

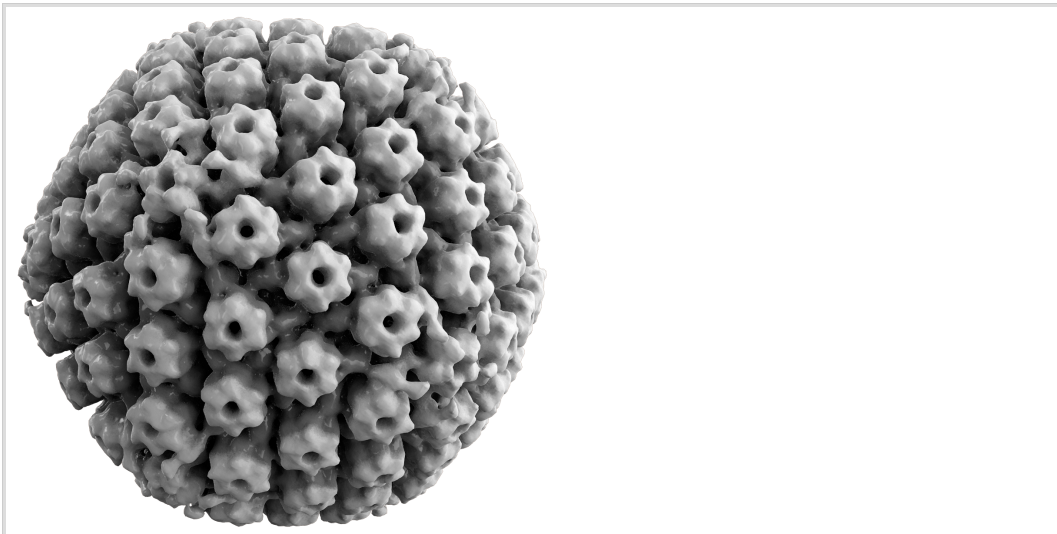
# Pathophysiology of Herpes Simplex Infections

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## **Definition / Overview:**

Herpes simplex is a general term for contagious chronic viral human infections that result from two serotypes of the herpes simplex virus (Centers for Disease Control and Prevention, 2014). The two main serotypes involved are Herpes Simplex 1 (HSV1) and Herpes Simplex 2 (HSV2) [collectively HSV].

Both serotypes are classified as being members of the Herpesviridae family of viruses. Viruses from this family are also responsible for other serious diseases such as epstein-barr, varicella zoster (chicken pox) and bovine encephalitis



3D reconstruction of herpes simplex virus 1 (HSV-1) [Image Credit 1]

Herpesviridae are distinct in that they contain double stranded DNA, are nuclear replicating, and possess a lipid envelope (Davison, 2007).

