

# Oral viral infections of adults

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The field of virology has advanced greatly over the past two decades, mainly because of the introduction of sophisticated molecular tools, such as monoclonal antibodies, polymerase chain reaction (PCR)-based amplification, DNA sequencing, DNA and protein microarray chip assays, and rapid diagnostic tests. These technologies have been the driving force in the identification of viral bodies, proteins and nucleic acids in body fluids and tissue samples, and in determining the host response to viral infections. The 5th (2007) edition of *Fields Virology* provides an in-depth description of viral methodology and medical virology, and is an important source of reference for this review (118).

Viruses replicate only when present within eukaryotic (animals, plants, protists and fungi) or prokaryotic (bacteria and archaea) cells, not on their own. The extracellular virion particle ranges in size from 20 to 300 nm and consists of either DNA or RNA contained within a protective protein capsid. Some viruses have an additional envelope comprising a lipid bilayer derived from the outer cellular membrane, the internal nuclear membrane, or the endoplasmic reticulum membrane of the infected cell. Taxonomically, viruses are classified according to the presence of DNA or RNA, single-stranded or double-stranded nucleic acid, and an enveloped or nonenveloped nucleocapsid. Additional taxonomical criteria include mode of replication, type of host, capsid shape, immunological properties and disease association.

The host recognizes and reacts to the infecting virus by innate and adaptive immune responses. Important cells of the innate immune system include macrophages, dendritic cells and natural killer cells. Viruses activate inflammatory cell types to release antiviral cytokines and cytotoxic agents, and to induce lymphocyte-mediated adaptive immunity. A significant cytokine release is stimulated through activation of the tumor necrosis factor- $\alpha$  receptor/nuclear factor- $\kappa$ B/extracellular signal-regulated kinase pathway (49). Virally derived proteins, which

are presented by major histocompatibility complex molecules on the surface of infected cells, serve as epitopes for specific host immune cells.

Nonenveloped viruses are mainly controlled by the humoral adaptive immunity. Enveloped viruses are controlled by the cellular immunity through the action of natural killer cells and cytotoxic CD8<sup>+</sup> T lymphocytes. After recognizing viral surface antigens on infected cells, cytotoxic T lymphocytes inhibit virus replication by cytolytic killing and by releasing interferons, chemokines, tumor necrosis factor- $\alpha$  or other pro-inflammatory mediators.

Viral disease may be a direct result of cell destruction or a secondary consequence of host immune reactions against viral proteins. Pro-inflammatory cytokines play important roles in the antiviral immune response, but interleukin-1 $\beta$ , interleukin-6 and tumor necrosis factor- $\alpha$  cytokines can also contribute to disease manifestation. The host usually performs a delicate balancing act between promoting antiviral cytokine responses and limiting the amount of tissue damage. To counteract the immune attack, viruses employ sophisticated immunoevasive strategies to suppress antiviral host responses. For example, some viruses produce proteins that alter the major histocompatibility complex and hence the exposure of viral proteins on the surface of infected cells. Viruses may encode viral homologs of host cytokines and decoy receptors capable of binding and neutralizing host-derived cytokines. A rapid rate of mutation in critical viral genes can help viruses avoid the adaptive host defense. Other viral gene products inhibit apoptosis, which facilitates a prolonged state of replication of infected cells and spread of the virus.

Viral diseases of the oral mucosa and the perioral region are often encountered in dental practice, but have received only limited research interest. Viruses are important ulcerogenic and tumorigenic agents of the human mouth. The finding of an abundance of mammalian viruses in periodontitis lesions may suggest a role for viruses in more oral diseases than

previously recognized (211). Optimal standard management of oral viral diseases remains to be established. New approaches to disease prevention and therapy may emerge as the significance and pathogenesis of oral viral infections become understood in more detail. An important future goal of oral microbiology would be to determine the diversity, frequency, magnitude, pathogenicity and treatment of oral viruses and their diseases. Viral diagnostic samples can be collected by a brushing technique of the oral mucosal lesion and the surrounding normal tissue (82). This review presents an overview of major mammalian viruses and viral diseases in the human oral cavity of adult individuals. Viral diseases of the mouth of children and adolescents are reviewed elsewhere in this volume of *Periodontology 2000* (197).

## Major viral families in the human oral cavity

Table 1 and the text below describe important viruses associated with oral diseases of adults.

### Herpesviruses

Herpesvirus virions vary in size from 120 to 250 nm and consist of a double-stranded linear DNA molecule surrounded by an icosahedral capsid, a proteinaceous tegument and a lipid-containing envelope with embedded viral glycoproteins (175). Herpesviruses infect most animal species, and almost 300 different types of herpesvirus have been identified to date. Eight human herpesvirus species with distinct biological and clinical characteristics have been described: herpes simplex virus-1, herpes simplex virus-2, varicella-zoster virus, Epstein-Barr virus, human cytomegalovirus, human herpesvirus-6, human herpesvirus-7 and human herpesvirus-8. The *Herpesviridae* family is divided into the alpha subfamily [herpes simplex virus-1 (oral-facial type), herpes simplex virus-2 (genital type), varicella-zoster virus], the beta subfamily (human cytomegalovirus, human herpesvirus-6 and human herpesvirus-7), and the gamma subfamily (Epstein-Barr virus and human herpesvirus-8). Each herpesvirus subfamily maintains latent infection in specific cell population(s). Alpha herpesviruses exhibit a relatively short reproductive cycle, rapid lysis of infected cells and latency in sensory ganglia. Beta herpesviruses demonstrate a long reproductive cycle, slowly progressing infection, sometimes enlargement of

infected cells (cytomegalia) and tropism for a large range of cells. Gamma herpesviruses are usually specific for B lymphocytes and T lymphocytes, and viral latency is typically found in lymphoid tissue. In contrast to a chronic infection, latency is not associated with infectious virions. A single individual can simultaneously show herpesvirus latent infection in some cells and active viral infection in other cells. Herpesviruses express proteins during the normal lytic and latent viral life cycle that can interfere with activities of the innate and adaptive immune systems and alter the cellular environment. The alteration of the host defense ensures a lifelong persistence of the viruses in the infected host and can contribute to disease development. Herpesvirus active infections can remain asymptomatic but still give rise to viral shedding, or can cause illness ranging from classic infectious diseases to benign and malignant tumors, especially in immunocompromised hosts. Herpes simplex and varicella-zoster viruses are significantly associated with Bell's palsy, an acute unilateral facial paralysis usually involving the seventh cranial nerve (79). Epstein-Barr virus and cytomegalovirus have been associated with multiple chronic 'auto-immune' diseases, including systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis, multiple sclerosis, pemphigus vulgaris, Sjögren's syndrome, giant cell arthritis, Wegener's granulomatosis and polyarteritis nodosa (19). Cytomegalovirus can cause serious infections in immunologically immature hosts (e.g. those with congenital infection) and in immune-compromised hosts [e.g. patients with acquired immunodeficiency syndrome (AIDS) and organ transplant recipients]. Severe cytomegalovirus infections may be more common than previously thought (180).

### Papillomaviruses

Papillomaviruses were previously included in the *Papovaviridae* family but are now assigned to a separate family, the *Papillomaviridae* (104). The papillomaviruses comprise a group of small, epitheliotropic, nonenveloped, icosahedral, double-stranded and circular DNA viruses. Human papillomaviruses reside in the ano-genital area, the larynx-tracheo-bronchial mucosa, the oral mucosa and the skin. Papillomaviruses occur globally but with a particularly high prevalence in South American native populations and in Inuits. More than 75% of sexually active adults are infected with at least one type of genital papillomaviruses. Based on phylogenetic differentiation, papillomaviruses are divided

**Table 1.** Human viruses in oral diseases of adults

Virus	Viral genome	Enveloped virus	Characteristics	Disease association	References
<i>Herpesviruses</i>	Double-stranded DNA	Yes			
Herpes simplex virus-1			Latency in sensory ganglia. Causes orolabial disease	Herpetic gingivostomatitis, recurrent orolabial lesions, herpetic Whitlow, keratoconjunctivitis, eczema herpeticum, pharyngitis, mononucleosis-like syndrome, encephalitis, neonatal infections	Roizman et al. (193), Whitley (251)
Herpes simplex virus-2			Latency in sensory ganglia. Causes genital and newborn infections	Genital infection, aseptic meningitis, sacral autonomic nervous system dysfunction	Roizman et al. (193), Whitley (251)
Varicella-zoster virus			Latency in sensory ganglia. Only three major genotypes of the wild-type virus are known. More than 90% are infected before adolescence in an unvaccinated population	Varicella (chickenpox), herpes zoster (shingles), central nervous system involvement, pneumonia, secondary bacterial infections and death. Available varicella vaccines (about 90% effectiveness) include a single-antigen vaccine and a combination vaccine against measles, mumps, rubella and varicella (MMRV)	Cohen et al. (51), Heininger & Seward (96)
Epstein-Barr virus			Identified initially in 1964 from African Burkitt lymphoma. Infects epithelial cells with a cytolytic infection and B lymphocytes with a latent infection	Infectious mononucleosis, hairy leukoplakia of the tongue, Burkitt lymphoma, B lymphoproliferative disease, Hodgkin's lymphoma, X-linked lymphoproliferative disease, nasal T-cell lymphoma, nasopharyngeal carcinoma, gastric carcinoma, parotid carcinoma and leiomyosarcoma	Pagano (168), Rickinson & Kieff (187), Williams & Crawford (254)
Human cytomegalovirus			Infects mainly T lymphocytes and macrophages. The gB protein in the virion envelope participates in the virus-cell interaction and is a major target of the immune response	Preterm birth, pre-eclampsia, transplant rejection, immunosenescence, hemorrhagic retinal necrosis (HIV patients), encephalitis, infectious mononucleosis, atherosclerosis, gastrointestinal disease, pneumonia and encephalitis	Mocarski et al. (153), Pass (172), Steininger et al. (230)

