Herpes Virus

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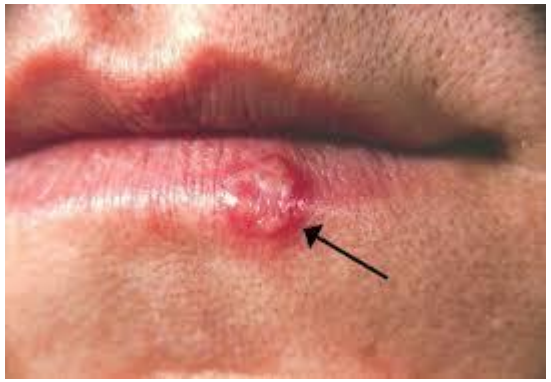
Classification

- Family Herpesviridae) are large, enveloped viruses that possess a linear double-strand DNA of 120–240 kb (Group I).
- Eight human herpesviruses were discovered, which are subdivided into three genera: alpha-, beta-, and gamma-herpesvirus.
- **α herpesviruses:** Herpes simplex virus types 1 and 2, and varicella-zoster virus, which have a short replicative cycle, induce cytopathology in monolayer cell cultures, and have a broad host range.
- **β herpesviruses:** Cytomegalovirus, and human herpesviruses 6 and 7, with a long replicative cycle and restricted host range.
- **γ herpesviruses:** Epstein-Barr virus and human herpesvirus 8, with a very restricted host range.
- Now, there are more than 130 herpesviruses are known, some of them from mammals, birds, fish, reptiles, amphibians, and mollusks. Nine herpesvirus types are known to infect humans.

Diseases caused by human herpesviruses

Virus	Disease	Signs/ Symptoms
Herpes Simpex virus HSV1, HSV2	Herpes simplex	Sores or ulcerations, fever blisters, flu-like discomfort
Varicella Zoster VSZ	Chickenpox, Shingles	Skin rash, blisters, fever, pain, sore throat, headache, stomach ache
CytoMegalo Virus CMV	CMV infections, Mononucleosis	Fever, rash, sore throat, nausea, muscle aches, swollen glands, fatigue
Epstein Barr Virus EBV	EBV infectious mononucleosis, associated with Burkitt's lymphoma and other malignancies	Fever, rash, sore throat, nausea, muscle aches, pain, swollen lymph nodes, fatigue, weight loss, vomiting
HHV6, HHV7	Roseola (exanthem subitum)	Fever, swollen glands, runny nose, mild diarrhea, swollen eyelids, fatigue, rash
KSHV	Kaposi's sarcoma (KS)	Characteristic skin lesions, lymphoma, non-specific symptoms (fever, weight loss, etc.)

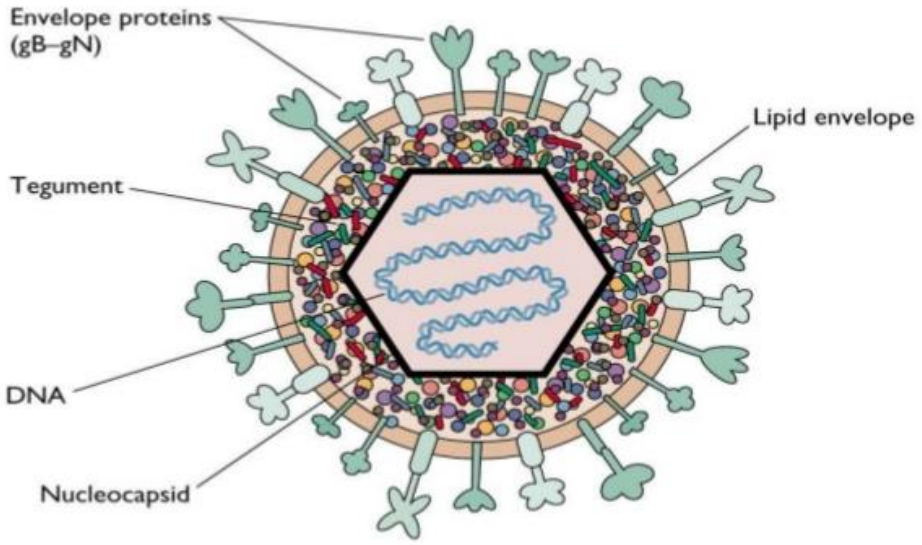
Herpes Simplex Virus Infection



- Herpes results from infection with the herpes simplex virus (HSV). It causes sores or blisters in or around the mouth or genitals, alongside other symptoms.
- **Oral herpes symptoms**
- Oral herpes causes blisters, sometimes called fever sores or cold sores, to develop in or around the lips and mouth.
- Sometimes these blisters form elsewhere on the face or tongue, and more rarely on other areas of skin.
- The sores usually last 2–3 weeks at a time before clearing up.
- **Genital herpes symptoms**
- These sores tend to develop on the penis, around or inside the vagina, on the buttocks, or on the anus, though they can form on other areas of skin.
- Herpes can also cause pain when urinating, and changes in vaginal discharge.
- The first time a person develops the sores, they may last 2–6 weeks before clearing up.
- Soon after this initial outbreak, symptoms may recur frequently. Over time, outbreaks may occur less often and the symptoms typically become less severe.

