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**Impact of different types of herpesviral infections in the oral cavity**

Thomasini RL *et al*. Herpesvirus in oral cavity

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**Abstract**

The herpesviruses are ubiquitous, doubled-stranded DNA viruses that can reactivate under conditions such as immunosuppressive therapy, acquired immunodeficiency syndrome, malnutrition, and immunosenescence. There are eight types of herpesviruses: Human herpesvirus simplex (HSV) type I (HSV-1) and HSV type II (HSV-2), varicella-zoster virus (VZV), epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus (HHV)-6, HHV-7, and HHV-8 or Kaposi’s sarcoma herpesvirus. Some of these viruses can infect the oral cavity, leading to different types of lesions. Specifically, labial herpes (HSV-1 and less frequently HSV-2), zoster (VZV), infectious mononucleosis and oral hairy leukoplakia (EBV), and Kaposi´s Sarcoma (HHV-8) are the most common viruses infecting the oral cavity. Some of these viruses can act in synergy with other herpesviruses or as distinct infectious agents. Other herpesviruses may have indirect effects in periodontal disease. The diagnosis is frequently based on signs and symptoms and depends on the experience of the examiner. Cytopathologic and/or histopathologic examination as well as immunological methods such as ELISA could help to elucidate cases. In addition, molecular techniques which can be sensitive and specific have been reported in the literature. These methods require low amounts of sample and could offer results faster than other traditional methods.

**Key words:** Herpesvirus; Oral cavity; Symptoms; Infection; Virus

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**Core tip:** The oral lesions caused by herpesviruses can be painful and not always easily diagnosed and treated. This review article intends to briefly describe the viral features, physiopathology, epidemiology, signs, symptoms, laboratory diagnosis and its limitation, and typical therapy and prevention (if it exists) of these oral lesions. The main aim of this present article is to help the clinical practice considering diagnosis of the oral herpesviral infections. In addition, there is a lack of an updated article concerning basic and clinical information about herpesvirus infections.

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**INTRODUCTION**

Human herpesviruses belong to the *Herpesviridae* family, and they are ubiquitous. After the primary infection, the individual remains latently infected during the individual’s lifetime. These viruses cause a wide variety of diseases, often benign, however, in immunocompromised individuals, they can cause clinical symptoms of varying severity[1].

The *Herpesviridae* family is divided into three sub-families: *Alphaherpesvirinae* (*α-herpesvirinae*), *Betaherpesvirinae* (*β-herpesvirinae*), and *Gammaherpesvirinae* (*γ-herpesvirinae*). All of these viruses are double-stranded DNA viruses and share similar structural features. There are eight different types of herpesviruses which infect humans, and some of them can also infect animals. Table 1 displays a list of viruses belonging to the herpes group that infect humans[1,2].

The viruses of the herpes group establish primary infections with few symptoms, which may result in efficient immune response to prevent a reinfection. However, the virus is not eliminated completely, and its genome is maintained in certain cells without a productive infection. Latent infections can become active (reactivation) due to host factors, and these events allow the spread of the virus[2,3].

Human herpesvirus simplex (HSV) type I (HSV-1) and HSV type II (HSV-2) are usually associated with labial and genital herpes, respectively. However, genital herpes may be a consequence of infection by HSV-1, and labial herpes can also be caused by HSV-2[4]. Varicella-zoster virus (VZV) causes varicella (chickenpox) in primary infection that occur especially in children, and the reactivation can cause the onset of zoster herpes, which occurs more frequent in the elderly[5,6]. Epstein-Barr virus (EBV) is associated with infectious mononucleosis, Burkitt's lymphoma, and nasopharyngeal carcinoma[7,8]. Human herpesvirus (HHV)-8 or Kaposi’s sarcoma herpesvirus (KSHV) is associated with Kaposi's Sarcoma and can lead to death in immunocompromised patients, particularly in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients[9]. A primary cytomegalovirus (CMV) infection causes a syndrome similar to mononucleosis known as ‘cytomegalic inclusion body disease’[1]. Primary infections of HHV-6 and HHV-7 cause a common infectious febrile syndrome in infancy known as exanthema subitum or roseola[10,11].

The labial lesion caused by HSV is the prototype of herpesviral infection, and it is the most well-known among the clinical manifestations to lay individuals. However, genital infections and other clinical manifestations caused by the other listed above herpesviruses are less well known.