Table 1. Continued

Virus	Viral genome	Enveloped virus	Characteristics	Disease association	References
Human herpesvirus-6			Cell tropism for T lymphocytes and neural cells. Frequently shed in the saliva of healthy donors	Roseola infantum ('sixth disease'), meningitis, encephalitis, possibly multiple sclerosis	Whitley & Lakeman (252), Yamanishi et al. (261)
Human herpesvirus-7			Latency in macrophages and T lymphocytes. Frequently shed in the saliva of healthy donors	Exanthema subitum, macular-papular rashes, transplant-recipient pathogen	Kempf (117), Yamanishi et al. (261)
Human herpesvirus-8			Six genetic subtypes with marked clustering to geographical areas. B lymphocytes and monocytes serve as reservoirs	Kaposi's sarcoma, multicentric Castleman disease, primary effusion lymphoma, mononucleosis-like illness, aplastic anemia. Unlike the Epstein-Barr virus, herpesvirus-8 is not involved in epithelial tumors	Ganem (77), Rimar et al. (189)
<i>Papillomaviruses</i>	Double-stranded DNA	No	Epithelial cell proliferation with specificity principally in the ano-genital area, urethra, skin, larynx, tracheo-bronchial and oral mucosa	Genital and cutaneous warts, cervical and ano-genital cancers, condylomata acuminata (sexually transmitted disease), recurrent respiratory papillomatosis	Howley & Lowy (104), Snoeck (226)
<i>Picornaviruses</i>	Single-stranded RNA	No			
Coxsackievirus			Coxsackie virus A16 is closely related to Enterovirus-71, and both belong to a discrete subgroup of type A enteroviruses that are prominently associated with hand, foot and mouth disease	Uncomplicated hand, foot and mouth disease (Coxsackie virus A serotypes 10 and 16), herpangina (mostly Coxsackie virus A), myocarditis, infectious type 1 diabetes (Coxsackie virus B), atherosclerosis	Pallansch & Roos (170)
Echovirus			Some echovirus replication occurs in the nasopharynx	Meningitis, pericarditis, myocarditis, herpangina, Guillain-Barré syndrome	Pallansch & Roos (170)
Enterovirus			Enterovirus-71 was first isolated in 1969 from a child with encephalitis. Can cause large epidemics of acute disease. Mutates readily	Hand, foot and mouth disease (enterovirus-71), herpangina (enterovirus-71), poliomyelitis-like illness, meningoencephalitis (enterovirus-71), acute pulmonary edema (enterovirus-71), hemorrhagic conjunctivitis	Modlin (154), Palacios & Oberste (169), Pallansch & Roos (170)

into 12 genera, each of which is designated by a letter of the Greek alphabet. Human papillomaviruses are grouped within five genera and comprise more than 100 types. Most of the papillomaviruses responsible for significant diseases in humans

belong to the genus alpha-papillomavirus (genital papillomaviruses), beta-papillomavirus (responsible for epidermodysplasia verruciformis) and gamma-papillomavirus (most of the viruses responsible for cutaneous lesions). As papillomaviruses are host

Table 1. Continued

Virus	Viral genome	Enveloped virus	Characteristics	Disease association	References
<i>Retroviruses</i>	Single-stranded RNA	Yes			
Human immunodeficiency virus-1			Global infection; infects cells containing CD4 receptor, such as T-helper lymphocytes and cells of the macrophage lineage	The rank order of AIDS-defining pathoses is as follows: <i>Pneumocystis pneumonia</i> (43%), esophageal candidiasis (15%), wasting (11%), Kaposi's sarcoma (11%), disseminated <i>Mycobacterium avium</i> infection (5%), <i>Mycobacterium tuberculosis</i> (5%), cytomegalovirus disease (4%), HIV-associated dementia (4%), recurrent bacterial pneumonia (3%) and toxoplasmosis (3%)	Freed & Martin (74), Kuritzkes & Walker (123), Yin et al. (264)
Human immunodeficiency virus-2			Infection occurring mainly in West-Central Africa (Guinea Bissau)	HIV-2 is associated with similar types of diseases as HIV-1, but is generally less virulent	Azevedo-Pereira et al. (16), Freed & Martin (74)

specific, the biology of human papillomavirus cannot be studied in animals. Papillomaviruses can induce benign lesions of the skin (warts) and mucous membranes (condylomas). Some papillomaviruses can cause epithelial malignancies, especially cancer of the uterine cervix. Worldwide, cervical cancer is the second most common malignancy among women. Papillomaviruses are also implicated in certain types of anal cancer, vulvar cancer, penile cancer, laryngeal cancer and oral cancer. Based on their association with cervical carcinoma, papillomaviruses are classified as exhibiting high (types 16, 18 and 31) or low (types 6, 11, 42 and 36) oncogenic risk. Papillomavirus type 16 exhibits the highest, and type 18 the second-highest, oncogenicity. Papillomaviruses, especially type 16, have been implicated in one-third of oropharyngeal squamous cell carcinomas and show a particularly strong relationship with cancer of the tonsils (90, 100). Head and neck cancers related to papillomaviruses exhibit relatively high mortality rates despite early diagnosis and treatment.

To prevent cervical cancer and probably also other types of papillomavirus-induced cancers, a prophylactic vaccine against the oncogenic papillomaviruses types 6, 11, 16 and 18 became available in 2006.

### Picornaviruses / enteroviruses

Picornaviruses are nonenveloped, single-stranded, positive-sense RNA viruses with a virion diameter of approximately 30 nm (170). The name of the virus family conveys the small size of the viruses (pico: Spanish for small) and the nucleic acid of the viral genome (RNA). The *Picornaviridae* family consists of nine genera and contains several serious pathogens, including poliovirus, hepatitis A virus, rhinovirus and the hand, foot and mouth disease virus. The *Enterovirus* genus in the picornavirus family includes Coxsackie virus (divided into groups A and B based on pathogenicity in experimental mice and into 23 serotypes), echovirus (28 serotypes), poliovirus (three serotypes) and human enterovirus (four serotypes).

Enteroviruses replicate in the alimentary tract. There are significant overlaps in the biological properties of viruses in the different enterovirus groups. Disease-producing enteroviruses generally cause acute rather than chronic illness, but persistent infections may occur in individuals with humoral immunodeficiency. Enteroviruses are common human pathogens that are associated with a broad spectrum of clinical presentations ranging from asymptomatic infections, various enanths and exanths, respiratory diseases, aseptic meningitis, severe illness in newborns and immunocompromised hosts, to fatal outcome (162). As enteroviruses are prevalent in most populations, primary infections usually take place in childhood, but can also occur in adults.

## Retroviruses

Retroviral virions are composed of one or two copies [human immunodeficiency virus (HIV) has two copies] of single-stranded, positive-sense RNA enclosed by a conical capsid and a phospholipid envelope. Retrovirus species inhabit virtually all vertebrates (74). A total of seven retrovirus genera have been established. HIV and T-lymphotropic virus are human pathogens. HIV belongs to the *Lentivirus* genus and includes two subspecies, namely HIV-1 and HIV-2. Lentiviruses are characterized by long incubation periods between infection of the host and the manifestation of clinical disease. HIV is thought to originate from zoonotic transmission from wild monkeys in Africa. HIV-1 is the more virulent type and is responsible for most HIV infections globally. HIV-1 infections are limited to humans and chimpanzees. The immunologically distinct HIV-2 subspecies infects mainly individuals in West-Central Africa. The most common form of HIV transmission is the sexual route, followed by blood-product exchange and mother-to-child spread *in utero*. HIV-related diseases in humans first appeared in the late 1950s and more than 25 million individuals worldwide are currently infected with HIV. It is estimated that 8500 new HIV infections occur every day.

The name retrovirus refers to the unique mode of replication of the viruses. After entering a cell, the viral RNA is transcribed by viral reverse transcriptase into a DNA molecule, which is integrated as a provirus into the host chromosomal DNA. The provirus DNA serves as a template for the formation of viral RNA and the proteins used in the assembly of new virions. The ability of the provirus to remain transcriptionally inactive, a feature that avoids exposing viral proteins or enzymes to immune attack, enables

retroviruses to maintain a persistent infection despite a functional host immune system. Also, HIV survives in a host by means of major antigenic shifts and rapid viral turnover, which produce a pool of genotypic and phenotypic new clones, sometimes termed quasi-species.