The two serotypes collectively referred to as HSV are distinguished by where the

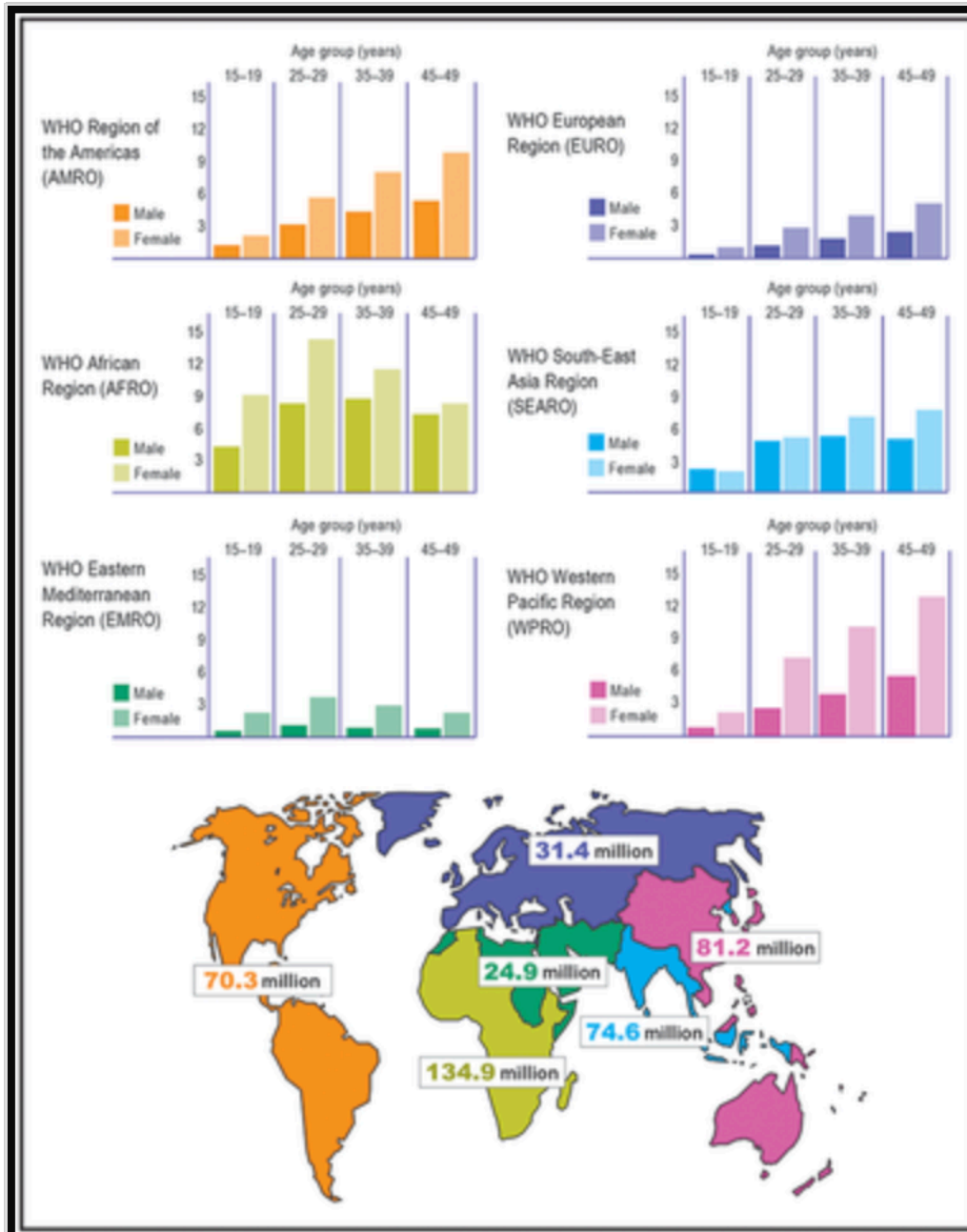
characteristic lesions they produce are localized. HSV1 typically affects the oro-labial region whereas HSV2 typically affects the ano-uro-genital region (Aymard, 2002). It is important to note that both serotypes may infect any area (Chayavichitsilp, Buckwalter, Krakowski, & Friedlander, 2009). Both types of virus are usually acquired through direct contact with infected lesions or body fluids (typically saliva) (Arduino & Porter, 2008). In both cases, the first infection is typically the most severe and is most likely to result in symptoms.

HSV infections can be asymptomatic (Aymard, 2002). Asymptomatic carriers play a major role in the epidemiology of herpes. HSV manifests initially with prodromal symptoms of itching/burning at the infection site followed by inflammation and ultimately the formation of vesicles. With HSV1, the initial lesion is an erythematous papule that evolves into a fluid-filled blister, which can be accompanied by ulcerative painful stomatitis that usually occurs in children and is often associated with fever, anorexia and local edema of oral mucosa interfering with swallowing (Wald & Corey, 2007). HSV2 symptoms include painful vesicles and ulcers at the infection site and can be accompanied by lymphatic edema and systemic flu-like symptoms (Wald & Corey, 2007).

Interventions focus on prevention and minimizing the severity and recurrence of outbreaks. There is currently no cure for HSV infection but vaccines for both serotypes are an area of active research (Bloom, 2016).

