblasts. *Int Dent J*. 2024;74(3):607-615. doi:10.1016/j.identj.2023.12.006.
12. Imai K, Inoue H, Tamura M, Cueno ME, Takeichi O, Kusama K, et al. Epstein-Barr virus promotes inflammatory cytokines and RANKL-induced osteoclast differentiation. *Int J Mol Sci*. 2022;23(2):809. doi:10.3390/ijms23020809.
13. Ly M, Abeles SR, Boehm TK, Robles-Sikisaka R, Naidu M, Santiago-Rodriguez T, et al. Altered oral viral ecology in association with periodontal disease. *mBio*. 2014;5(3):e01133-14. doi:10.1128/mBio.01133-14.
14. Chu T, Liu J, Zhang Y, Yang K, Li S, Yan Q, Li Y. Metagenome-based virome analysis identifies oral viral signatures for periodontitis. *J Oral Microbiol*. 2026;18(1):2662091. doi:10.1080/20002297.2026.2662091.
15. Martinez A, Kuraji R, Kapila YL. The human oral virome: shedding light on the dark matter. *Periodontol* 2000. 2021;87(1):282-298. doi:10.1111/prd.12396.
16. Emecen-Huja P, Danaher RJ, Dawson DR 3rd, Wang C, Kryscio RJ, Ebersole JL, et al. Relationship between herpesviruses and periodontal disease progression. *J Clin Periodontol*. 2020;47(4):442-450. doi:10.1111/jcpe.13239.
17. Herrero-Sanchez A, Haroyan-Darbinyan E. Prevalence of Epstein-Barr virus, cytomegalovirus, and periodontopathic bacteria in patients with periodontitis: a case-control study. *Clin Exp Dent Res*. 2025;11:e70084. doi:10.1002/cre2.70084.
18. Tonoyan L, Chevalier M, Vincent-Bugnas S, Marsault R, Doglio A. Detection of Epstein-Barr virus in periodontitis: a review of methodological approaches. *Microorganisms*. 2021;9(1):72. doi:10.3390/microorganisms9010072.
19. Bostanci N, Manoil D, Van Holm W, Belibasakis GN, Teughels W. Microbial markers for diagnosis and risk assessment for periodontal diseases: a systematic literature search and narrative synthesis. *J Clin Periodontol*. 2025;52(Suppl 29):125-154. doi:10.1111/jcpe.14183.
20. Dong A, Proctor G, Zaric S. Diagnostic accuracy of microbiome-derived biomarkers in periodontitis: systematic review and meta-analysis. *J Periodontal Res*. 2025;60(8):748-761. doi:10.1111/jre.13377.
21. Geng M, Li M, Li Y, Zhu J, Sun C, Wang Y, et al. A universal oral microbiome-based signature for periodontitis. *iMeta*. 2024;3(4):e212. doi:10.1002/imt2.212.
22. Baima G, Dabdoub S, Thumbigere-Math V, Ribaldone DG, Caviglia GP, Tenori L, et al. Multi-omics signatures of periodontitis and periodontal therapy on the oral and gut microbiome. *J Periodontal Res*. 2025;60(12):1237-1253. doi:10.1111/jre.70055.
23. Sunde PT, Olsen I, Enersen M, Grinde B. Patient with severe periodontitis and subgingival Epstein-Barr virus treated with antiviral therapy. *J Clin Virol*. 2008;42(2):176-178. doi:10.1016/j.jcv.2008.01.007.
24. Jakovljevic A, Andric M, Jacimovic J, Milasin J, Botero JE. Herpesviruses in periodontitis: an umbrella review. In: Nibali L, ed. *Periodontitis: Advances in Experimental Research*. Cham: Springer; 2022:107-123. doi:10.1007/978-3-030-96881-6_7.