**HSV**

***Labial herpes and stomatitis***

The most cases of labial herpes are caused by HSV-1,whereas HSV-2 usually infects the genital area. However, cases of HSV-1 in the genital area have been reported[12-14]. The primary HSV infection could occur in early childhood by direct contact with lesions of an infected individual or via domestic utensils contaminated with biological fluids derived from lesions or saliva[12,15].

The main symptoms of labial herpes are painful bullous lesions occasionally accompanied by fever[4]. Normally, the infections self-limited and disappears four or five days after onset of symptoms. However, in some individuals, the lesions could have more severe outcomes affecting extensive labial areas and internal parts of the mouth referred to as stomatitis or gingivostomatitis, occasionally presenting esophagitis[16-18]. Immunosuppressive states such as chemotherapy, immunosupresive therapy in autoimmune diseases, or transplantation[19], malnutrition, and AIDS manifestation increase the risk of disease[1,20].

After the contact with viable viral particles, the virus infects and replicates in epithelial cells and local nerves, causing lesion and pain[21]. Furthermore, cellular immune responses try to eliminate infected cells followed by neutralization of extracellular viral particles, leading to disappearance of viral replication and symptoms. Residual pain and signs of lesion cicatrix may linger, despite clearing of viral replication.

The contact with individuals who present lesions increases the rate of viral transmission, but HSV could theoretically be transmitted by contact with non-symptomatic persons. Occasionally, viral particles are shed in saliva of healthy individuals, therefore transmission of the virus by this pathway may be possible[15]. It is important to note that viral load is crucial for transmission and direct contact with symptomatic individuals (*e.g.*, kisses) or sharing of cups, dishes, and forks should be avoided.

After primary infection, the virus can remain latent during its lifetime and can be reactivated intermittently, or nevermore to cause symptoms. The virus can be latently harbored in peripheral neurons or ‘at a low’ level of replication well controlled by the immune system. Under immunosuppressive conditions, the virus can escape immune vigilance via evasion mechanisms, causing new lesions, frequently with the same topography of the past infection[4,15,21]. However, severe immunosuppression does not seem to be strictly necessary to herpesviral reactivation. For instance, labial lesions caused by recurrent HSV may occur in immunocompetent individuals after exposure to cold, sunlight, lip injury, and stress[4]. To note, 60%-90% of the adult population has an IgG positive serostatus for HSV, but not all experience HSV reactivation.

The diagnosis of labial herpes and stomatitis is based on signs and symptoms, but it is important to ensure differential diagnosis of other oral manifestations such as aphthosis and stomatitis caused by *Candida albicans*. The laboratory diagnosis is frequently not necessary, but it can be made by detection of IgM antibodies against the virus, smears of lesions stained by Giemsa[16], biopsy, or by molecular methods[17].

The use of IgM detection is limited specially by two different conditions. In the reactivation state, the infection may not produce IgM antibodies to detectable levels, leading to a false negative result. In addition, the level of IgM antibodies from a previous episode of infection can remain high (residual IgM), causing a false positive result. The determination of specific IgG avidity may help to elucidate and better guide diagnosis because high IgG avidity suggests recent HSV infection.

The histological sections of tissue obtained by biopsy or smears of secretions collected by deep scrape from lesions can be stained by Hematoxylin-Eosin (H&E), Giemsa, or Papanicolaou[16]. The cytopathic effects are relatively easy to be identified by an experienced pathologist. However, the cytopathic effects cannot be distinguished from the effects of other herpesviruses (*e.g.*, VZV). Immunohistochemistry/immunocytochemistry using specific anti-HSV mAbs can be employed to discern between other herpesviruses. Naturally, due to an invasive feature of biopsies procedures and pain caused by lesions, the actual importance of these procedures in each case must be carefully evaluated.

The molecular methods are the most conclusive tests, although they are more expensive. Polymerase chain reaction (PCR) is a sensitive and specific molecular method used to detect viral agents, and the results can be obtained in a few hours. There are different PCR methods which can vary in several technical and economical aspects. Typically, DNA is extracted from swabs of lesions, and viral DNA is amplified by the use of specific primers followed by qualitative or quantitative detection of specific products (amplicons). It is important to note that the primers must be able to amplify either HSV-1 and HSV-2[17].

