

Viral Infections of the Oral Cavity: Oral Manifestations, Salivary Biomarkers, and Prosthodontic Implications

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ABSTRACT

Viral infections can cause variable oral disease manifestations, and saliva and oral samples are readily available sources of viral and host-derived biomarkers. This review provides a horizon scan of the oral manifestations of viral infections and assesses the potential of oral and salivary biomarkers for viral detection, monitoring, and disease prognosis. Evidence was examined of the herpesviruses, including human papillomavirus (HPV), Epstein–Barr virus (EBV), and SARS-CoV-2. We reviewed a variety of biomarkers, including viral nucleic acids, antibodies, microRNAs, cytokines, and host-derived markers, along with rapid advances in molecular, immunological, sequencing, and biosensor-based detection methods and their applications. Oral manifestations include vesicles and ulcerative lesions, mucosal changes, salivary gland involvement, taste alterations, and virus-associated neoplastic changes. Saliva can detect viral nucleic acid and antibodies in SARS-CoV-2 and herpesvirus infections, and new biomarker-based methods may offer more insight into host response and disease status. However, clinical application is limited because viral load, disease stage, specimen collection, processing, and analytical methods vary. Further studies with standardized protocols and larger prospective studies are required to validate salivary biomarkers and use them in routine viral diagnosis and monitoring.

Keywords: Viral infections; Oral manifestations; Saliva; Salivary biomarkers; Viral nucleic acids; MicroRNAs

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Introduction

The oral cavity is a dynamic and diverse ecosystem that contains bacteria, fungi, archaea, protozoa and viruses; all of these contribute to the oral

microbiome and virome. It has a number of interfaces with microorganisms and host, including mucosal surfaces, periodontal tissues and the salivary glands and associated lymphoid tissues. The

oral cavity is an interface between the microbial environment and host immunity, and alterations to the oral microbial environment can have a profound effect on the local oral environment, and on systemic disease processes (1,2).

Viral infections can manifest in many forms and may involve the oral cavity, including the oral mucosa, periodontal tissues, salivary glands and other components of the oral cavity. They include lesions of the vesicles or ulceration, changes in the mucous membranes at various sites, involvement of the salivary glands, changes in taste, and lesions due to virus associated neoplastic processes (1,3). Viral reactivation and opportunistic infections may cause oral disease, which may aggravate systemic viral infection (3). Thus, oral signs and symptoms may be clinically relevant in identifying an underlying viral disease, and in certain diseases, oral changes may have a role in disease follow-up and disease progression (1,3).

Understanding of the oral cavity as a site of clinical manifestation, but also as a potential site of viral persistence, shedding, transmission and detection has been greatly affected by clinical manifestation of the oral cavity and the re-emergence of viral pathogens. Advanced molecular diagnostic methods have been developed that have increased the range of viruses and other microorganisms and can be detected using oral samples.

Specifically, metagenomic next-generation sequencing (mNGS) can be used to detect more than one pathogen at a time, and could be valuable in the diagnosis of complex oral infections in which traditional diagnostic techniques may fail (2,4). This was further accentuated during the COVID-19 pandemic where the potential of oral specimen collection for diagnosis and monitoring of respiratory virus infections was demonstrated (5).

Over the years, saliva has emerged as an important bio-sample for detection of viruses which can be self-collected and sampled multiple times, depending on the context, and collected easily. Viral nucleic acids can exist in saliva, as well as proteins, immunoglobulin, microRNAs, metabolites and other host derived molecules that may contain information about infection, disease-associated biological changes (6). Saliva has been reported as an effective source of detection for several viruses, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), monkeypox virus (MPXV), human papillomavirus (HPV), and herpesviruses, and could prove to be valuable for diagnosis, surveillance, and monitoring of viral infections (6).

Biological and clinical evidence of the use of saliva in viral detection has been provided, in primary studies. SARS-CoV-2 RNA was found in saliva at all times, highlighting the potential for saliva as a diagnostic sample (5). Also, research into the salivary glands has revealed that they could act as a

source of infection with SARS-CoV-2 and may become contaminated with the virus in saliva (7). Some post-mortem findings, related to oral and salivary involvement in COVID-19 have been also supporting the involvement of the virus into oral tissues (8). These findings show that oral cavity and salivary glands could be involved in the diagnosis of viral detection and pathobiology.