All retroviral genomes contain open-reading frames (HIV has a total of nine genes) designated the *gag*, *pro*, *pol* and *env* genes, which contain information related to the production of virion structural proteins (74). The *env* gene codes for the viral envelope glycoprotein gp160, which is broken down by a retroviral enzyme to form gp120 and gp41. The glycoproteins gp120 and gp41 then mediate the attachment and fusion of the virus to target cells in the initial step of the virus life cycle (197). The gp120 and other surface proteins are candidates for developing an anti-HIV vaccine. However, the gene encoding the envelope glycoprotein, gp160, shows extensive genetic heterogeneity. *Lentivirus* genomes contain additional regulatory genes that participate in viral genome transcription and virion production. The retrovirus enzymes needed for the development of virions include reverse transcriptase, proteases, ribonucleases and integrase.

HIV uses the CD4 receptor and a chemokine co-receptor (CCR5 or CXCR4) for entry into susceptible cells (197). Based upon the chemokine receptor usage, HIV-1 isolates are designated R5 when using the CCR5 receptor, X4 when using the CXCR4 receptor and R5/X4 when using both coreceptors. T-helper lymphocytes, cells of the macrophage lineage and some dendritic cells contain CD4 receptor and thus are receptive to HIV infection. The HIV infection gives rise to a selective depletion of CD4<sup>+</sup> T lymphocytes by mechanisms of apoptosis or necrosis.

HIV diseases result from the progressive loss of cell-mediated immunity, which ordinarily protects against a variety of normally innocuous insults to the immune system (123). The hallmark of HIV infection is depletion of circulating CD4<sup>+</sup> T cells. Opportunistic infections and malignancies become increasingly more common and severe when the CD4 count falls below 500 cells/ $\mu$ l. The time from acute infection to the development of advanced disease (AIDS), defined by a CD4 count of less than 200 cells/ $\mu$ l or the appearance of AIDS-defining opportunistic infections or cancers, can, in untreated patients, vary from as little as 6 months to more than 25 years. Viral and host genetics determine the time of onset of AIDS.

The course of HIV infection can be divided into primary (or acute) infection, chronic (asymptomatic) infection and AIDS (123). Early stage diseases include

oral and vulvovaginal candidiasis, pneumococcal infections, tuberculosis and re-activation of herpes simplex virus and varicella-zoster virus. Later-stage infections include *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia, *Candida esophagitis*, disseminated histoplasmosis, toxoplasma encephalitis and cryptococcal meningitis. Late-stage diseases include disseminated *Mycobacterium avium* complex infection, recurrent or disseminated cytomegalovirus infection, cryptosporidiosis and microsporidiosis. Cytomegalovirus viremia predicts lower survival rates of AIDS patients receiving antiretroviral therapy (255). Malignancies in patients with AIDS are generally virally related and include Epstein-Barr virus lymphomas, human herpesvirus-8 Kaposi's sarcoma and papillomavirus cervical and anal carcinomas.

Current treatment for HIV infection consists of HAART (highly active antiretroviral therapy), which includes a cocktail of at least three drugs belonging to at least two classes of antiretroviral agents: typically two nucleoside analogue inhibitors of reverse transcriptase, together with either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (123, 197). A newly approved class of HIV drugs, known as CCR5 antagonists, blocks the CCR5 coreceptor and is prescribed to patients who are infected with HIV-1 R5 strains that are resistant to multiple antiretroviral agents.

## Oral diseases with a viral component

### Oral ulcers

Ulcers/erosions are relatively common in the oropharyngeal mucosa (209). Oral ulcers involve an excavation of the epithelium and lamina propria, and are typically painful, covered by a white-to-yellow pseudomembrane and surrounded by an inflammatory halo. Oral erosion denotes loss of tissue limited to the epithelial layer, but the term is often used interchangeably with oral ulcer (212). Ulcers range in diameter from a few millimeters to 2 cm and can appear as single or multiple lesions. Oral ulcers occur as a result of infection with viruses or microorganisms, physical or chemical trauma, immunodeficiency and autoimmunity, systemic diseases, burns, drugs, nutritional deficiencies and malignancies (211). More than 75 drugs can trigger oral ulceration (214).

Scully et al. (212) provided guidelines for a tentative identification of oral ulcers. Solitary ulcers

should be considered to be caused by either local trauma or malignancy until proven otherwise; small multiple ulcers in an otherwise healthy person probably reflect aphthous stomatitis (if recurrent) or a primary herpes simplex virus infection (if acute with fever or systemic symptoms); widespread and multiple oral ulcers should raise the suspicion of skin disease or vasculitis, particularly if associated with mucocutaneous lesions (e.g. blistering, hyperkeratosis or scarring); and ulcers limited to the commissures (angular cheilitis) have typically a microbial basis (often a candida or staphylococcal infection). However, as the clinical appearance of oral ulcers is often not pathognomonic, and several different ulcerogenic conditions of the mouth may currently be lumped together under one diagnosis, it is difficult to determine the prevalence, the etiology and the best treatment of the various types of oral ulcers.

A viral cause of oral ulcers has been established for primary and recurrent herpetic gingivostomatitis, varicella/herpes zoster outbreak, herpangina, hand, foot and mouth disease, and verrucous carcinoma, and is suspected in acute necrotizing ulcerative gingivitis. Viruses may also play a role in some cases of recurrent aphthous stomatitis and in systemic diseases with an oral ulcerogenic component (Table 2). It is probable that several of the risk factors for oral ulceration cause lesion outbreak by activating a latent viral infection. Also, some viruses may induce oral ulceration when co-infecting with other viruses.

Herpetic gingivostomatitis is the most common clinical manifestation of a primary herpes simplex virus infection of the mouth. The disease can also occur as a recrudescence intra-oral herpes simplex virus infection in healthy children and young adults (47). Although herpetic gingivostomatitis typically affects children, the disease can appear in older adults (45, 137). Herpes simplex virus-1 causes most orofacial herpesvirus infections, but infection with herpes simplex virus-2 is increasingly common (11). Prodromal symptoms, such as fever, anorexia, irritability, malaise and headache, may occur in advance of the disease (120). Shallow ulcers form on attached gingiva and on the buccal and sublingual mucosa, and may also involve the hard palate, but typically not gingival papillae. Herpetic gingivostomatitis is often accompanied by fever and submandibular lymphadenopathy. Herpetic Whitlow denotes an autoinoculation of herpes simplex virus from the primary site of infection to, most commonly, the distal phalanx of the fingers and occasionally to the toes (259), and poses an occupational

**Table 2.** Oral mucosal ulcers with a putative viral etiology

Ulcer type	Virus	Comments	References
Adult herpetic gingivostomatitis	HSV	Otherwise healthy adults up to 62 years of age have experienced an acute course of herpetic gingivostomatitis similar to that seen in children	Christie et al. (47), Holbrook et al. (101)
Herpangina	Coxsackie virus A and other enteroviruses	An enterovirus enanthema characterized by high fever and sudden onset in young children. Vesicles and ulcerations occur in the soft palate and in the tonsils	Pallansch & Roos (170)
Hand, foot and mouth disease	Enterovirus-71 and Coxsackie virus A16	A self-limited febrile illness displaying tender papulovesicular lesions of the hands, feet, oropharyngeal mucosa, and other body sites. Disease mostly occurs in children but can affect adults in a milder way	Chang et al. (43), McMinn (144), Modlin (154), Zhang et al. (268)
Pure red cell aplasia / systemic lupus erythematosus	Human parvovirus B19	Characterized by fever, polyarthritis and oral ulcers. Pure red cell aplasia and systemic lupus erythematosus often exhibit similar clinical features	Ideguchi et al. (106)
Unspecified oral ulcers	HPV	HPV type 18 was detected in 86% of HPV-positive lesions	Giovannelli et al. (83)
Uvulo-palatoglossal junctional ulcers	HHV-6	The presence of uvulo-palatoglossal junctional ulcers may be a useful pathognomic clinical sign of primary symptomatic HHV-6 infection (exanthem subitum)	Chua et al. (48)
HIV / AIDS-related oral ulcers	HSV / HCMV	Human cytomegalovirus and herpes simplex virus are the most predominant <i>Herpesviridae</i> in oral ulcers of patients with AIDS. Persistent oral ulcers with a nonspecific clinical appearance in HIV-infected patients have yielded human cytomegalovirus alone (23%), HSV-HCMV co-infection (28%) or HSV alone (19%). Ulcers can occur on the palate, retromolar pad, tongue and lips	Flaitz et al. (72), Itin & Lautenschlager (107), Regezi et al. (185), Woo & Lee (256)
Recurrent oral aphthous stomatitis	HCMV, HSV-1, EBV, VZV, HHV-8 and HPV have revealed inconclusive relationships	Recurrent oral aphthosis affects about 20% of most populations. Lesions are painful, tend to recur and may last for up to 6 weeks. The disease must be differentiated from classic herpesvirus infections and herpangina. No treatment has been uniformly successful, but levamisole shows promise	Lin et al. (130), Pedersen & Hornsleth (174), Sun et al. (234)
Behçet's syndrome	HSV, HCMV	Behçet's disease is a multisystemic disorder characterized by oral and genital ulcers	Al-Otaibi et al. (7), Studd et al. (232), Sun et al. (234)
Oral pemphigus vulgaris	HSV, HCMV	Large recalcitrant oral lesions of pemphigus vulgaris harbor HSV and sometimes HCMV	Kalra et al. (113), Schlüpen et al. (208), Takahashi et al. (240)

**Table 2.** *Continued*

Ulcer type	Virus	Comments	References
Erythema multiforme	HSV, EBV, HCMV	Herpesvirus infection may constitute a possible erythema multiforme-precipitating factor. Patients may show acutely painful oral and labial ulcers	Al-Johani et al. (4), Ayangco et al. (15), Sinha et al. (220), Wanner et al. (249)

EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HHV-6, human herpesvirus-6; HHV-8, human herpesvirus-8 (Kaposi's sarcoma virus); HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

hazard for healthcare workers not wearing protective gloves (14).