The therapy for labial herpes is regularly not necessary, but the use topic acyclovir[22] can accelerate recuperation. In association with an adequate analgesic drug, this is a good therapeutic strategy. Extensive labial lesions or stomatitis can be treated with oral or injectable acyclovir. Preventive anti-HSV treatment with oral acyclovir has been used for solid organs and bone marrow transplantations[23].

**VZV**

***Varicella and zoster***

VZV primary infection occurs mainly in childhood, and it is called varicella or ‘chickenpox,’ which affects the skin and mucosa. The illness appears as a bullous lesion in the overhaul of the body, and it often affects the internal mouth and lips[1,24]. Among the symptoms included are itch, pain in the lesion area, and fever. Chickenpox is typically benign and requires only symptomatic treatment, but in some cases, it can lead to severe disease such as hepatitis or encephalitis.

In the oral mucosa, secondary infection can occur and treatment with antibiotics or with antifungal drugs must be considered in these cases. VZV, like HSV, remains latent in the peripheral nerves, and it can reactivate in immunosuppressive states, being classified as ‘zoster’[25]. Indeed, the zoster is the reactivation of latent VZV virus acquired by a past varicella episode. Zoster differs from varicella due to the fact that it only generally infects locally along nerve. The most common affected areas are dorsal, lateral parts of the chest, the legs, and the face. Also, zoster can infect the lips[26]. When the virus infects the lips, the lesions are clinically indistinguishable from HSV lesions[26].

Zoster causes discomfort, reduces physical, emotional, and social functioning, induces lower vitality, and impairs physical and mental health. Zoster-causing lesions are frequently accompanied by neuralgia[27]. AIDS and therapy with immunosuppressive drugs are the main causes of zoster, however, malnutrition and aging are also strongly associated with zoster. Indeed, the frequency of zoster in the elderly is relatively higher compared to younger people[28]. The vaccine for varicella is available but has mainly been used in epidemic cases and outbreaks. It is rarely included in routine vaccinations. Recently, the use of vaccination in the elderly for prevention of zoster has been proposed[27,29,30]. However, the efficacy has not been completely established, and it seems to prevent neuralgia but not zoster *per se*[29]. Obviously, the prevention of neuralgia helps to minimize the severity of disease and enhances the welfare of the elderly. Unfortunately, the vaccination is not yet economically affordable to a great part of the population.

The laboratory diagnosis of VZV is relatively easy by use of immunological methods for detection of IgM against VZV. However, the immunological diagnosis of zoster is not easily achievable due to the same conditions described above for HSV infections. The biopsy or smears of secretions (Tzanck smear) help to elucidate and discern VZV infections[31], but the cytopathic effects are indistinguishable of HSV lesions unless mABs against VZV are used in immunohistochemistry/immunocytochesmisty procedures. Furthermore, PCR using specific primers for VZV can make the diagnoses definitive[32].

**EBV**

The most known and common syndrome of EBV infection is mononucleosis. Many teenagers and young adults develop symptoms of mononucleosis. Acute mononucleosis causes sore throat, fever, and swollen lymph nodes. Sore throat is very painful and is the usual reason for people to seek medical attention. The tonsils may become very swollen. In addition, loss of appetite, fatigue, chills, headache, bloating, sore muscles, body aches, weakness, and sweats are commonly described and experienced. Most of the symptoms disappear completely in days to a few weeks, however, signs of fatigue could remain for a few additional weeks[7,33].

Some patients can have neurological complications such as encephalitis, meningitis, or inflammation of an individual nerve[34]. The majority of patients with neurological complications recover completely. However, some patients can develop EBV-induced lymphoproliferative disorders which may be either related to immunocompetent or immunosuppressed patients[35,36].

EBV has been related to some forms of neoplasia, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and conditions associated with HIV such as oral hairy leukoplakia, and lymphoma of the central nervous system[37,38]. EBV is also associated with oral hairy leukoplakia which consist of a white plaque on the lateral part of the tongue that cannot be removed by gentle scraping[39]. It is most common in people with HIV/AIDS as aforementioned or other immunosuppressive states, such as organ transplantation.

Other types of tumor are associated with EBV, however, the mechanism which EBV contributes the transformation of normal lymphocytes in tumor cells is not completely known.