Saliva has also been demonstrated to be valid for novel emerging viral infections such as mpox. The saliva during infection is a source of MPXV viral material and MPXV DNA has been found in saliva specimens from infected individuals (9). The molecular testing of saliva has been evaluated in further studies and is promising as a clinical test for MPXV infection (10). Studies have also investigated the detection of MPXV in saliva along with the environment, which may contribute to support MPXV infection surveillance. (11)

It is worth mentioning that oral or salivary biomarker can not only detect viral nucleic acids. Possible markers for infection or for changes associated with the disease include viral DNA/RNA, viral proteins/antigens, virus-specific antibodies, host-made molecules (microRNAs), and alterations in the oral microbial environment (1,6). The use of salivary microRNA as an alternative non-invasive method to detect molecular signatures with diagnostic relevance is investigated and holds great promise for diagnostic applications, but needs to be validated further before it is ready for clinical use (12).

New technologies also have enhanced the detection of viral biomarkers. While polymerase chain reaction (PCR) and reverse-transcription quantitative PCR (RT-qPCR) plays an important role in the detection of viral DNA and RNA, mNGS may be able to detect a wider array of pathogens in complex clinical specimens (2,4). Recently, electrochemical and impedimetric platforms have been employed also to study viral antigen detection, nucleic acids and antibodies, with the potential of being more accessible at the point of care for viral diagnostics (13).

Despite considerable efforts to translate oral and salivary biomarkers into clinical practice, several limitations remain. Studies differ substantially in the viruses investigated, patient populations, specimen types, sampling procedures, analytical methods, and definitions of clinically meaningful biomarkers.

Viral nucleic acid does not necessarily indicate the presence of viral activity in the oral cavity or a causal relationship with a particular oral lesion. Furthermore, a variety of individual factors may influence the amount of a biomarker in saliva, such as saliva flow, collection protocol, foods, medications, and stability of the biomarker. These biomarkers and their diagnostic value also might differ between stimulated and unstimulated saliva

and between the different sources of saliva (salivary glands) (1,6).

Thus, a thorough examination of all the available evidence is needed to elucidate the range of oral changes linked to viral infections and to establish the possible relevance of oral and salivary markers in clinical practice. This review aims to assess oral changes related to re-emerging and emerging viral infections to find possible indicators for diagnosis, prognosis, surveillance, or disease monitoring that can be detected in the oral cavity or the salivary glands. The review also covers the current knowledge of available detection methods, biological and clinical relevance of detected biomarkers, as well as some of the limitations and ongoing research needs that need to be resolved before they can be widely used in clinical practice.

Oral manifestations associated with viral infections

Oral viral infections can manifest in many different ways, depending on the type of virus, site of infection, immune status of the host and whether this is a primary infection or reactivation. Oral findings may include vesicles, ulcers, erythema, exophytic lesions, salivary gland involvement, and changes in taste or salivary function (1, 3, 14). The oral cavity may also be a reservoir for viral shedding, and viral nucleic acids have been found in saliva even in people with no clinical evidence of oral disease, which is why there is a difference between clinically apparent oral disease and asymptomatic viral carriage (3,14).

Oral disease and shedding of saliva are an important group of viruses associated with herpesviruses. Oral and perioral lesions (vesicular or ulcerative) can be caused by herpes simplex virus type 1 (HSV-1) in the course of primary infection or reactivation, and by varicella-zoster virus (VZV) during reactivation (14). In immunocompromised patients, particularly those with HIV infection and patients receiving organ or hematopoietic stem-cell transplantation, cytomegalovirus (CMV) typically presents as an oral ulceration and/or other mucosal disease (3,14). CMV, HSV, and other herpesviruses can shed in saliva without any clinical signs of disease, so viral DNA detection in saliva may be useful to investigate viral reactivation and host–virus interactions (14).

Epstein–Barr virus (EBV) is a virus of special interest to oral diseases due to its latent infection and lifelong shedding in saliva. A variety of lymphoid and epithelial malignancies have been linked to oral hairy leukoplakia, usually seen in immunocompromised patients, and to oral epithelial infection with EBV (3,14). Salivary EBV DNA has been found in symptomatic and asymptomatic people, including HIV infected and transplant recipients, and saliva may be a useful sample to investigate EBV infection and viral shedding (14). Findings by Slots and Slots have also been supported by studies showing altered EBV detection in saliva

under conditions of immune dysfunction, suggesting that measuring EBV nucleic acid in saliva may detect viral activity or reactivation (14).