The great majority of recurrent or secondary herpes simplex virus-1 infections manifest as oro-facial disease (24, 80). Herpes simplex virus-related ulcers can be widespread in immunocompromised or severely debilitated individuals, including children with oncological diseases (213) and renal transplant patients (114, 129). Herpes simplex virus may also play a role in radiation-induced oral mucositis (160). Typically, lesions of a secondary herpes simplex virus infection are located on the Vermillion border of the lips (herpes labialis, 'cold sores' or 'fever blister'), but may develop elsewhere in the mouth, on the face or inside the nose. The initial primary episode of herpes labialis occurs 1–26 days after inoculation and can appear as multiple blisters, 1–2 mm in size, associated with severe discomfort that lasts for 10–14 days (41). Recurrent herpes labialis affects about one-third of the US population, with episodes usually occurring from one to six times per year (41). Orolabial recurrent herpesvirus infections can be triggered by stimuli such as fever, stress, cold, menstruation and ultraviolet radiation. Prodromal symptoms, including paraesthesia, tenderness, pain, burning sensation, tingling or itching sensation at the site of viral re-activation, arise in 46–60% of patients, and last for about 6 h (11).

Acute necrotizing ulcerative gingivitis is characterized by necrosis of the gingival papillae, bleeding, pain and occasionally fever. In severely immunocompromised patients, acute necrotizing ulcerative gingivitis may progress to ulcerative necrotizing periodontitis or stomatitis, and to the potentially fatal disease termed noma or cancrum oris. Acute necrotizing ulcerative gingivitis has been reported to occur in predominantly stressed but otherwise healthy young individuals. Acute necrotizing ulcerative gingivitis and its progressive disease variants are currently typically found in HIV-infected patients and in severely malnourished individuals of the developing world. Jiménez et al. (108) described 45 HIV-free

children and young adults from Colombia with severe acute necrotizing ulcerative gingivitis or noma. All patients were from low socioeconomic groups and presented with potential predisposing factors, such as acute herpetic gingivostomatitis, measles and acute lymphoblastic or chronic lymphoid leukemia. Malnutrition and poor oral hygiene favored the necrotizing process and the disease progression from gingiva to deeper oral and facial tissues. A measles outbreak among Israeli military personnel was associated with acute necrotizing ulcerative gingivitis-like lesions (116). Contreras et al. (53) found acute necrotizing ulcerative gingivitis in 3–14-year-old children in Nigeria to be related to malnourishment and the subgingival presence of human cytomegalovirus and Epstein-Barr virus-1. The potential for cytomegalovirus and other herpesviruses to cause necrosis has also been established in acute retinal necrosis of severely immunocompromised patients (25), acute necrotizing esophagitis (157), necrotizing enterocolitis of preterm infants (186), necrotizing glomerulonephritis of renal transplant patients (60), necrotizing myelitis (54) and necrotizing encephalitis (158). In acute necrotizing ulcerative gingivitis, HIV infection, malnutrition, psychosocial stress and other immunosuppressive factors may trigger a prolonged activation of periodontal herpesviruses, which may provoke direct cytotoxic reactions, an abundant release of pro-inflammatory cytokines, a weakened host defense, overgrowth of virulent bacteria, necrosis of gingiva, and gingival invasion of medium-size and large-size spirochetes (131).

Varicella-zoster virus causes varicella (chickenpox) as a primary infection of children, and herpes zoster (shingles) as a recurrent infection of older adults. Varicella appears as a skin rash of blister-like lesions that cover the body, but is usually more concentrated on the face, scalp and trunk. The herpes zoster infection classically distributes via dermatomes. Herpes zoster starts on one side of the face or body as a rash, which scabs after 3–5 days and usually resolves within 2–4 weeks. Approximately 1 million new cases

of herpes zoster occur annually in the USA, and about one in three persons in the general population will develop herpes zoster during their lifetime (91). Trigeminal herpes zoster infection can give rise to vesicles and pustules on the external ear, lip, chin and cheek, and ulcerations of the soft palate, buccal mucosa and tongue. The Ramsay Hunt syndrome is characterized by herpes zoster vesicles on the ear, hard palate or tongue and peripheral facial nerve palsy (236). Serious oral complications of trigeminal herpes zoster are neuralgia and occasionally osteonecrosis of the jaw and tooth exfoliation (12, 210, 245). Deaths attributable to herpes zoster are uncommon among persons who are not immunocompromised. A vaccine for preventing initial varicella-zoster virus infection was introduced in the USA in 1995, and a vaccine for preventing shingles in older individuals became available in 2006 (ZOSTAVAX<sup>®</sup>; Merck & Co., Whitehouse Station, NJ, USA) (91).

Herpangina is an acute, febrile illness of sudden onset that is characterized by the presence of vesicles and ulcerations in the oral cavity. Herpangina occurs typically in children less than 5 years old and is usually self-limiting and resolves in 7–10 days. The oral ulcers of approximately 2 mm in size on an erythematous base are located on the anterior tonsillar pillars, the posterior edge of the soft palate, the uvula, the tonsils and the posterior pharynx (170). The absence of oral lesions on the hard palate, and the acute onset and short duration of morbidity, help to differentiate herpangina from other ulcerative diseases of the mouth. Herpangina is most frequently caused by Coxsackie virus group A serotypes and to a lesser extent by Coxsackie virus group B serotypes, echovirus serotypes and enterovirus-71 (170). No difference in clinical characteristics seems to exist among the different enteroviral infections. Studies in rhesus monkeys found that after oral inoculation, Coxsackie virus replicates in epithelial cells of the lower gastrointestinal tract, which is then followed by a viremia and a seeding of the virus to the oropharynx (219).

Hand, foot and mouth disease is typically a mild exanthematous illness with vesicular lesions, 2–10 mm in diameter, of the hands, feet and mouth, and occasionally other body sites. The disease has no relationship to hoof and mouth disease of cattle and other animals. Hand, foot and mouth disease affects mainly young children in winter and spring, but can also occur in older children and adults (44). Several enteroviruses can cause hand, foot and mouth disease, but the most important are human enterovirus-71 and Coxsackie virus A serotype 16 (144, 268). Enterovirus-71 illness is more severe with signifi-

cantly greater frequency of serious complications and fatality (43).

HIV-infected subjects, even those taking HAART medication, show high salivary presence of multiple herpesviruses (85, 151). HIV-infected patients also frequently suffer from a variety of painful oral ulcers (177). The incidence and severity of ulcerous lesions increase with increasing degree of immunosuppression. Flaitz et al. (72) found the most common oral sites of involvement to be the buccal/labial mucosa (27%), the tongue (25%) and the gingiva (18%), and the mean ulcer size to be 1.8 cm with a mean duration of 5.6 weeks. Oral ulcers in HIV-infected and in other immunocompromised patients are closely related to herpes simplex virus and human cytomegalovirus (75, 95, 129, 256). Other viruses associated with oral ulceration in HIV-infected individuals include Epstein-Barr virus (238) and human herpesvirus-8 (61). Cytomegalovirus and Epstein-Barr virus often occur as a co-infection in oral ulcers of HIV-positive patients (238). The ulcerogenicity of herpesviruses in HIV-infected individuals is probably caused by HIV-induced immune suppression and herpesviral re-activation rather than by a direct HIV-herpesvirus interaction. Herpesviruses and papillomaviruses of the mouth, in turn, can also enhance oral HIV replication (140).