**HHV-8/****KSHV**

HHV-8 is the least prevalent among all human herpesviruses. Asymptomatic infection can occur, but the most known manifestation of this infection is Kaposi’s Sarcoma (KS)[40].

KS is a neoplasia of the endothelial cells, and it presents as four epidemiological types: classic, endemic, post-transplantation, and associated with AIDS. The tumors mainly affect the skin, but it can cause lesions in internal organs and the mouth. Especially in AIDS patients, the oral manifestations can appear as a pustular lesion. Screening for HIV is a standard procedure when KSHV-induced oral lesions are found in the patient. The oral lesions can affect the tongue, lips, gums, tonsils, and the inner cheek. Biopsies with immunohistochemistry using mAbs against HHV-8 or PCR are the conclusive diagnostic methods[41,42].

KS tumors are treated with chemotherapy, radiotherapy, or immunotherapy, and the use of anti-HIV prophylactic drugs decreases the risk of developing KS.

**ASSOCIATION BETWEEN HERPESVIRUSES WITH GINGIVITIS AND PERIODONTITIS**

While gingivostomatitisis caused by HSV, the role of other herpesviruses in periodontal tissue remains to be elucidated. Some studies have suggested that the presence of herpesvirus in periodontal regions could play a role in the pathogenesis of human periodontitis[43-45]. As mentioned before, herpesviruses are ubiquitous and can persist latently after primary infection in various types of host cells, including cells of the immune system. CMV is the most studied member of the *Betaherpesvirinae* sub-family in the periodontal regions. Recently, other herpesvirus (EBV, HHV-6, and HHV-7) have been investigated with regards to periodontitis since these viruses are often found in the saliva[43-45]. Herpesviruses have also been studied in other diseases, and some studies have suggested that these viruses may act directly or indirectly by immunomodulation, specifically by influencing the immune responses due to viral replication in lymphocytes and monocytes/macrophages.

Inflammatory cells harboring herpesvirus present in periodontal inflammation sites may contribute to the development and progression of periodontitis[46-48]. CMV can induce direct cytopathic effects on fibroblasts, keratinocytes, endothelial cells and inflammatory cells, polymorphonuclear cells, T-lymphocytes, macrophages, and possibly bone cells. In patients with periodontitis, T-cells are activated, and specific lymphocyte responses are moved by the nature of the original antigenic stimulus. This process is supported by a complex cascade of events involving cytokines, chemokines, and other inflammatory mediators that can be changed due to CMV infection. Balance between pro-inflammatory and anti-inflammatory activities controlled by different sub-populations of lymphocytes seem to be pivotal in the pathogenesis of periodontitis[49].

Local immunomodulatory effects caused by infection with herpesviruses may facilitate bacterial growth and increase the virulence or inducing release of cytokines and chemokines from inflammatory cells and connective tissue. Furthermore, viruses and bacteria can act in synergy to produce pathology. Moreover, the presence of betaherpesviruses in regions affected by periodontitis could merely reflect latent virus in periodontal tissue or cell inflammatory infiltrate present in this kind of pathology[43,48].

Studies conducted in our center found that 30% of periodontitis patients have CMV and/or HHV-7 as detected by qualitative nested-PCR in the tissue[50]. CMV was associated with inflammatory infiltrates that presented higher amounts of T-cells, and HHV-7 infection presented with higher amount of CD4+ T-cells. Based on those findings, two hypotheses were formulated: (1) The viruses may be active, and they may have direct or indirect effects on periodontitis; and (2) The viruses may be latent, and the presence of viral genomes merely indicates that cells harboring virus migrated to the affected area due to inflammation.

Posteriorly, we studied the viral replication by use of immunohistochemistry to detect viral antigen in gingival biopsies collected from periodontitis-affected areas. The study aimed to differentiate active or latent infection because detectable viral antigens appear only in active infections. Interesting, none of the samples presented viral antigens suggesting latent infection (unpublished data). The use of nested-PCR yielded is very sensitive results as this method can detect low amounts of viral DNA that typically is found in latent infections, thus being therefore able to indicate ‘true’ infection in the samples.

**CONCLUSION**

Among the eight herpesviruses, HSV-1 (maybe HSV-2), VZV, EBV and HHV-8 can be directly linked to oral lesions. The conditions of the immune system significantly influence the risk of developing these infections. Additionally, immunosuppression, malnutrition, and immunosenescence are the most frequent disorders involved in the reactivation of herpesviruses. The differential diagnosis of other infections is very important to ensure the proper treatment of patients.