Another significant oral virus is human papillomavirus (HPV) which has been linked to oral carcinogenesis by persistent infection with high-risk HPV types, especially HPV16. The researchers have been working on HPV DNA in saliva and oral rinse samples as a minimally invasive biomarker for HPV-associated head and neck disease, and meta-analytic evidence indicates that there is HPV DNA/oral or oropharyngeal cancer association (6). As noted above, however, detecting HPV DNA from an oral specimen does not necessarily indicate persistent infection, transcriptionally active infection, or a causal link to an individual oral lesion, so molecular detection should be considered alongside clinical and pathological criteria (6). This distinction matters when assessing viral nucleic acids as biomarkers rather than as indicators of exposure or carriage.

Recently, other viral diseases have been identified and added to the list of oral diseases and oral-based detection. The oral cavity is relevant for SARS-CoV-2 infection, as viral RNA has been identified in periodontal tissues, saliva and in salivary glands (7,8), and symptoms of dysgeusia and oral mucosal changes have been reported (5). Likewise, mpox can cause lesions of the oral cavity and oropharynx, and MPXV DNA has been identified in saliva, which could be used for diagnosis and surveillance (9–11). Overall, the results suggest that oral involvement and determining viral presence in the oral cavity may be complementary aspects of the viral disease, clinically and molecularly. Clinical information may help detect early viral infection, while molecular information may assess viral presence in the oral cavity, shedding, and potentially support disease monitoring.

Biomarkers in oral and salivary samples of viral infections

Saliva is increasingly being investigated as a non-invasive biological specimen for the detection and monitoring of viral infections. Unlike conventional blood-based sampling, saliva collection is simple, painless, inexpensive and can be performed with minimal exposure of healthcare personnel. Saliva contains a complex mixture of viral nucleic acids, proteins, antibodies, host-derived nucleic acids, cytokines, metabolites and microbial components, making it a potentially useful source of both pathogen-derived and host-response biomarkers (1,6,14). The diagnostic value of these biomarkers varies according to the virus, stage of infection, viral load, sampling site, salivary flow, collection technique and analytical platform.

Viral DNA and RNA

Viral DNA and RNA are among the most extensively investigated biomarkers in oral and salivary specimens. Molecular detection is primarily performed using polymerase chain reaction (PCR),

reverse-transcription PCR (RT-PCR) and quantitative real-time PCR (RT-qPCR). These techniques enable the detection and, in some settings, quantification of viral nucleic acids directly from saliva or oral fluid. Salivary detection has been reported for several DNA viruses, including herpesviruses and human papillomavirus (HPV), as well as RNA viruses such as SARS-CoV-2 (1,6,14). SARS-CoV-2 provided substantial evidence supporting saliva as a molecular diagnostic specimen. To *et al.* demonstrated consistent detection of SARS-CoV-2 RNA in saliva, supporting its potential as a non-invasive alternative or adjunct to conventional upper respiratory tract sampling (5). Detection of viral RNA in saliva may also reflect viral presence within the oral cavity and contribution from infected salivary glands. Histopathological evidence shows that salivary glands can be targets of SARS-CoV-2 infection, providing a biological basis for viral material in saliva (7).

Salivary viral nucleic-acid detection has also demonstrated utility during emerging viral outbreaks. During the 2022 mpox outbreak, viral DNA was frequently detected in saliva and other clinical specimens, indicating that oral fluid can serve as a readily accessible specimen for molecular investigation (9,10,11). However, detection of viral DNA or RNA does not necessarily indicate the presence of infectious or replication-competent virus. Therefore, molecular positivity should be interpreted in relation to clinical findings, timing of sampling and, where relevant, viral culture or other measures of infectivity (6,9).

Viral Proteins and Antigens

Viral proteins and antigens represent another important category of salivary biomarkers. Antigen-based approaches have the potential to identify active infection more directly than antibody-based assays because they detect components of the virus itself. Depending on the virus, target molecules may include structural proteins, nucleocapsid proteins, surface glycoproteins or other virus-specific antigens.

For SARS-CoV-2, viral proteins have been investigated as potential markers of infection, while the presence of viral material within salivary glands provides a biological rationale for detecting viral components in saliva (7). Antigen-based assays can potentially provide rapid results and may be particularly valuable in point-of-care settings. However, their performance may be affected by the relatively low concentration of viral proteins in saliva, particularly during periods of low viral burden. Consequently, highly sensitive analytical platforms are required to achieve reliable detection (6).