Recurrent aphthous stomatitis ('canker sores') is the most common nontraumatic type of oral ulcer, with a prevalence of about 20% in most populations (217), but can exceed 50% in some groups of people (110). The disease is often mistaken for a recrudescient infection with herpes simplex virus (63, 257). Recurrent aphthous stomatitis, in contrast to recurrent herpes virus simplex oral infections, usually involves the nonkeratinized mucosa (labial mucosa, buccal mucosa, ventral tongue and the vestibule). Ulcers that are clinically similar to recurrent aphthous stomatitis can also occur with systemic diseases, such as HIV/AIDS, Behçet's syndrome, pemphigus vulgaris and inflammatory bowel disease (110). Aphthous ulcers can be classified according to clinical characteristics as minor (<1 cm in diameter), major (>1 cm in diameter) and herpetiform (multiple minute ulcers that may coalesce into plaques) (191, 257). Most aphthae are of the minor variety and heal within 10 days. Disease outbreak depends on host and environmental factors, with important triggers being trauma, stress, nutritional state, infection and hormonal fluctuation (141). Recurrent aphthous stomatitis has traditionally been characterized as an immunological disorder and is associated with increases in peripheral blood CD8<sup>+</sup> T lymphocytes,

natural killer cells and pro-inflammatory cytokines, and a low level of the anti-inflammatory interleukin-10 in lesional mucosa (110). The cellular and cytokine immune profile of patients with recurrent aphthous stomatitis resembles that of a herpesvirus infection (221, 267). However, studies on the association between recurrent aphthous stomatitis and varicella-zoster virus (174), cytomegalovirus (174, 234), other herpesviruses (130, 198), adenoviruses (196) or measles virus (58) have been mostly inconclusive (32, 110, 257). Association studies are facing the difficulty that oral ulcers presently diagnosed as recurrent aphthous stomatitis in fact comprise several distinct disease entities (63). The employment of increasingly precise molecular techniques to detect viral genomes or antigens directly in aphthous lesions may clarify the etiopathogenic importance, if any, of viruses in oral aphthosis.

Some autoimmune diseases may have an infectious component. Erythema multiforme ranges from mild, severe to potentially life-threatening, and can involve acutely painful oral and labial ulcers (4). Herpes simplex virus or other viral infections may precipitate erythema multiforme in the oral cavity (4, 15, 220, 249). Behçet's syndrome is a chronic, relapsing multisystem vasculitis, with oral ulcerations being an important disease feature (7, 66). Herpes simplex virus (232) and cytomegalovirus (234) are potential pathogens of Behçet's syndrome ulcerations. Pemphigus vulgaris is an intraepidermal bullous disease, which frequently involves large recalcitrant oral ulcers that precede the onset of skin lesions. Herpes simplex virus and human cytomegalovirus have been linked to oral pemphigus vulgaris (113, 208, 240). Systemic lupus erythematosus has been associated with the Epstein-Barr virus (135, 203), perhaps as a result of molecular mimicry between Epstein-Barr virus nuclear antigen 1 and lupus-specific antigens, induction of Toll-like receptor hypersensitivity by Epstein-Barr virus latent membrane protein 2A, or loss of apoptosis giving rise to immortal B cells and T cells (18). Further research is needed to determine the extent to which viruses are involved in the oral ulcerogenesis of these and other systemic diseases, including Crohn's disease, ulcerative colitis and neutropenia.

The goal of therapy of oral ulcers is to limit the severity and duration of pain and to accelerate healing. Management of oral ulcers is mainly supportive and consists of a short course of treatment. Scully et al. (212) recently reviewed common over-the-counter medications for oral ulcers. Medications

used in the management of oral ulcers include benzylamine-HCl analgesic topical rinse; lidocaine or benzocaine anesthetic ointments or sprays; anti-inflammatory topical corticosteroids; chlorhexidine, triclosan or sodium hypochlorite mouthwashes; nystatin or miconazole gel for candida infections; fusidic acid cream for *Staphylococcus aureus* angular cheilitis; and topical acyclovir or pencyclovir cream for herpesvirus infections. Treatment of herpes labialis may involve intermittent episodic therapy, intermittent suppressive therapy or chronic suppressive therapy based on defined clinical characteristics and patient preference (41). Initial primary herpes labialis may be treated with valacyclovir hydrochloride (1 g twice daily for 7 days) or famcyclovir (500 mg twice daily for 7 days) (41). Recurrent episodes of herpes labialis may be managed by early intervention (during the prodrome or erythema stages) using short-course, high-dose systemic antiviral therapy, such as famcyclovir (three 500-mg tablets as a single dose or 500 mg three times daily for 5 days) or valacyclovir (2000 mg twice daily for 1 day) (41, 80). Herpes labialis may also respond to topical medication, such as 10% docosanol cream, 1% pencyclovir cream, 5% acyclovir ointment or 15% idoxuridine solution (69). However, immunocompromised/HIV-infected patients generally show a poor response to topical antiviral therapy and often require systemic acyclovir, gancyclovir, valgancyclovir, foscarnet, cydofovir or fomivirsen to treat acute herpesvirus infections. Unfortunately, little research data exist on the efficacy of most over-the-counter products against oral ulcers, and large randomized double-blind studies are still needed to compare the efficacy and safety of different types of anti-ulcer medication.

## Oral tumors

Studies carried out during the past 25 years have etiologically linked viruses with human cancers. The current estimate is that about 20% of human cancers worldwide are virally related. Viruses are implicated in oncogenesis based upon the consistency of association with specific cancer types and upon the ability to produce cancer-like transformation in animal models or cell cultures. Detection of viral genomes within tumor cells strengthens a virus-tumor relationship. Viruses can be connected to a single or to a limited number of tumor types (e.g. hepatitis B virus) or to multiple tumor types (e.g. Epstein-Barr virus), a difference that probably reflects the extent of tissue tropism(s) of the viruses. Some viruses may

**Table 3.** Oral tumors related to viruses

Tumor	Virus	Comments	References
<i>Epithelial type EBV tumors</i>			
Lymphoepithelioma-like carcinoma	EBV	A nonkeratinizing undifferentiated carcinoma with lymphocytic infiltration. Affects mostly the parotid gland. Similar to nasopharyngeal carcinoma but occurs outside the nasopharynx. Is mainly found in southern China, southeast Asia and Greenland	Hamilton-Dutoit et al. (89), Leung et al. (128), Lu et al. (136), Tsai et al. (243)
Salivary gland lymphoepithelial carcinoma	EBV	A rare malignant tumor of salivary glands demonstrating malignant epithelial cells with a dense lymphoid stroma. Occurs almost exclusively in the parotid gland. May be identical to lymphoepithelioma-like carcinoma	Larbcharoensub et al. (126), Saqui-Salces et al. (203), Zhang et al. (269)
Warthin's tumor (cystadenolymphoma) of the parotid gland	EBV	Warthin's tumor is a benign lymphoepithelial neoplasm of the parotid glands. The epithelial component of the tumor can undergo malignant transformation. EBV may be related to multiple/bilateral but not to solitary Warthin's tumors	Santucci et al. (202), Wang et al. (248)
Oral squamous cell carcinoma	EBV/HHV-6	Squamous cell carcinoma lesions were positive for EBV (40%) and HHV-6 (80%)	Bagan et al. (17), Flaitz & Hicks (71), Yadav et al. (260)
Tonsillar carcinoma	EBV	50% showed EBV DNA	Kruk-Zagajewska et al. (122)
Oral undifferentiated carcinomas	EBV	Too poorly differentiated to be classified as any of the specific groups of carcinoma	Wakisaka et al. (246)
Oral hairy leukoplakia	HIV/EBV	HIV-associated. Abundant EBV replication. Activation of signaling pathways and up-regulation of the EBV receptor, proliferative and anti-apoptotic genes induce epithelial acanthosis and hyperproliferation	Brandwein et al. (31), Hille et al. (99)
<i>Lymphoid-type EBV tumors</i>			
Hodgkin's lymphoma	EBV	Eight reports of primary Hodgkin's lymphoma arising in the oral mucosa in the absence of nodal disease. EBV antigens have been detected in 67% of Hodgkin's lymphoma involving the Waldeyer ring	Quiñones-Avila et al. (179), Whitt et al. (253)
T-cell/natural killer cell lymphoma	EBV	Lesions in the oral cavity often present as ulceration of the palate and/or maxillary gingiva. The histological feature is a diffuse infiltration of lymphoid tumor cells. Occurs mostly in east Asian countries	Ott et al. (166), Yin et al. (265)
Burkitt's lymphoma	EBV	70% of oral Burkitt's lymphomas showed EBV DNA. A 2-year survival rate of 62%	Ardekian et al. (10), Syrjänen et al. (237)
Cyclosporine-related post-transplant lymphoproliferative disorder	EBV	Five transplantation patients with a history of cyclosporine use presented hyperplastic gingiva, which showed evidence of EBV infection	Broudy & Sabath (33), Oda et al. (163), Rolland et al. (192)
Oral post-transplant lymphoproliferative disorder/B-cell lymphoma	EBV	A rare oral pathosis, manifesting on the tongue, palate or gingiva as mucosal masses after solid-organ transplantation and is characterized histologically by abnormal lymphoid cell proliferation. Lesional cells show EBV-encoded small nuclear RNA (EBER)	Bruce et al. (34), Ojha et al. (165)