**REFERENCES**

1. **Bannoehr J**, Franco A, Iurescia M, Battisti A, Fitzgerald JR. Molecular diagnostic identification of Staphylococcus pseudintermedius. *J Clin Microbiol* 2009; **47**: 469-471 [PMID: 19091817 DOI: 10.1128/JCM.01915-08]
2. **Grinde B**. Herpesviruses: latency and reactivation - viral strategies and host response. *J Oral Microbiol* 2013; **5**: [PMID: 24167660 DOI: 10.3402/jom.v5i0.22766]
3. **Prasad A**, Remick J, Zeichner SL. Activation of human herpesvirus replication by apoptosis. *J Virol* 2013; **87**: 10641-10650 [PMID: 23885073 DOI: 10.1128/JVI.01178-13]
4. **El Hayderi L**, Raty L, Failla V, Caucanas M, Paurobally D, Nikkels AF. Severe herpes simplex virus type-I infections after dental procedures. *Med Oral Patol Oral Cir Bucal* 2011; **16**: e15-e18 [PMID: 20526251 DOI: 10.4317/medoral.16.e15]
5. **Goldman GS**, King PG. Review of the United States universal varicella vaccination program: Herpes zoster incidence rates, cost-effectiveness, and vaccine efficacy based primarily on the Antelope Valley Varicella Active Surveillance Project data. *Vaccine* 2013; **31**: 1680-1694 [PMID: 22659447 DOI: 10.1016/j.vaccine.2012.05.050]
6. **Poletti P**, Melegaro A, Ajelli M, Del Fava E, Guzzetta G, Faustini L, Scalia Tomba G, Lopalco P, Rizzo C, Merler S, Manfredi P. Perspectives on the impact of varicella immunization on herpes zoster. A model-based evaluation from three European countries. *PLoS One* 2013; **8**: e60732 [PMID: 23613740 DOI: 10.1371/journal.pone.0060732]
7. **Tzellos S**, Farrell PJ. Epstein-barr virus sequence variation-biology and disease. *Pathogens* 2012; **1**: 156-174 [PMID: 25436768 DOI: 10.3390/pathogens1020156]
8. **De Paschale M**, Clerici P. Serological diagnosis of Epstein-Barr virus infection: Problems and solutions. *World J Virol* 2012; **1**: 31-43 [PMID: 24175209 DOI: 10.5501/wjv.v1.i1.31]
9. **Lodi S**, Guiguet M, Costagliola D, Fisher M, de Luca A, Porter K. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. *J Natl Cancer Inst* 2010; **102**: 784-792 [PMID: 20442214 DOI: 10.1093/jnci/djq134]
10. **Caserta MT**, Hall CB, Schnabel K, Lofthus G, Marino A, Shelley L, Yoo C, Carnahan J, Anderson L, Wang H. Diagnostic assays for active infection with human herpesvirus 6 (HHV-6). *J Clin Virol* 2010; **48**: 55-57 [PMID: 20211581 DOI: 10.1016/j.jcv.2010.02.007]
11. **Schneider CL**, Hudson AW. The human herpesvirus-7 (HHV-7) U21 immunoevasin subverts NK-mediated cytoxicity through modulation of MICA and MICB. *PLoS Pathog* 2011; **7**: e1002362 [PMID: 22102813 DOI: 10.1371/journal.ppat.1002362]
12. **Miranda CA**, Lima EG, de Lima DB, Cobucci RN, Cornetta Mda C, Fernandes TA, de Azevedo PR, de Azevedo JC, de Araújo JM, Fernandes JV. Genital infection with herpes simplex virus types 1 and 2 in women from natal, Brazil. *ISRN Obstet Gynecol* 2014; **2014**: 323657 [PMID: 25006480 DOI: 10.1155/2014/323657]
13. **Beydoun HA**, Dail J, Ugwu B, Boueiz A, Beydoun MA. Socio-demographic and behavioral correlates of herpes simplex virus type 1 and 2 infections and co-infections among adults in the USA. *Int J Infect Dis* 2010; **14 Suppl 3**: e154-e160 [PMID: 20418142 DOI: 10.1016/j.ijid.2009.12.007]