Emerging biosensor technologies have further expanded the potential for salivary viral protein and nucleic-acid detection. Electrochemical and impedimetric biosensors have been investigated for

rapid virus detection and may facilitate portable and point-of-care diagnostic applications (13). Nevertheless, many such technologies remain under development, and their clinical performance requires validation in larger and more diverse populations.

Recent evidence also indicates a shift in saliva-based viral diagnostics toward point-of-care biosensor platforms. Zhou *et al.* identified nucleocapsid (N) antigen as an emerging target for salivary SARS-CoV-2 detection, owing to its relatively high abundance and lower susceptibility to mutation compared with the spike protein. The authors also highlighted increasing interest in electrochemical, field-effect transistor, SERS, and aptamer-based platforms for rapid salivary testing. However, standardization of saliva collection and processing remains necessary for reliable clinical application.(15)

Virus-Specific Antibodies

Virus-specific antibodies in saliva represent an important biomarker of mucosal and systemic immune responses to viral infection. Saliva contains predominantly secretory immunoglobulin A (IgA), together with smaller amounts of IgG and IgM. Salivary IgA is particularly relevant because it represents an important component of mucosal immunity and may reflect local immune responses at the oral and upper respiratory surfaces (14).

SARS-CoV-2 has provided substantial evidence for the diagnostic potential of salivary antibodies. Yu *et al.* evaluated SARS-CoV-2-specific IgA, IgG and IgM in saliva from 44 patients with confirmed COVID-19 and 24 negative controls. Salivary IgA demonstrated the highest positivity among the three immunoglobulin classes, with 14 of 44 patients positive for IgA, compared with 7 for IgG and 4 for IgM. All three antibodies were negative in the control group. The study also found that salivary IgG and IgM levels were generally lower than corresponding serum levels, whereas salivary IgA showed a relatively distinct pattern, supporting its potential role as a mucosal biomarker (16).

Importantly, combining salivary IgA detection with viral nucleic-acid testing increased the proportion of patients identified during the first two weeks of hospitalization compared with either approach alone. These findings suggest that salivary antibody testing may complement rather than completely replace molecular testing. However, salivary antibody concentrations are generally lower than those in serum, and assay sensitivity, timing of specimen collection and disease severity can substantially influence detection (16).

Beyond SARS-CoV-2, saliva-based antibody detection has been investigated for several viral infections, including hepatitis viruses, dengue, Ebola virus and herpesviruses. These findings support the broader concept that oral fluid can provide measurable virus-specific immune markers,

although the clinical utility and validation of such assays differ considerably among viruses (14).

Salivary MicroRNAs and Other Non-Coding RNAs

MicroRNAs (miRNAs) are small non-coding RNA molecules involved in post-transcriptional regulation of gene expression. Because they are relatively stable in biological fluids and can be detected using molecular techniques, salivary miRNAs have attracted interest as potential non-invasive biomarkers. They may reflect disease-associated alterations in host cellular pathways and therefore have potential value as biomarkers of infection, inflammation, malignancy and disease progression (1,6).

Genome-wide analysis of salivary miRNAs has demonstrated the feasibility of identifying disease-associated miRNA signatures in saliva. Wu et al. identified salivary miRNA profiles with potential utility for the non-invasive detection of nasopharyngeal carcinoma (12). Although this study was not a direct investigation of an acute viral infection, its findings demonstrate the feasibility of salivary miRNA profiling as a molecular biomarker strategy. This approach may be particularly relevant to virus-associated diseases, including virus-related malignancies, where host-response signatures may complement direct viral detection.

Recent evidence has further expanded the application of salivary miRNA profiling through the analysis of exosomal miRNAs. A prospective case-control study involving 140 participants evaluated salivary exosomal miR-21, miR-31, miR-155, and miR-200c in patients with oral squamous cell carcinoma (OSCC), benign oral lesions, and healthy controls. All four miRNAs were significantly elevated in OSCC patients ($p < 0.001$). Among the individual markers, miR-21 showed the highest diagnostic performance (AUC = 0.89), while the combined four-miRNA panel achieved an AUC of 0.93, with sensitivity exceeding 90% and specificity above 88%. miR-21 and miR-155 also showed correlations with tumor stage. These findings support the potential of salivary exosomal miRNAs as stable, non-invasive host-derived biomarkers for oral malignancy and disease progression.(17)

The potential application of salivary miRNAs in viral disease therefore extends beyond identifying viral nucleic acids themselves. Alterations in host miRNA expression may provide information regarding cellular responses, inflammation or disease-associated tissue changes. However, viral-specific salivary miRNA biomarkers remain insufficiently validated, and differences in extraction methods, normalization strategies and patient characteristics currently limit comparison between studies.