## **Who is affected**

Most people infected with HSV are asymptomatic or have very mild symptoms that go unnoticed or are mistaken for another condition. As a result, 87.4% of infected individuals remain unaware of their infection (Centers for Disease Control and Prevention, 2016). Symptoms typically appear after an average incubation period of 4 days (range, 2 to 12) after exposure (Kimberlin & Rouse, 2004).



Global Estimates of Prevalent and Incident Herpes Simplex Virus Type 2 Infections in 2012 [Image Credit 2]

HSV infections are extremely common. 90% of the global population has developed antibodies for one or both of the serotypes (Wald & Corey, 2007).

In the US, the latest CDC data on herpes infections rates is from 2010. They estimate the prevalence of HSV1 infection at 54% of the population and HSV2

infection at 16.2% of the population (Centers for Disease Control and Prevention, 2016). Notably, infection rates in the US have been decreasing since the 1970's (Fanfair et al., 2013) & (Bradley, Markowitz, Gibson, & McQuillan, 2014).

Within the US the disease continues to disproportionately burden African-Americans (39.2% prevalence), particularly women (48.0% prevalence). This is due to higher community prevalence and biological factors such as increased mucosal surface area that put women of all races at greater risk for HSV-2 than men (Bradley, Markowitz, Gibson, & McQuillan, 2014).

As of 2012, 3.7 billion people (range: 3440–3878 million) under 50 were infected with HSV1 (67% global prevalence) 50% of HSV1 infections are genital. The global prevalence of HSV2 is 417 million people aged 15–49 years (range: 274–678 million) world-wide (11.3% global prevalence) (Looker et al., 2015).

The disease is often more severe in women than in men, also with regard to the prevalence of complications, including aseptic meningitis and urinary retention (Sauerbrei, 2016).

While all humans are capable of being infected by HSV, there is increasing evidence of a genetic component to cold sore susceptibility. Researchers have noted that individuals with H1, H2, and H4 haplotypes tend to have more frequent and severe episodes (Kriesel, Bhatia, & Thomas, 2014). The specific gene identified has been coined the “Cold Sore Susceptibility Gene” or CSSG-1 (Kriesel et al., 2011).

### **Development/Pathogenesis**

Both serotypes of HSV are neurovirulent, meaning they are capable of infecting nervous tissue. The viruses leverage this trait in two distinct ways during pathogenesis. Initially they invade and replicate in the central nervous system and they also establish a latent infection in dorsal root ganglia (Fields, Knipe, &

Howley, 2007)

HSV must come in contact with mucosal surfaces or abraded skin for infection to occur. (Whitley, Kimberlin, & Prober, 2007).

Langerhans cells (antigen presenting immune cells) present in the epidermis are the first immune cells to become infected. These cells are not the cells that initiate the subsequent immune response. The dermal dendritic cells thought to be responsible for initiating the immune response are not likely to be infected (Kim et al., 2015).

During the course of the primary infection, HSV replication is restricted to the epidermis prior to infiltration of the virus into sensory nerve endings where it begins to replicate and is transported to the dorsal root ganglion (Koelle & Corey, 2003).

Upon infection of the dorsal root ganglia after another round of viral replication, latency is established. During latency HSV persists in neuronal tissue with viral genome but no virions present (Harris & Harris, 2015). After latency is established, stimulus (discussed later) can cause reactivation, virions are produced, begin to replicate and the virus becomes evident at mucocutaneous sites, appearing as skin vesicles or mucosal ulcers (Whitley, Kimberlin, & Prober, 2007).

Reactivation can also lead to asymptomatic shedding of live virus (Koelle & Corey, 2003). This creates a scenario where an asymptomatic carrier could have an asymptomatic reactivation of a latent HSV infection and shed live virus capable of infecting other individuals.

A recurrence of HSV is known as “recurrent infection.” Reinfection with a different strain of HSV can occur, but this is very uncommon (Whitley, Kimberlin, & Prober, 2007).