14. **Pereira VS**, Moizeis RN, Fernandes TA, Araújo JM, Meissner RV, Fernandes JV. Herpes simplex virus type 1 is the main cause of genital herpes in women of Natal, Brazil. *Eur J Obstet Gynecol Reprod Biol* 2012; **161**: 190-193 [PMID: 22424592 DOI: 10.1016/j.ejogrb.2011.12.006]
15. **Kaufman HE**, Azcuy AM, Varnell ED, Sloop GD, Thompson HW, Hill JM. HSV-1 DNA in tears and saliva of normal adults. *Invest Ophthalmol Vis Sci* 2005; **46**: 241-247 [PMID: 15623779 DOI: 10.1167/iovs.04-0614]
16. **Vidyanath S**, Balan U, Ahmed S, Johns DA. Role of cytology in herpetic stomatitis. *J Cytol* 2014; **31**: 122 [PMID: 25210248 DOI: 10.4103/0970-9371.138697]
17. **Jazeron JF**, Barbe C, Frobert E, Renois F, Talmud D, Brixi-Benmansour H, Brodard V, Andréoletti L, Diebold MD, Lévêque N. Virological diagnosis of herpes simplex virus 1 esophagitis by quantitative real-time PCR assay. *J Clin Microbiol* 2012; **50**: 948-952 [PMID: 22170921 DOI: 10.1128/JCM.05748-11]
18. **Wilson SS**, Fakioglu E, Herold BC. Novel approaches in fighting herpes simplex virus infections. *Expert Rev Anti Infect Ther* 2009; **7**: 559-568 [PMID: 19485796 DOI: 10.1586/eri.09.34]
19. **Nappalli D**, Lingappa A. Oral manifestations in transplant patients. *Dent Res J (Isfahan)* ; **12**: 199-208 [PMID: 26005458]
20. **Stona P**, da Silva Viana E, Dos Santos Pires L, Blessmann Weber JB, Floriani Kramer P. Recurrent Labial Herpes Simplex in Pediatric Dentistry: Low-level Laser Therapy as a Treatment Option. *Int J Clin Pediatr Dent* 2014; **7**: 140-143 [PMID: 25356015 DOI: 10.5005/jp-journals-10005-1252]
21. **Hafezi W**, Lorentzen EU, Eing BR, Müller M, King NJ, Klupp B, Mettenleiter TC, Kühn JE. Entry of herpes simplex virus type 1 (HSV-1) into the distal axons of trigeminal neurons favors the onset of nonproductive, silent infection. *PLoS Pathog* 2012; **8**: e1002679 [PMID: 22589716 DOI: 10.1371/journal.ppat.1002679]
22. **Kakiuchi S**, Nonoyama S, Wakamatsu H, Kogawa K, Wang L, Kinoshita-Yamaguchi H, Takayama-Ito M, Lim CK, Inoue N, Mizuguchi M, Igarashi T, Saijo M. Neonatal herpes encephalitis caused by a virologically confirmed acyclovir-resistant herpes simplex virus 1 strain. *J Clin Microbiol* 2013; **51**: 356-359 [PMID: 23100343 DOI: 10.1128/JCM.02247-12]
23. **Costa FA**, Soki MN, Andrade PD, Bonon SH, Thomasini RL, Sampaio AM, Ramos Mde C, Rossi CL, Cavalcanti TC, Boin Ide F, Leonard M, Leonard LS, Stucchi RB, Costa SC. Simultaneous monitoring of CMV and human herpesvirus 6 infections and diseases in liver transplant patients: one-year follow-up. *Clinics (Sao Paulo)* 2011; **66**: 949-953 [PMID: 21808857 DOI: 10.1590/S1807-59322011000600005]
24. **Gilden D**, Mahalingam R, Nagel MA, Pugazhenthi S, Cohrs RJ. Review: The neurobiology of varicella zoster virus infection. *Neuropathol Appl Neurobiol* 2011; **37**: 441-463 [PMID: 21342215 DOI: 10.1111/j.1365-2990.2011.01167.x]
25. **Kawai K**, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open* 2014; **4**: e004833 [PMID: 24916088 DOI: 10.1136/bmjopen-2014-004833]
26. **Kobayashi T**, Yagami A, Suzuki K, Yoshikawa T, Matsunaga K. Concurrent reactivation of herpes simplex and varicella zoster viruses confirmed by the loop-mediated isothermal amplification assay. *Case Rep Dermatol* 2014; **6**: 5-9 [PMID: 24575004 DOI: 10.1159/000358005]