Cytokines and Host immune biomarkers

Host-derived inflammatory and immune mediators represent another potential biomarker category in

oral and salivary diagnostics. Cytokines, chemokines, immunoglobulins and other immune mediators can reflect the host response to viral infection and may provide information that is complementary to direct pathogen detection (1,6).

The major advantage of host-response biomarkers is that they may remain informative even when the amount of detectable viral nucleic acid declines. However, these biomarkers are generally less virus-specific than viral DNA, RNA or antigen detection because similar inflammatory responses can occur in different infectious and non-infectious conditions. Consequently, cytokines and other host-response markers may be more useful when incorporated into a multi-marker diagnostic panel rather than used as standalone indicators.

Salivary IgA represents a particularly relevant host immune biomarker because of its association with mucosal immunity. In SARS-CoV-2 infection, salivary IgA has been investigated as an indicator of mucosal immune response and has also been proposed as a potential marker associated with clinical disease characteristics (16). Thus, host-derived biomarkers may provide complementary information regarding both infection and the immune response to infection.

Oral microbiome and virome-associated biomarkers

The oral cavity contains a complex microbiome consisting of bacteria, fungi, viruses and other microorganisms. Viral infection may alter the composition and functional characteristics of this microbial ecosystem, while the pre-existing oral microbiome may also influence susceptibility to infection and disease manifestations (2).

Changes in the oral microbiome can therefore potentially serve as indirect biomarkers of disease. Advances in metagenomic sequencing have made it possible to simultaneously characterize bacterial and viral components of oral samples, allowing identification of microbial signatures that may not be detected using conventional targeted assays (2). Metagenomic next-generation sequencing has also been successfully applied to complex oral infections where conventional diagnostic methods may be insufficient (4).

The oral virome provides an additional area of interest. Detection of viral sequences in saliva may facilitate identification of known as well as previously unrecognized viruses, while longitudinal profiling may help characterize changes in the oral viral environment during infection. However, the interpretation of microbiome- and virome-associated biomarkers remains challenging because microbial composition is influenced by oral hygiene, diet, medications, age, periodontal status, systemic disease and other environmental factors (2,6).

Metabolomic and Proteomic Biomarkers

Saliva contains a wide range of proteins, peptides, metabolites and other small molecules that may

undergo measurable changes during infection or inflammation. Proteomic and metabolomic approaches therefore provide opportunities to identify complex biomarker signatures rather than relying on a single molecular target (1,6).

Proteomic analysis can identify changes in salivary proteins associated with host immune responses, inflammation and tissue injury, whereas metabolomic approaches can characterize alterations in metabolic pathways associated with disease. These approaches may be particularly useful for identifying host-response signatures that complement direct detection of viral nucleic acids or antigens.

However, metabolomic and proteomic biomarkers are influenced by multiple physiological and environmental variables. Salivary flow rate, collection method, circadian variation, diet, medications, oral health and sample storage can all influence the composition of saliva (6,14). Consequently, standardized collection, processing and analytical procedures are essential before these biomarkers can be translated into clinically applicable diagnostic tests.

Overall, oral and salivary biomarkers encompass both direct viral markers, such as viral DNA, RNA and antigens, and indirect host-response markers, including antibodies, miRNAs, cytokines, proteins and metabolites. The greatest clinical potential may lie in combining complementary biomarker classes rather than relying on a single analyte. Such multimodal approaches could improve diagnostic sensitivity, provide information regarding the stage of infection and potentially support monitoring of disease progression and immune responses.

Diagnostic approaches for detection of viral infections using oral and salivary samples

Oral and salivary specimens have gained attention as non-invasive alternatives for viral diagnosis because they are easy to collect, require minimal equipment, and can facilitate repeated sampling. The presence of viral genetic material, proteins, antibodies, and host-derived molecules in saliva enables multiple diagnostic strategies. (1,6)

Nucleic Acid-Based Methods

PCR and RT-qPCR are the primary molecular techniques used to detect viral DNA or RNA in saliva. Their application has been demonstrated particularly well for SARS-CoV-2, with studies showing that viral RNA can be consistently detected in saliva, supporting its use as an alternative diagnostic specimen. (5)

Researchers have also investigated saliva-based molecular testing for other viruses, including monkeypox virus, where viral DNA has been detected in saliva from infected individuals. However, interpret the presence of viral nucleic acid cautiously, because detection alone does not necessarily indicate active or transmissible infection. (9,10)