Table 3. Continued

Tumor	Virus	Comments	References
Follicular lymphoid hyperplasia	EBV	A 49-year-old Japanese woman presenting with a hard mass in the right cheek	Kojima et al. (119)
Plasmablastic lymphoma	HIV/EBV	HIV-associated non-Hodgkin's lymphoma that primarily affects the oral cavity and jaws and exhibits a poor prognosis. 10% of oral plasmablastic lymphoma occurs in gingiva. 87% of lesions showed HIV and 75% of lesions showed EBV	Scheper et al. (206)
<i>Tumors associated with herpesviruses other than EBV</i>			
Cyclosporine-steroid associated lymphoproliferative disorder	HCMV	Tonsillar involvement	Starzl et al. (229)
Benign infantile hemangioendothelioma	HCMV	Parotic gland involvement	Horie & Kato (102)
Kaposi's sarcoma	HIV/HHV-8/HCMV	Kaposi's sarcoma appears etiologically related to HHV-8 and occurs typically in HIV-infected patients. HCMV may act as a pathogenic cofactor in some Kaposi's sarcoma lesions. HHV-8 can be transmitted between individuals as a result of deep kissing	Meer & Altini (145), Newland & Adler-Storthz (159), Pauk et al. (173), Siegel et al. (218)
<i>Human papillomavirus</i>			
Focal epithelial hyperplasia	HPV	Focal epithelial hyperplasia occurs predominantly on the lower lip, buccal mucosa and tongue, and the disease shows a high prevalence of HPV type 13	Borborema-Santos et al. (26), Cuberos et al. (56)
Oral squamous cell carcinoma / verrucous carcinoma	HPV	Oral infection with HPV high-risk genotypes is a significant independent risk factor for oral squamous cell carcinoma. HPVs were detected in 24% and HPV type 16 in 16% of oral squamous-cell carcinomas	Acay et al. (3), da Silva et al. (59), D'Souza et al. (62), Kreimer et al. (121), Miller & Johnstone (152)

EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HHV-6, human herpesvirus-6; HHV-8, human herpesvirus-8 (Kaposi's sarcoma virus); HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus.

contribute to tumorigenesis only in a subset of a given type of cancer, or may merely accelerate tumor formation of an already established cancer. Also, the genomes of some viruses, such as Epstein-Barr virus and cytomegalovirus, show regions with substantial

polymorphisms, and only certain genotypes may be oncogenic (178).

Viruses differ from other cancer-causing agents, such as chemicals and radiation, by their ability to induce oncogenic changes through interaction

between the infecting virus and the related host response. Viruses may cause cell transformation and proliferation by directly expressing oncogenic genes in infected cells, or by acting as a necessary or a noncompulsory cofactor in the development of malignancy. However, even though most individuals harbor oncogenic viruses in the oral cavity, cancer occurring as a result of infection with such viruses is relatively rare. Risk factors apart from the viral infection are obviously important for cancer development, including family history, age, tobacco smoking and alcohol consumption.

Oral cancer is associated with geographic, behavioral and socioeconomic factors. Cancers of the mouth occur with the highest relative prevalence in India, Pakistan and Taiwan (139), perhaps as a result of extensive tobacco use and chewing of betel quid (263). South Asian men and women living in England demonstrate higher relative risks of oral cancers than individuals of non-South Asian ancestry (155). In 2007, oral cancers in the USA were estimated to comprise at least 22,000 new cases (8). The incidence rate of oral cancer, which in the USA is about twice as high in men as in women, has declined in both sexes over the past three decades. Oral cancer in the USA has a 5-year and a 10-year relative survival rate of 60 and 48%, respectively (8), and is the sixth leading cause of cancer mortality (111).

The most important oncoviruses of the human mouth are Epstein–Barr virus, herpesvirus-8 and papillomaviruses (198), and the most common virally related malignancies in the oral cavity are epithelial neoplasms, lymphomas and Kaposi's sarcoma (Table 3). Oral tumors are frequently located in the floor of the mouth, the tongue, the salivary glands and the lips. It is unclear whether oral tumors arise from activation of endogenous viruses or from an exogenous virus infection.

Periodontitis has been associated with an increased risk of tongue cancer (242), pancreatic cancer (149), and lung, kidney, pancreatic and hematological cancers (150). The periodontitis–cancer association may be caused by a shared viral infection or another type of joint etiology of the diseases, or by a commonality in host response functions. Whether the observed association between periodontitis and cancer constitutes a causal connection or merely a spurious relationship remains to be determined (105).

Epstein–Barr virus is involved in a great variety of cancers. The virus possesses factors capable of immortalizing B lymphocytes and epithelial cells, contains several potentially oncogenic antigens

(EBNA1, EBNA2, EBNA3A, EBNA3C and LMP1) and can induce several oncogenic gene products (bcl-2, bcl-10, c-fgr and jun/fos) (84). In addition, the nuclear antigen EBNA-LP of the Epstein–Barr virus can interfere with the function of the tumor-suppressor proteins p53 and pRb, thereby dysregulating the cell cycle (84).

Epstein–Barr virus is associated with numerous lymphoid proliferations, including African Burkitt's lymphoma, classical Hodgkin's disease, angiocentric natural killer cell/T-cell lymphoma, chronic lymphocytic lymphoma with Reed–Sternberg-like neoplastic cells, angioimmunoblastic lymphadenopathy-like T-cell lymphoma, AIDS-associated lymphoma, transplant-associated lymphoproliferative disease, X-linked lymphoproliferative disorder and virus-associated hemophagocytic syndrome (247). The Epstein–Barr virus is present in two-thirds of AIDS-related lymphomas (88). In the oral cavity, Epstein–Barr virus has been identified in Hodgkin's lymphoma, natural killer cell/T-cell lymphoma, Burkitt's lymphoma, cyclosporine-related post-transplant lymphoproliferative disorder, post-transplant diffuse B-cell lymphoma, follicular lymphoid hyperplasia and plasmablastic lymphoma (Table 3). The association between Epstein–Barr virus and different lymphomas varies from strong to weak, indicating that some of the lymphoma types have etiologies not exclusively related to the Epstein–Barr virus.

Oral epithelial tumors that have an association with Epstein–Barr virus include lymphoepithelioma-like carcinoma, salivary gland lymphoepithelial carcinoma, multiple/bilateral Warthin's tumor (cystadenolymphoma) of the parotid gland, tonsillar carcinoma, highly undifferentiated carcinomas and oral hairy leukoplakia (Table 3). Epstein–Barr virus thus has been related to tumors of the salivary glands, and cytomegalovirus also has the ability to induce salivary gland neoplasm in immunosuppressed mice (57). However, studies in Finland (13, 115) and the USA (125) failed to identify a relationship between Epstein–Barr virus or human cytomegalovirus and salivary gland tumors. Demographic, geographic and environmental factors may be important, as most studies showing a herpesviral association with oral tumors originate from Asian countries. Epstein–Barr virus-related nasopharyngeal carcinoma is known to occur with a high relative prevalence in natives of southern China and southeast Asia (42, 65), which may be a result of ethnically determined host–virus interactions or distinct Epstein–Barr genotypes predominating in some Asian populations (201). Differences in tumor

diagnostic criteria, tissue-sampling techniques and viral-detection methods may also be important sources of discrepancy in research findings.

Human cytomegalovirus genome and antigens have been identified in malignant tumors, including colon cancer, malignant glioblastoma, Epstein–Barr virus-negative Hodgkin's lymphoma, prostatic carcinoma and breast cancer; and, interestingly, noncancerous cells in close proximity to these tumors are cytomegalovirus negative (227). Söderberg-Nauclér (227) suggested that the immune system would recognize a cancer cell arising in the body as 'altered self' and, in an attempt to eliminate it, would create a local inflammation. Cytomegalovirus would subsequently enter the inflamed area in infected monocytes/macrophages and become re-activated and transmitted to and persist as a 'microinfection' in the tumor cells. Through specialized proteins, the cytomegalovirus could then interfere with cellular differentiation, proliferation, migration, angiogenesis, epigenetic functions, DNA repair mechanisms, and the production and action of cytokines, chemokines and growth factors. Very little information is available on the possible role of cytomegalovirus in oral tumors.

Immunocompromised hosts show increased susceptibility to malignant diseases. Oral tumors in HIV-infected individuals are virtually all virus related. Lymphoid neoplasms in the oral cavity of HIV-infected individuals are typically aggressive B-cell neoplasms (Table 3). Epstein–Barr virus-associated non-Hodgkin's lymphomas in the oral cavity of patients with AIDS can involve gingiva, alveolar and palatal mucosa as well as other oral tissues (64). Some Epstein–Barr virus-associated lymphomas can also occur in immunocompetent patients, but at a lower incidence, whereas other Epstein–Barr virus-associated lymphomas are virtually restricted to HIV-infected individuals (86). Plasmablastic lymphoma is a diffuse B-cell lymphoma that is strongly associated with immunodeficiency, and most notably with HIV infection, and which exhibits a high prevalence of the Epstein–Barr virus (188). The prognosis of oral plasmablastic lymphoma is poor, with a high mortality rate within 6 months.