27. **Schmader KE**, Johnson GR, Saddier P, Ciarleglio M, Wang WW, Zhang JH, Chan IS, Yeh SS, Levin MJ, Harbecke RM, Oxman MN. Effect of a zoster vaccine on herpes zoster-related interference with functional status and health-related quality-of-life measures in older adults. *J Am Geriatr Soc* 2010; **58**: 1634-1641 [PMID: 20863322 DOI: 10.1111/j.1532-5415.2010.03021.x]
28. **Studahl M**, Petzold M, Cassel T. Disease burden of herpes zoster in Sweden--predominance in the elderly and in women - a register based study. *BMC Infect Dis* 2013; **13**: 586 [PMID: 24330510 DOI: 10.1186/1471-2334-13-586]
29. **Langan SM**, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med* 2013; **10**: e1001420 [PMID: 23585738 DOI: 10.1371/journal.pmed.1001420]
30. **Gilden D**. Efficacy of live zoster vaccine in preventing zoster and postherpetic neuralgia. *J Intern Med* 2011; **269**: 496-506 [PMID: 21294791 DOI: 10.1111/j.1365-2796.2011.02359.x]
31. **Shin BS**, Na CH, Song IG, Choi KC. A case of human immunodeficiency virus infection initially presented with disseminated herpes zoster. *Ann Dermatol* 2010; **22**: 199-202 [PMID: 20548914 DOI: 10.5021/ad.2010.22.2.199]
32. **Gershon AA**, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. *Clin Microbiol Rev* 2013; **26**: 728-743 [PMID: 24092852 DOI: 10.1128/CMR.00052-13]
33. **Balfour HH**, Dunmire SK, Hogquist KA. Infectious mononucleosis. *Clin Transl Immunology* 2015; **4**: e33 [PMID: 25774295 DOI: 10.1038/cti.2015.1]
34. **Martelius T**, Lappalainen M, Palomäki M, Anttila VJ. Clinical characteristics of patients with Epstein Barr virus in cerebrospinal fluid. *BMC Infect Dis* 2011; **11**: 281 [PMID: 22018204 DOI: 10.1186/1471-2334-11-281]
35. **Ok CY**, Li L, Young KH. EBV-driven B-cell lymphoproliferative disorders: from biology, classification and differential diagnosis to clinical management. *Exp Mol Med* 2015; **47**: e132 [PMID: 25613729 DOI: 10.1038/emm.2014.82]
36. **Mynarek M**, Schober T, Behrends U, Maecker-Kolhoff B. Posttransplant lymphoproliferative disease after pediatric solid organ transplantation. *Clin Dev Immunol* 2013; **2013**: 814973 [PMID: 24174972 DOI: 10.1155/2013/814973]
37. **Navari M**, Fuligni F, Laginestra MA, Etebari M, Ambrosio MR, Sapienza MR, Rossi M, De Falco G, Gibellini D, Tripodo C, Pileri SA, Leoncini L, Piccaluga PP. Molecular signature of Epstein Barr virus-positive Burkitt lymphoma and post-transplant lymphoproliferative disorder suggest different roles for Epstein Barr virus. *Front Microbiol* 2014; **5**: 728 [PMID: 25566237 DOI: 10.3389/fmicb.2014.00728]
38. **Rowe M**, Fitzsimmons L, Bell AI. Epstein-Barr virus and Burkitt lymphoma. *Chin J Cancer* 2014; **33**: 609-619 [PMID: 25418195 DOI: 10.5732/cjc.014.10190]
39. **Brasileiro CB**, Abreu MH, Mesquita RA. Critical review of topical management of oral hairy leukoplakia. *World J Clin Cases* 2014; **2**: 253-256 [PMID: 25032199 DOI: 10.12998/wjcc.v2.i7.253]
40. **Cousins E**, Nicholas J. Molecular biology of human herpesvirus 8: novel functions and virus-host interactions implicated in viral pathogenesis and replication. *Recent Results Cancer Res* 2014; **193**: 227-268 [PMID: 24008302 DOI: 10.1007/978-3-642-38965-8\_13]