Antigen, Protein, and Antibody-Based Methods

Immunological approaches such as ELISA and related assays can detect viral antigens or virus-specific antibodies in oral fluids. Salivary IgA and IgG measurements may provide information regarding mucosal or systemic immune responses and have been investigated for several viral infections. (14)

Metagenomic and Next-Generation Sequencing

Metagenomic next-generation sequencing (mNGS) provides a broad diagnostic approach capable of identifying viral genetic material without requiring prior selection of a specific pathogen. This can be particularly useful in complex oral infections in which the causative organism is uncertain or multiple microorganisms may be present. (4)

Biosensor and Point-of-Care Technologies

Recent developments in electrochemical and impedimetric biosensors have created opportunities for rapid detection of viral targets in saliva. Field-effect transistor- and graphene-based platforms are also being investigated because they may permit rapid testing with limited sample preparation and potential point-of-care applications. (13)

Pre-analytical Factors Affecting Salivary Testing

The accuracy of salivary viral testing is influenced by pre-analytical factors such as stimulated versus unstimulated saliva, collection technique, salivary flow rate, sampling time, and the anatomical source of the specimen. Appropriate processing, transportation, and storage are therefore essential for maintaining biomarker stability and ensuring reproducible results. (14)

Overall, saliva-based diagnostics offer considerable potential for **non-invasive viral detection, screening, surveillance, and point-of-care testing**. Nevertheless, differences in collection procedures, analytical platforms, viral loads, and clinical validation remain important barriers to their widespread routine implementation. (6)

Virus-specific evidence and biomarker profiling

Herpesviruses and Other DNA Viruses

Herpesviruses are among the viral pathogens most frequently detected in oral fluids because the oral cavity can serve as a site of viral persistence and intermittent shedding. Salivary and oral specimens have therefore been investigated for the detection of herpesviral DNA, particularly Epstein-Barr virus (EBV), human cytomegalovirus (HCMV), and herpes simplex virus (HSV). (16,18)

Saygun *et al.* demonstrated that periodontal lesions can contribute to the presence of HCMV and EBV in saliva, supporting the concept that diseased oral tissues may act as local reservoirs for viral shedding. The study also highlighted the potential relationship between periodontal inflammation and salivary detection of herpesviruses. (18)

Imbronito *et al.* compared different sampling approaches for detecting EBV and HCMV in blood and oral specimens. Their findings demonstrated

that viral genetic material could be detected in oral samples, supporting the use of oral fluids as an accessible specimen for herpesviral molecular investigation. (19)

Raggam *et al.* further evaluated standardized molecular detection of viral nucleic acids in oral fluid and demonstrated the feasibility of reliable viral nucleic-acid detection using standardized collection and automated molecular procedures. Such approaches are important because methodological variability in saliva collection and processing can substantially influence viral detection. (20)

The detection of herpes viral DNA in saliva should nevertheless be interpreted cautiously. Viral DNA detection may represent shedding or latent infection rather than active disease, and therefore molecular positivity should be correlated with clinical manifestations and, where possible, quantitative viral burden. This distinction is particularly relevant for herpesviruses because asymptomatic oral shedding may occur. (18,20)

Overall, the available evidence indicates that saliva and other oral fluids have potential for non-invasive detection and monitoring of herpesviral infections, although further standardized studies are required to establish viral-load thresholds and the clinical significance of salivary positivity.

Human Papillomavirus (HPV)

Human papillomavirus (HPV), particularly high-risk HPV16, is an important viral factor in oral and oropharyngeal carcinogenesis. HPV DNA can be detected in saliva and oral rinse specimens, making these samples attractive for non-invasive assessment of HPV infection. (21)

A meta-analysis of studies evaluating salivary HPV demonstrated that salivary HPV DNA was detected more frequently in patients with oral and oropharyngeal cancer than in controls. The pooled analysis reported a prevalence of 43.2% for salivary HPV DNA among patients with oral/oropharyngeal carcinoma and showed a significant association between salivary HPV detection and cancer, particularly for HPV16. (21)

Primary studies have evaluated different approaches for detecting HPV DNA in oral rinse and saliva, including PCR-based and quantitative molecular assays. These findings support the potential role of oral fluids as minimally invasive specimens for HPV detection and risk assessment. (22,23)

However, salivary HPV DNA detection should not be considered equivalent to persistent or transcriptionally active HPV infection. Viral DNA may reflect transient infection or viral shedding, and therefore positive results require appropriate clinical interpretation. (21,23)

Overall, salivary HPV testing represents a promising non-invasive biomarker approach, particularly for HPV-associated oropharyngeal disease, but standardized sampling, molecular testing methods,

and clinically validated thresholds are still required before routine implementation.