## Pathophysiology

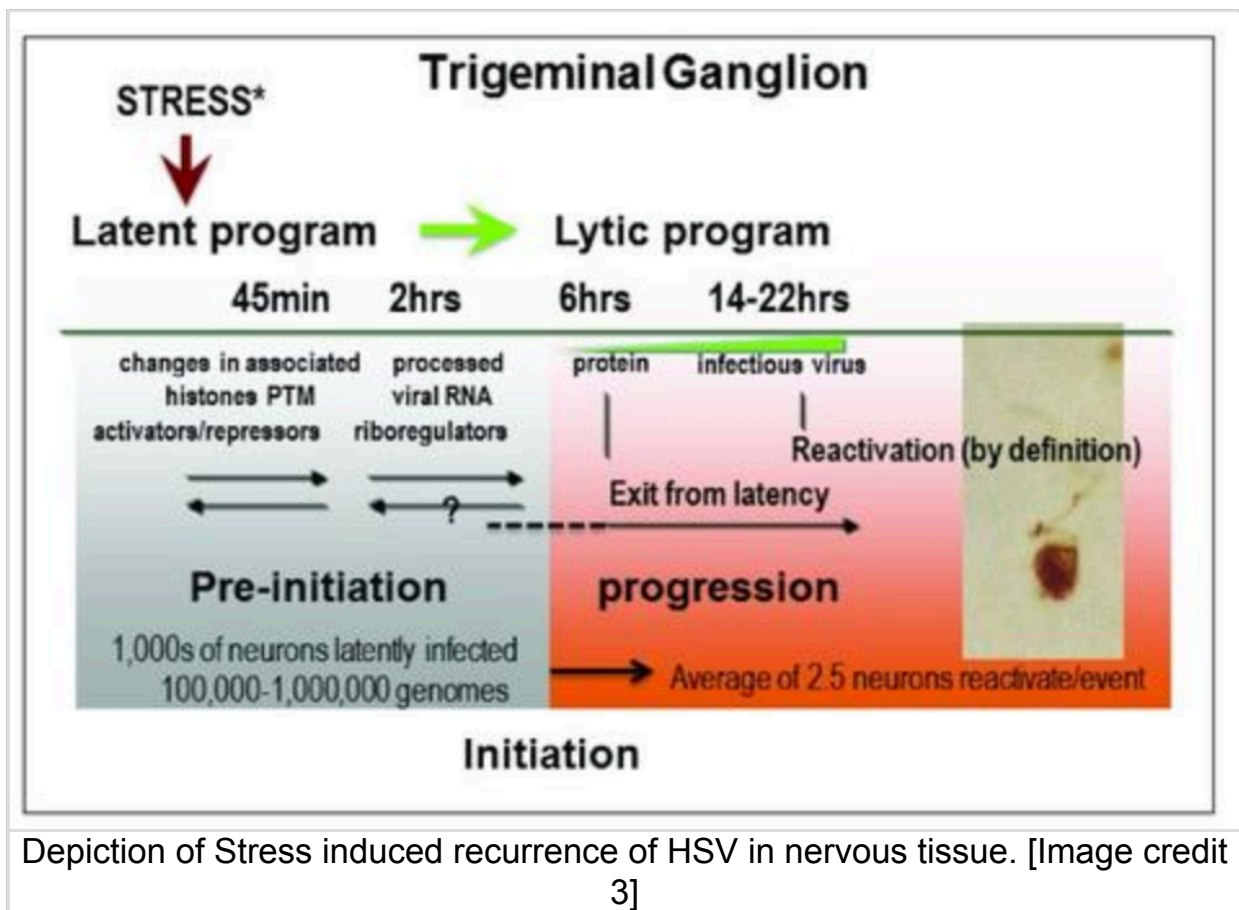
Both primary or recurrent HSV infections cause viral-mediated cellular lysis and an inflammatory response. The infection induces ballooning of cells followed by nuclear degeneration. This generally occurs within parabasal and intermediate cells of the epithelium. The plasma membranes of these cells degrade and form multinucleated giant cells. When cell lysis occurs a clear fluid containing large quantities of live virus appears between the epidermis and dermal layer. This vesicular fluid contains cell debris, inflammatory cells, and often multinucleated giant cells. In deeper layers of the dermis there is classic inflammatory response. With healing, the vesicular fluid becomes pustular with the recruitment of inflammatory cells and scabs. Scarring is uncommon. When mucous membranes are involved, vesicles are replaced by shallow ulcers (Whitley, Kimberlin, & Prober, 2007).