Kaposi's sarcoma is a lymphoid vascular tumor that is typically found in HIV-infected individuals, but which can also occur with other forms of immunosuppression. Human herpesvirus-8 is recognized as the principal pathogen of Kaposi's sarcoma. Although herpesvirus-8 appears to be necessary for development of Kaposi's sarcoma, the virus is not sufficient without additional cofactors. An HIV infection con-

stitutes the most important cofactor in the pathogenesis of Kaposi's sarcoma. Herpesvirus-8 and cytomegalovirus may sometimes co-operate in the development of oral Kaposi's sarcoma (Table 3). Herpesvirus-8 can reach salivary loads of several million genome copies/ml in patients with Kaposi's sarcoma (6) and in renal allograft recipients (5). Kaposi's sarcoma can appear in HIV-infected patients as an asymptomatic radiolucency at the apical area of teeth with vital pulps (161) and be associated with severe marginal periodontitis (127).

Oral hairy leukoplakia is associated with immunosuppression and mainly HIV infection (225). The oral hairy leukoplakia lesion appears on the lateral borders of the tongue as a whitish hyperkeratotic hair-like growth that cannot be rubbed off. Biopsies of hairy leukoplakia lesions show epithelial hyperplasia and mild inflammation, and Epstein–Barr virus can be detected in the superficial layers of the epithelium. Epstein–Barr virus-infected periodontal pockets in intimate contact with the lateral borders of the tongue are the most likely source of the viral infection (200). Malignant transformation of hairy leukoplakia has not been reported. Most oral hairy leukoplakia lesions respond well to high-dose valacyclovir (187), and topical treatment with gentian violet shows promising results (23).

Human papillomaviruses infect most individuals and are serious pathogens in persons infected with HIV or who are receiving immunosuppressive treatment. Papillomaviruses are almost always the cause of cancer of the uterine cervix. Studies describe the presence of papillomavirus in 31–74% of all oral cancers (215). Tonsillar cancer shows a particularly close relationship with papillomaviruses (90, 100). Warts (papillomas) on the hands or the genitalia, and verrucas on the feet, rarely pose a health risk but can cause psychological and social problems for affected individuals.

Oral squamous cell carcinoma accounts for 2–3% of all malignancies and 300,000 new cases occur worldwide every year (111). Papillomaviruses have been related to oral squamous cell carcinoma and focal epithelial hyperplasia (Table 3). Some squamous cell carcinoma lesions contain both papillomavirus and Epstein–Barr virus (97, 98, 239). The oncogenic papillomavirus type 16 is present in about two-thirds of papillomavirus-positive oral tumors (215), but rarely infects normal oral mucosa (30). Papillomavirus-16 DNA was detected in 72% of paraffin-embedded tumor specimens, and the papillomavirus-16 oncoprotein E6 or E7, or both, were serologically detected in 64% of patients with oral

**Table 4.** Various oral pathoses with a putative viral etiology

Pathosis	Virus	Comments	References
Infectious mononucleosis	EBV, occasionally HCMV	An annual incidence of 0.7% in patients 10–30 years of age, and up to 5% in college student populations. Patients present with sore throat, significant fatigue, palatal petechiae and adenopathy	Candy et al. (36), Kutok & Wang (124)
Xerostomia (Sjögren's syndrome)	HCV, HTLV-1, HIV, herpesviruses	Xerostomia exposes patients to rampant dental caries, dysphagia, candidiasis and parotitis	Carrozzo (37), Eveson (68), Fox & Howell (73), Ohyama et al. (164), Ramos-Casals et al. (182), Schiødt (207), Sharma et al. (216), Sugai (233)
Sialadenitis	HCV, HIV/HCMV	33% of HCV-infected individuals reveal sialadenitis. Cytology examination showed characteristic HCMV intranuclear inclusions	Carrozzo (37), Wax et al. (250)
Osteomyelitis	HIV/HCMV, HZV/HCMV	An AIDS patient with a periodontal abscess and osteomyelitis showed numerous cells with inclusion bodies characteristic of a HCMV infection. Co-infection with HZV and HCMV can produce osteomyelitis and necrotizing gingivitis	Berman & Jensen (22). Meer et al. (145)
Herpes zoster (Hunt syndrome)	HZV	Oral herpes zoster can lead to osteonecrosis of the jaw and spontaneous tooth exfoliation of middle-age and elderly persons	Arikawa et al. (12), Cooper (52), Owotade et al. (167), Mendieta et al. (148)
Dry socket following tooth extraction	HSV-1	Patients with dry socket after molar extraction reported a higher incidence of cold sores than controls, and molar extraction caused re-activation of HSV-1. Similar findings were obtained in a rat model	Hedner et al. (93, 94)
Oral leukoplakia	HPV, HHV-6	Studies have shown HPV in 30, 22 and 18% of leukoplakia lesions and in 0–6% of control sites. HPV types 18 and 16 predominated. EBV has been detected in 60% of proliferative verrucous leukoplakia lesions	Acay et al. (3), Bagan et al. (17), Campisi et al. (35), Miller & Johnstone (152), Sand et al. (199), Yadav et al. (260)
Oral lichen planus	HPV, HCV, HHV-6	Studies have shown HPV in 75, 27, 20 and 0% of lichen planus lesions and in 0–6% of control sites. HPV types 18 and 16 predominated. Lichen planus may be significantly associated with HCV infection in southern Europe and Japan but not in northern Europe. Oral lichen planus may become malignant	Campisi et al. (35), Carrozzo (38), Cox et al. (55), Lodi et al. (132), Sand et al. (199), Yadav et al. (260), Young & Min (266)

EBV, Epstein-Barr virus; HCMV, human cytomegalovirus; HCV, hepatitis C virus; HHV-6, human herpesvirus-6; HIV, human immunodeficiency virus; HPV, human papillomavirus; HSV, herpes simplex virus; HTLV-1, human T-lymphotropic virus type I; HZV, herpes zoster virus.

cancer (62). D'Souza et al. (62) showed that oropharyngeal cancer is significantly associated with oral infection by any of 37 types of papillomaviruses (odds ratio, 12.3), with oral papillomavirus type 16 infection (odds ratio, 14.6) and with seropositivity for the human papillomavirus-16 L1 capsid protein (odds ratio, 32.2). Papillomavirus type 16 carcinoma in the oropharynx has been linked to alcohol consumption

and tobacco use (215), but can also occur in papillomavirus-16 L1 seropositive subjects with no history of heavy tobacco and alcohol usage (62). Papillomavirus-16-positive head and neck squamous cell carcinoma was recently found to be independently associated with several measures of sexual behavior and exposure to marijuana but, in contrast to squamous cell carcinomas free of papillomavirus-16, was

not linked to cumulative measures of tobacco smoking, alcohol drinking or poor oral hygiene (81). Rintala et al. (190) showed the importance of the oral route for papillomavirus transmission between partners; a spouse had a 10-fold higher risk of acquiring persistent oral papillomavirus infection if the other spouse had a persistent oral papillomavirus infection. Papillomavirus-positive oral tumors also show a strong association with multiple oral sex partners (62). Fortunately, current papillomavirus vaccines, designed to prevent cervical cancer, will probably also decrease the incidence of papillomavirus-related oral cancers.

## Various oral pathoses

Infectious mononucleosis is a self-limiting lymphoproliferative disease characterized by sore throat, fever, adenopathy and splenomegaly. The causative agent is a primary Epstein–Barr virus infection and occasionally a primary cytomegalovirus infection (Table 4). Infectious mononucleosis occurs most commonly in adolescents and young adults, and is a very mild illness in small children. Patients with initial symptoms of infectious mononucleosis show high titers of cell-free infectious viruses in saliva. The Epstein–Barr virus is usually acquired by intimate contact, giving rise to the term ‘kissing disease’. Infectious mononucleosis patients generally receive only symptomatic and/or supportive treatments; however, aspirin is not used because of the risk of Reye’s syndrome.

Xerostomia (Sjögren syndrome) is an autoimmune disorder associated with infiltration of activated autoantibody-producing B cells in affected glands. Sjögren syndrome has been related to hepatitis C virus, human T-lymphotropic virus type I, HIV and herpesviruses (Table 4). Chronic infections with lymphtropic viruses (hepatitis C virus, Epstein–Barr virus and human herpesvirus-6 and -8) may induce anti-apoptotic signals, which prolong the survival of the offending B cells (70).

Acute infection of the salivary glands (‘symptomatic sialadenitis’) has an incidence of about 27–59 per million population per annum in the UK (67). Sialadenitis may occur in about 33% of individuals with clinical hepatitis C virus infection and exhibits clinical characteristics different from those of the Sjögren syndrome (37). Hepatitis C virus genomes were detected in the saliva of 83% of patients with hepatitis C virus-associated sialadenitis (109). In HIV-infected individuals, cytomegalovirus may cause sialadenitis and xerostomia (250). A murine model

demonstrated the potential of cytomegalovirus to be dysmorphic to embryonic salivary glands (147).

Herpesviruses can cause diseases of oral bone (Table 4). In a patient with AIDS, cytomegalovirus was related to a periodontal abscess with osteomyelitis (22). Oral Kaposi’s sarcoma lesions can cause severe alveolar bone loss (127). Co-infection with herpes zoster virus and cytomegalovirus can result in osteomyelitis of the jaw, extensive necrotizing gingivitis and spontaneous tooth exfoliation (146). Oral herpes zoster may also lead to osteonecrosis of the jaw and spontaneous tooth exfoliation in middle-aged and elderly persons (52, 87, 148, 156, 258). Herpes simplex virus re-activation has been associated with dry socket formation following tooth extraction (94). The Epstein–Barr virus-related African Burkitt’s lymphoma can affect the jaws of young children (244).