Epstein–Barr Virus (EBV)

Epstein–Barr virus (EBV) is an important oral-associated herpesvirus that establishes persistent infection and can shed intermittently into saliva. Because of this continuous or episodic oral shedding, saliva has been investigated as a convenient specimen for non-invasive detection of EBV genetic material.

Studies evaluating oral fluids have demonstrated that EBV DNA can be detected and quantified in saliva, supporting molecular detection as a potential biomarker of viral presence and shedding. Researchers have also investigated salivary EBV detection in relation to oral conditions in which local viral shedding may increase. (20)

Salivary EBV detection may be relevant in oral and systemic disease, particularly where viral reactivation or increased shedding occurs. However, interpret EBV DNA in saliva carefully because EBV commonly persists in the host, and molecular positivity alone cannot reliably distinguish latent infection from active replication.

From a biomarker perspective, salivary EBV DNA is a readily accessible viral nucleic-acid marker, and quantitative assessment may provide additional information about the magnitude of viral shedding. Standardization of specimen collection, processing, and molecular assays remains important for improving the clinical reproducibility of salivary EBV testing.

Overall, saliva represents a promising non-invasive specimen for EBV molecular detection, although its value as a standalone diagnostic or prognostic biomarker requires further validation in well-characterized clinical populations.

SARS-CoV-2

SARS-CoV-2 has provided some of the strongest evidence supporting saliva as a non-invasive specimen for viral detection. Viral RNA can be detected in saliva, and studies have demonstrated that saliva-based molecular testing can provide a practical alternative to nasopharyngeal sampling, particularly because collection is simple and can be performed without invasive procedures. (5)

Evidence also supports the presence of SARS-CoV-2 in saliva, as the virus can infect salivary glands and oral tissues, providing a potential local source of viral material entering oral fluid. (7)

Clinical studies have further demonstrated the feasibility of saliva-based SARS-CoV-2 testing. Consistent detection of viral RNA in saliva supports its use for diagnosis and potentially for repeated monitoring, although viral detection may vary by disease stage, viral load, and sampling conditions. (5)

Postmortem investigations have also shown SARS-CoV-2-related changes in oral tissues and salivary glands, suggesting that the oral cavity may play an

active role in infection pathobiology rather than serving only as a passive site of viral contamination. (7)

SARS-CoV-2 represents an important model for the development of saliva-based viral diagnostics, demonstrating the potential of oral fluids for molecular detection while also highlighting the importance of standardized sampling and interpretation of viral RNA positivity.

Prosthodontic Implications of Oral and Salivary Viral Biomarkers

The close relationship between saliva, oral tissues, prosthetic materials, and prosthodontic procedures makes viral infections relevant to prosthodontic practice. Saliva may serve both as a source of viral biomarkers and as a potential medium for contamination of prostheses and dental materials. Therefore, understanding viral shedding, salivary changes, prosthetic surface contamination, and appropriate infection-control measures may help improve the safety of prosthodontic treatment. The following section summarizes the current evidence and potential clinical implications of oral and salivary viral biomarkers in prosthodontics.

Viral Contamination of Removable Prostheses

Removable prostheses are frequently exposed to saliva and oral secretions and therefore require appropriate infection-control measures in patients with transmissible viral infections. A cross-sectional study evaluating acrylic resin denture bases in patients with COVID-19 detected SARS-CoV-2 RNA on some dentures; however, the association between patients' clinical PCR results and denture PCR results was not statistically significant. These findings suggest that although prosthetic surfaces may come into contact with viral material, detection of viral RNA does not necessarily establish that dentures act as reservoirs or sources of transmission (24).

Denture Wearing, Viral Shedding and the Oral Environment

The relationship between removable dentures and oral viral shedding remains an emerging area of interest. Detection of human herpesvirus-8 DNA in saliva has been investigated among removable denture wearers, highlighting the potential relevance of prosthetic status when studying oral viral shedding. However, molecular detection of viral DNA alone does not establish active infection, viral replication, or transmission. Further longitudinal studies are required to clarify whether denture use influences viral persistence, shedding, or the oral microenvironment (25).