**[Video: Pathophysiology of herpes | Infectious diseases | NCLEX-RN | Khan Academy](#)**

The innate immune response plays a primary role in resistance to HSV. This response involves the production of type I interferon (both alpha and beta). Natural killer cells are associated with cytokine production, recognition of compromised cells, and infected cell lysis. Plasmacytoid dendritic cells contribute by producing elevated levels of type I interferon (Chew, Taylor, & Mossman, 2009).

Adaptive antibodies are produced against HSV following infection but appear to play a minor role in pathogenesis and immune protection. Evidence in the literature now supports the primary role of cellular immunity, particularly a type of Cytotoxic T cell known as CD8+ T against HSV. Specifically, the IFN $\gamma$ -mediated effector functions of CD8+ T cells contribute to survival against challenge, maintenance of latency, and limiting of HSV spread.

HSV is highly infectious even in “healthy” hosts engaged in multiple synergistic salutogenic inputs. Exposure to viral shedding on abraded skin or mucosal membranes must be avoided. The literature ranges from advising abstinence to avoiding contact with an infected partner if they are having an outbreak (Mayo Clinic Staff, 2014).



Stress has been implicated as playing a major role in recurrent HSV infections. The mechanisms underlying this role are still imperfectly understood.

One potential understanding involves the response of the CNS or PNS to trauma, stress, or immunosuppression.

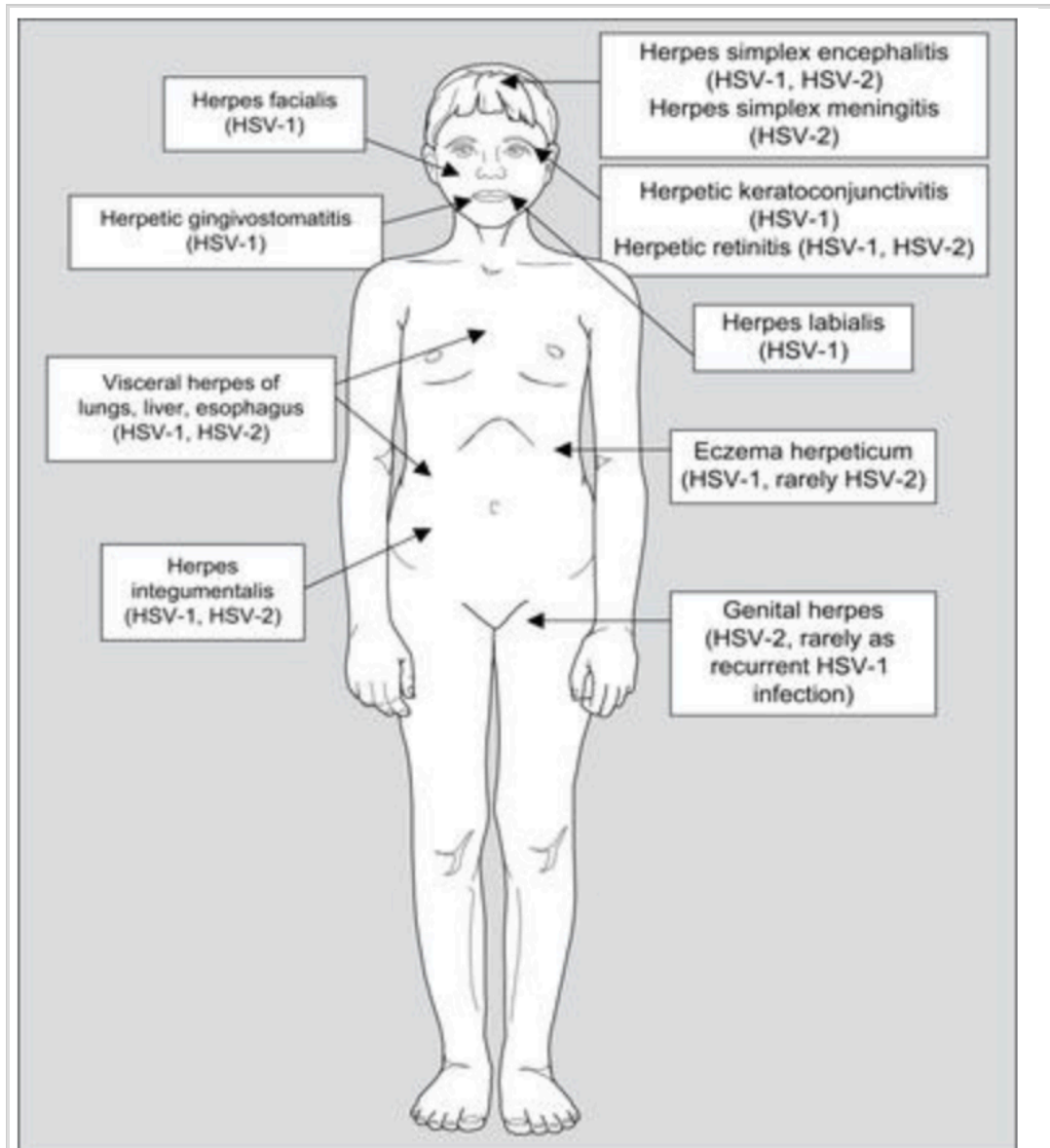
Elevated corticosteroid levels potentially induce viral gene expression and stimulates HSV to replicate in neurons.