41. **Giffin L**, Damania B. KSHV: pathways to tumorigenesis and persistent infection. *Adv Virus Res* 2014; **88**: 111-159 [PMID: 24373311 DOI: 10.1016/B978-0-12-800098-4.00002-7]
42. **Ganem D**. KSHV and the pathogenesis of Kaposi sarcoma: listening to human biology and medicine. *J Clin Invest* 2010; **120**: 939-949 [PMID: 20364091 DOI: 10.1172/JCI40567]
43. **Contreras A**, Slots J. Herpesviruses in human periodontal disease. *J Periodontal Res* 2000; **35**: 3-16 [PMID: 10791704 DOI: [10.1034/j.1600-0765.2000.035001003.x](http://dx.doi.org/10.1034/j.1600-0765.2000.035001003.x" \t "_blank)]
44. **Rotola A**, Cassai E, Farina R, Caselli E, Gentili V, Lazzarotto T, Trombelli L. Human herpesvirus 7, Epstein-Barr virus and human cytomegalovirus in periodontal tissues of periodontally diseased and healthy subjects. *J Clin Periodontol* 2008; **35**: 831-837 [PMID: 18691217 DOI: 10.1111/j.1600-051X.2008.01301.x]
45. **Cassai E**, Galvan M, Trombelli L, Rotola A. HHV-6, HHV-7, HHV-8 in gingival biopsies from chronic adult periodontitis patients. A case-control study. *J Clin Periodontol* 2003; **30**: 184-191 [PMID: 12631175 DOI: [10.1034/j.1600-051X.2003.00220.x](http://dx.doi.org/10.1034/j.1600-051X.2003.00220.x" \t "_blank)]
46. **Contreras A**, Umeda M, Chen C, Bakker I, Morrison JL, Slots J. Relationship between herpesviruses and adult periodontitis and periodontopathic bacteria. *J Periodontol* 1999; **70**: 478-484 [PMID: 10368051 DOI: 10.1902/jop.1999.70.5.478]
47. **Slots J**, Kamma JJ, Sugar C. The herpesvirus-Porphyromonas gingivalis-periodontitis axis. *J Periodontal Res* 2003; **38**: 318-323 [PMID: 12753371 DOI: [10.1034/j.1600-0765.2003.00659.x](http://dx.doi.org/10.1034/j.1600-0765.2003.00659.x" \t "_blank)]
48. **Slots J**. Herpesviral-bacterial synergy in the pathogenesis of human periodontitis. *Curr Opin Infect Dis* 2007; **20**: 278-283 [PMID: 17471038 DOI: 10.1097/QCO.0b013e3280964da0]
49. **Slots J**. Human viruses in periodontitis. *Periodontol 2000* 2010; **53**: 89-110 [PMID: 20403107 DOI: 10.1111/j.1600-0757.2009.00325.x]
50. **Thomasini RL**, Bonon SH, Durante P, Costa SC. Correlation of cytomegalovirus and human herpesvirus 7 with CD3+ and CD3+ CD4+ cells in chronic periodontitis patients. *J Periodontal Res* 2012; **47**: 114-120 [PMID: 21895663 DOI: 10.1111/j.1600-0765.2011.01413.x]

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**Table 1 Complete list of the human herpesviruses**

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| --- | --- | --- | --- |
| **Virus** | **Synonymous** | **Subfamily** | **Abbreviation** |
| Human herpesvirus -1 | Herpes simplex-1 | α | HSV-1/HHV-1 |
| Human herpesvirus -2 | Herpes simplex-2 | α | HSV-2/HHV-2 |
| Human herpesvirus -3 | Varicella-zoster | α | VZV/HHV-3 |
| Human herpesvirus -4 | Epstein-Barr | γ | EBV/HSV-4 |
| Human herpesvirus -5 | Cytomegalovirus | β | CMV/HHV-5 |
| Human herpesvirus -6 | None | β | HHV-6 |
| Human herpesvirus -7 | None | β | HHV-7 |
| Human herpesvirus -8 | None | γ | KSHV/HHV-8 |

HSV-1: Herpes simplex virus type 1; HSV-2: Herpes simplex virus type 2; VZV: Varicella-zoster virus; EBV: Epstein-Barr virus; CMV: Cytomegalovirus; KSHV: Kaposis’s sarcoma-associated virus; HHV: Human herpesvirus.