Oral leukoplakia has been linked to papillomaviruses, mainly the types 16 and 18 (Table 4). Acay et al. (3) found a predominance of papillomavirus types 16/18 in oral leukoplakias with varying degrees of epithelial dysplasia, and the less virulent papillomaviruses 6/11 in leukoplakias with mild or no dysplasia. Miller & Johnstone (152), in a meta-analysis, showed that papillomaviruses occurred in 22% (95% confidence interval, 16–30%) of oral leukoplakia lesions. Proliferative verrucous leukoplakia affecting gingiva and other oral sites has a high risk of malignant transformation to squamous cell carcinoma and may be related to the Epstein–Barr virus (17).

Oral lichen planus typically appears as white hyperkeratotic striae on buccal mucosa and shows, histologically, a submucosal infiltrate of lymphocytes. Oral lichen planus can be part of a vulvovaginal–gingival syndrome (181). Biopsy may be necessary to distinguish oral lichen planus, pemphigoid and pemphigus vulgaris. Cases of oral lichen planus have been related to papillomaviruses and hepatitis C virus (Table 4). A recent review suggested that the oral type of lichen planus was significantly associated with hepatitis C virus infection in southern Europe and Japan but not in northern Europe, perhaps owing to genetic factors (39). Human herpesvirus-6 may play a role in some types of oral lichen planus (260). Oral lichen planus may rapidly progress to squamous cell carcinoma in transplant patients (92), and malignant transformation may occur especially in patients with hepatitis C virus infection (1). However, the cancer transformation rate of oral lichen planus remains uncertain (133) and may not be as high as previously thought (181).

## Periodontitis

The notion that a bacteria-induced uncontrolled gingival hyperinflammation causes periodontitis has been questioned. Current research suggests that the host response to periodontopathic agents includes both synergistic and antagonistic interactive processes that can involve heightened inflammatory reactions as well as immune suppression (78). Also, human viruses seem to participate in the development of destructive periodontal disease. Indeed, as discussed elsewhere (205, 221), a viral–bacterial interpretation of the cause of periodontitis seems biologically plausible, whereas a hypothesis based purely on a bacterial cause of the disease is confounded by several inexplicable clinical realities.

Several lines of evidence incriminate herpesviruses in the etiopathogeny of marginal and apical periodontitis (221). Advanced periodontitis lesions harbor high counts of herpesviral genomes, often exceeding 1 million in a single subgingival site (205). Herpesvirus-infected periodontitis sites show more extensive tissue breakdown than herpesvirus-free sites, and a herpesviral active infection or multiple transactivating herpesviruses in the periodontium are associated with an elevated risk of progressive disease (221). The great majority of chronic periodontitis sites, which have a low probability of disease progression, show a latent rather than an active cytomegalovirus infection (29). The expression level of the Toll-like receptors 7 and 9, which recognize viral DNA, is significantly elevated in periodontitis lesions compared with gingivitis lesions (21, 112). Immunoglobulin G serum antibody against cytomegalovirus can be detected more frequently in patients with periodontitis than in patients with gingivitis (112). A refractory periodontitis patient with high Epstein–Barr virus load was treated with the anti-herpesvirus drug Valtrex® (valacyclovir HCl, 500 mg twice daily for 10 days), which suppressed the viral infection to undetectable levels and resulted in a ‘dramatic’ reversal of the disease (235). In endodontic lesions, Epstein–Barr virus and cytomegalovirus have been identified transcriptionally (262) and serologically in enlarged periapical cells (195), suggestive of an active viral infection (238). Herpesvirus-infected periodontal cells are particularly prominent in HIV-infected patients (50, 195). The cytomegalovirus genome can also be detected in periapical cysts, especially in those with a previous episode of acute infection (9).

The periodontopathic potential of herpesviruses was recently reviewed and is only briefly summarized

here (221, 222). Herpesvirus-associated cytopathogenic effects, immune evasion, immunopathogenicity, latency, re-activation from latency and tissue tropism are thought to constitute important pathogenetic aspects of periodontitis. Herpesvirus active infections cause a release of pro-inflammatory cytokines, which are capable of activating antiviral T lymphocytes as well as bone-resorbing osteoclasts (27, 221). Cytomegalovirus and other herpesviruses can up-regulate the expression of tissue-destructive matrix metalloproteinases from gingival fibroblasts and presumably also from other cell types of the inflamed periodontium (28).

An important pathogenetic synergy probably exists between periodontal herpesviruses and periodontopathic bacteria (205, 223). Herpesviruses may create a milieu for the up-growth of periodontopathic bacteria by inducing immunosuppression (221), or by generating new attachment sites for bacteria in infected cells (241) or in the basement membrane following destruction of the periodontal pocket epithelium (222). Conversely, periodontopathic bacteria may support the multiplication of periodontal herpesviruses. In experimental mice, *Porphyromonas gingivalis* augmented the virulence of a co-infecting cytomegalovirus, presumably by decreasing tissue levels of interferon- $\gamma$  (231). Interferon- $\gamma$ , acting alone or in concert with other interferons, can suppress herpesvirus reactivation from latency, inhibit herpesvirus replication and accelerate cell apoptosis (176).

The ability of herpesviruses to subvert antibacterial immune mechanisms may constitute a critical aspect of periodontal pathosis (205). Herpesviruses can interfere with complement (134), neutrophil (2) and macrophage (76) functions. Herpesvirus infections induce cytotoxic T-cell proliferation and pro-inflammatory cytokine release, which may adversely affect the production of antibacterial antibodies (134). Patients with a low level of specific antibodies against major periodontopathic bacteria seem to pose an increased risk of periodontal breakdown (183). *P. gingivalis* and other exogenous-like pathogenic species may exploit the decline in antibacterial immunity and outgrow co-existing indigenous bacteria.

Conceivably, the progressive phase of periodontitis consists of immunosuppressive events that trigger an activation of periodontal herpesviruses and a release of pro-inflammatory cytokines and matrix metalloproteinases. Perhaps not coincidentally, virtually all established risk indicators of periodontitis are potential activators of a latent herpesvirus infection (184, 224). Subsequent disease mechanisms would then

include a suppression of local antibacterial host defenses and an overgrowth of specific periodontopathic bacteria, resulting in periodontal tissue breakdown.

Papillomaviruses (103, 138, 171), HIV (46, 143), human T-lymphotropic virus type I (40, 228), hepatitis B (20) and C (142) viruses and torquetenovirus (194) can also inhabit periodontitis lesions. Indeed, the inflamed periodontium may constitute the major oral reservoir for Epstein–Barr virus (204), cytomegalovirus (204), papillomaviruses (103) and hepatitis C virus (142). Little information is available on the periodontopathic importance of mammalian viruses not belonging to the herpesvirus family.

## Summary

Human viruses are involved in the development of various types of oral ulcers, oral tumors, classical oral infectious diseases and periodontitis. Herpes simplex virus-1 and cytomegalovirus are linked to oral ulcers; Epstein–Barr virus, herpesvirus-8 and papillomaviruses to oral tumors; and Epstein–Barr virus and cytomegalovirus to aggressive periodontitis. Deep kissing can spread Epstein–Barr virus, herpesvirus-8 and papillomaviruses, and should perhaps be considered a risky sex practice. Also, parents may avoid kissing infants and small children on their mouth. The host mounts formidable innate and adaptive immune defenses against infecting viruses. In turn, herpesviruses and papillomaviruses modify antiviral host responses in order to persist for the lifetime of the infected host. Important virus-encoded countermeasures include avoidance or inhibition of innate and adaptive immune responses and of apoptosis. Major clinical signs and symptoms of viral diseases are frequently the result of the virally induced host responses. Hence, the controversy of whether infectious agents or abnormal host responses, or whether hyperimmune vs. hypo-immune responsiveness, is the main cause of periodontitis may constitute an oversimplification and partly a biological misconception. However, substantial gaps exist in our knowledge about the viral component of oral diseases. This shortcoming is regrettably caused by limited research in oral virology and by a lack of suitable animal models. Also, as Epstein–Barr virus, cytomegalovirus and papillomaviruses infect the great majority of individuals and persist in latent forms in various cells throughout life, it is difficult to define the prevalence of diseases caused by these viruses. Studies are needed to elucidate determinants of oral

colonization of viruses, virally related opportunistic infections of the mouth, and antiviral immunity of saliva and oral mucosa. Fortunately, there are grounds for optimism. Rapid advances in medical virology may also help to uncover the pathogenesis and treatments of viral diseases of the mouth. Research is encouraged on the topics of antiviral chemotherapeutic therapy and augmentation of host defenses by means of vaccination. Prevention and therapy based upon antiviral approaches may avert the debut of periodontitis or result in long-lasting arrest and ultimate cure of existing periodontitis, as well as of other virally related diseases of the human mouth.

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