Infection Control in Prosthodontic and Implant Procedures

Prosthodontic procedures involve close contact with saliva, contaminated impressions, prostheses, instruments, and laboratory materials, creating potential opportunities for cross-contamination. Guidelines developed during the COVID-19

pandemic emphasized appropriate patient screening, personal protective equipment, hand hygiene, disinfection of impressions and prostheses, and careful handling of laboratory materials. In implant procedures, minimizing aerosol generation, using high-volume suction, and appropriately disinfecting or sterilizing impression components and prosthetic materials were also emphasized. Digital workflows may additionally reduce repeated patient contact and some potential routes of contamination (26).

Salivary Dysfunction and Prosthodontic Considerations

Saliva plays an important role in lubrication, mucosal protection, swallowing, oral clearance, and maintenance of the oral environment. Salivary gland dysfunction can reduce salivary flow and alter its composition, potentially affecting oral comfort and the functional tolerance of removable prostheses. Patients with reduced salivary flow may experience increased mucosal discomfort and difficulties associated with prosthetic rehabilitation. Therefore, assessment of salivary function may be relevant during prosthodontic treatment planning, particularly in patients with xerostomia or salivary gland dysfunction (27).

Future Role of Salivary Biomarkers in Prosthodontics

Salivary biomarkers may have future applications in prosthodontics beyond the detection of viral infections. Advances in molecular profiling have enabled the identification of viral nucleic acids, antibodies, proteins, microRNAs, and other host-derived biomarkers from saliva. These approaches may eventually support non-invasive screening of patients before prosthodontic procedures, monitoring of oral and systemic conditions, and identification of patients requiring closer preventive or maintenance care. Integration of salivary biomarker assessment with conventional clinical examination may therefore contribute to a more personalized approach to prosthodontic treatment. Despite this potential, clinical application remains limited by variability in salivary flow, specimen collection, processing methods, analytical platforms, and clinically validated thresholds. Future prospective studies should therefore evaluate salivary biomarkers alongside prosthodontically relevant outcomes such as xerostomia, mucosal health, denture tolerance, peri-implant tissue status, and prosthetic complications. Such evidence could clarify whether saliva-based biomarkers can provide clinically meaningful information for personalized prosthodontic care (27).

Conclusion

The oral cavity represents an important interface between viral infection, oral manifestations, salivary biology, and host response. Current evidence indicates that saliva and other oral specimens can provide a broad range of biomarkers, including viral DNA/RNA, antibodies, viral proteins, microRNAs,

and other host-derived markers, supporting their potential for non-invasive viral detection and disease monitoring. Evidence from SARS-CoV-2, HPV, EBV, and other viral infections further demonstrates the expanding role of saliva-based diagnostics, while emerging evidence on salivary exosomal miRNAs and prosthodontic applications broadens their clinical relevance.

Despite this progress, differences in viral shedding, disease stage, specimen collection, processing, and analytical methods remain important barriers to routine clinical application. In prosthodontics, salivary dysfunction, prosthetic surface contamination, and infection-control considerations further highlight the clinical importance of understanding the oral viral environment. Future research should focus on standardized sampling protocols, validated biomarker panels, larger prospective studies, and clinically relevant diagnostic thresholds. With continued advances in molecular diagnostics and saliva-based technologies, oral and salivary biomarkers have the potential to move from promising research applications toward practical, non-invasive tools for precision viral diagnosis, monitoring, and integrated oral healthcare.

Table 1. Oral Manifestations, Salivary Biomarkers, and Prosthodontic Relevance of Viral Infections

Viral infection	Major oral manifestations	Salivary/oral biomarker	Potential prosthodontic relevance
<i>SARS-CoV-2</i>	Taste alteration, mucosal lesions, salivary gland involvement	Viral RNA, antibodies	Infection-control considerations; contamination of prostheses/materials
<i>HPV</i>	Oral/oropharyngeal lesions, HPV-associated malignancy	HPV DNA	Relevance to oral cancer assessment and prosthodontic treatment planning
<i>EBV</i>	Mucosal changes, viral shedding	EBV DNA	Salivary viral shedding and oral/prosthetic environment

<i>HHV-8</i>	Oral lesions; salivary viral shedding	HHV-8 DNA	Potential relevance in denture-wearing patients
<i>Other viral infections</i>	Vesicles, ulcers, mucosal changes, salivary dysfunction	Viral DNA/RNA, antibodies, host biomarkers	Consideration of salivary function, prosthetic tolerance and infection control

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