Corticosteroids may also alter viral RNA splicing patterns in the absence of protein synthesis. Corticosteroids, or other forms of stress or trauma can induce neuronal neurodegeneration and/or apoptosis. In this case, HSV antiapoptotic genes would be expressed and prolong neuronal survival, thus enhancing virus production.(Perng & Jones, 2010)

The disease course for HSV is as follows: After 2–12 days of incubation people may develop the typical herpes blisters at the infection site. But, 99% of the infected people, show a clinically unapparent course (Sauerbrei, 2016). This can be because the initial outbreak is misconstrued as another phenomenon and remains sub-clinical or it may be that the person is entirely asymptomatic.

If an HSV-2 outbreak does occur the lesions usually appear 4–7 days after exposure and last up to 3 weeks. Symptoms include pain, itching, burning, and dysuria. In primary infections, it may be accompanied by lymphadenopathy, fever, cervicitis, and proctitis (Sauerbrei, 2016).





Localized names for diseases caused by HSV1 and 2 [Image Credit 4]

The antivirals Acyclovir, valacyclovir, and famciclovir are considered the allopathic standard antiviral treatment of genital herpes both during an outbreak and for prophylaxis of recurrent outbreaks (Sauerbrei, 2016).

## Integration

HSV infection has recently been implicated in Sporadic Alzheimer's disease (AD). Brains of AD patients have elevated levels of pro-inflammatory cytokines. Infection by HSV induces expression of cytokines and pro-inflammatory molecules and as a result of the subsequent inflammatory response neuronal oxidative damage can occur. These Interactions between HSV and oxidative stress promote neurodegenerative processes found in AD (Harris & Harris, 2015).

HSV has also been implicated in viral (aseptic) meningitis (Berger & Houff, 2008). Retrograde infection of the meninges by HSV can occur via peripheral and cranial nerves. This leads to an inflammatory response. Cytokines as well as lymphocytes can accumulate which further enhances the inflammatory response. This can lead to increased permeability of the blood brain barrier and potentially result in Encephalitis (Chadwick, 2005).

HSV can also complicate pregnancy if the mother develops the disease while pregnant. Pregnant women who are infected with HSV have a higher risk for miscarriage, premature labor, retarded fetal growth, or transmission of the herpes infection to the infant while in the uterus or at the time of delivery. While rare, neonatal infections can occur and the chance is increase if the mother acquired HSV late in the pregnancy. This is due to the fact that during a first infection, the virus is shed for longer periods, and more viral particles are excreted. Also an infection that first occurs in the late term does not allow the mother to develop antibodies that would help her baby fight off the infection at the time of delivery. Transmission can occur if the amniotic membrane of an infected woman ruptures prematurely, or as the infant passes through an infected birth canal (Simon, 2013).

## **Big Picture**

The disease process induced by infection does not make sense when viewed through the lens of an adaptive response that contributes to pathophysiologic changes in humans. Even though there is extensive information on HSV biology, the absolute mechanism of HSV latency and endogenous virus reactivation is currently unknown (Sauerbrei, 2016). But, It can be argued that HSV has adapted to uniquely thrive in humans. The virus is prevented from overwhelming the host during the initial infection by the innate and adaptive immune systems. But these same immune mechanisms are ill equipped to prevent viral shedding and lifelong latent infection in the nervous tissue.

SELF CHECK: What percent of the global population present HSV antibodies?

SELF CHECK: What type of tissue does HSV establish latency in?

### **Optional extras**

#### ***Papers:***

### **Recent Progress in Herpes Simplex Virus Immunobiology and Vaccine Research**

(Koelle & Corey, 2003)

### **The Effect of Aqueous Extract of //Glycyrrhiza glabra// on //Herpes Simplex Virus// //1//**

(Sabouri Ghannad et al., 2014)

### **Natural remedies for Herpes simplex.**

(Gaby, 2006) (requires Sherman Cohn Login for fulltext)

## [Antiviral effect of aqueous extracts from species of the Lamiaceae family against Herpes simplex virus type 1 and type 2 in vitro.](#)

(Nolkemper, Reichling, Stintzing, Carle, & Schnitzler, 2006)  
(requires Sherman Cohn Login for fulltext)

## [Aqueous extracts from peppermint, sage and lemon balm leaves display potent anti-HIV-1 activity by increasing the virion density.](#)

(Geuenich et al., 2008)  
(requires Sherman Cohn Login for fulltext)

### ***Lectures:***

## [\\*\\*Genital Herpes: Epidemiology and Public Health Perspectives\\*\\*](#)

- H. Hunter Handsfield, M.D. - Professor of Medicine University of Washington
- Director, STD Control Program Public Health - Seattle King county

## [Natural History and Pathogenesis of Herpes Virus Infections](#)

Prof. Richard Whitley – University of Alabama at Birmingham, USA

Video: [3D herpes simplex Virus animation](#)

Image Credits:

**Image 1:** Published under a Creative Commons License Original Image: [https://en.wikipedia.org/wiki/Herpes\\_simplex\\_virus#/media/File:HSV-1-EM.png](https://en.wikipedia.org/wiki/Herpes_simplex_virus#/media/File:HSV-1-EM.png)

**Image 2:** Looker, K. J., Magaret, A. S., Turner, K. M. E., Vickerman, P., Gottlieb, S. L., & Newman, L. M. (2015). Global Estimates of Prevalent and Incident Herpes Simplex Virus Type 2 Infections in 2012. *PLOS ONE*, 10(1), e114989. <https://doi.org/10.1371/journal.pone.0114989>

**Image 3:** Sawtell, N. M., & Thompson, R. L. (2016). Herpes simplex virus and the lexicon of latency and reactivation: a call for defining terms and building an integrated collective framework. *F1000Research*, 5. <https://doi.org/10.12688/f1000research.8886.1>

**Image 4:** Sauerbrei, A. (2016). Optimal management of genital herpes: current perspectives. *Infection and Drug Resistance*, 9, 129–141. <https://doi.org/10.2147/IDR.S96164>

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