Structure

- The herpesvirus virion comprises four concentric layers: an inner core, surrounded by an icosahedral capsid, an amorphous tegument, and an envelope .
- The DNA genome is wound like a ball of wool and is associated with a protein core in the shape of a doughnut suspended by fibrils anchored to the inner side of the surrounding capsid.
- The capsid is an icosahedron, 100 nm in diameter, composed of 162 hollow capsomeres: 150 hexamers, and 12 pentamers
- Surrounding the capsid is a layer of globular material, the tegument, and this is enclosed by the lipoprotein envelope containing numerous small embedded glycoprotein peplomers.
- The envelope is fragile and the enveloped virion is somewhat pleomorphic, with a diameter ranging from 120 to 200 nm.

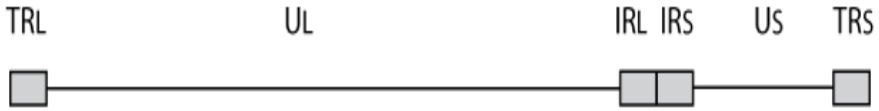


source; slideshare

- **Size:** 120-200nm in diameter
- **Genome:** linear ds DNA
- Enveloped
- Replication and assembly occur in nucleus of infected cell

Genome

The genome of HHV-1 is linear, double stranded DNA composed of 152,000 base pairs. It contains two unique regions (UL and US), each flanked by inverted repeats (TRL/IRL and TRS/IRS). This structure is characteristic of Alphaherpesvirinae.



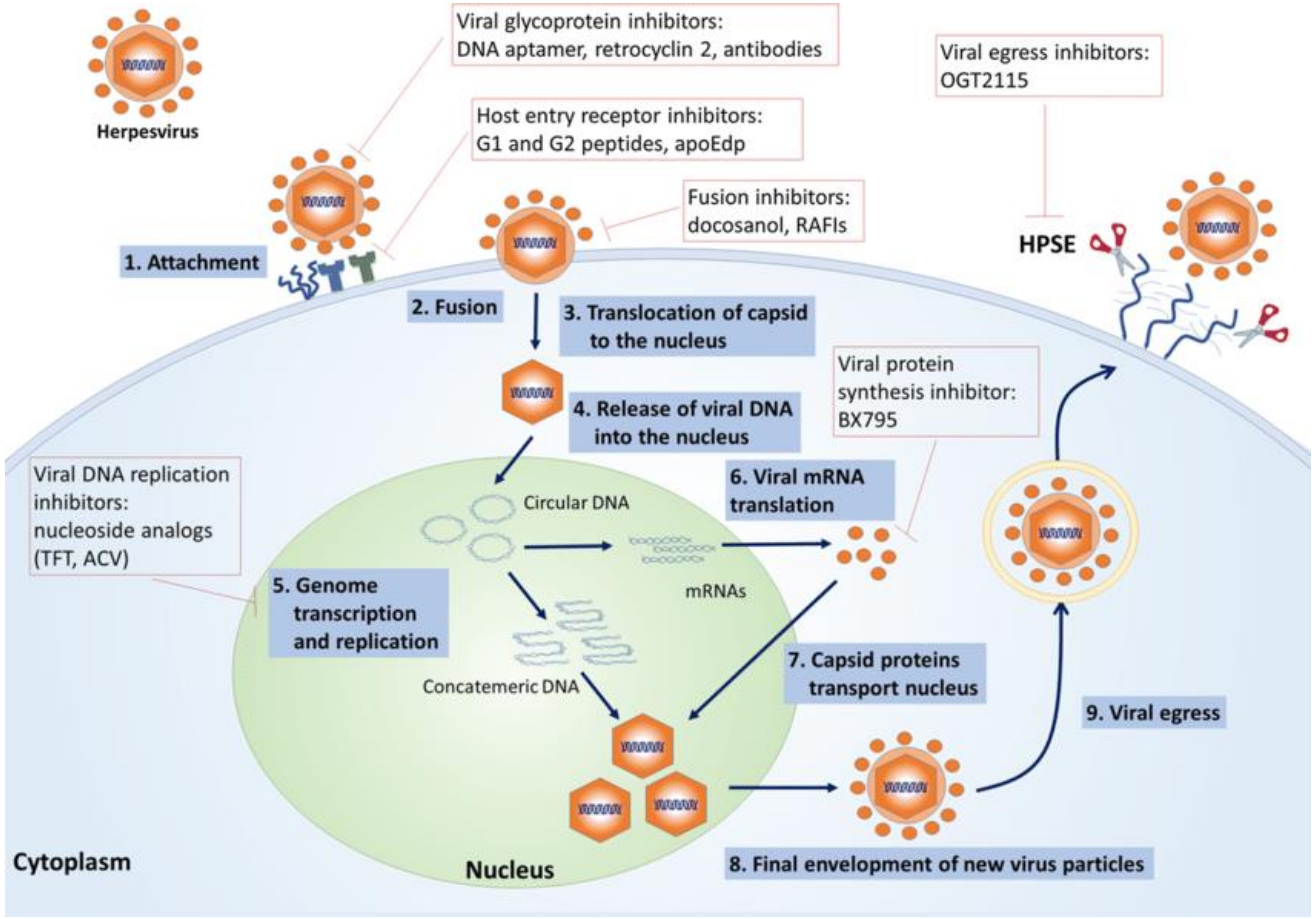
HHV-1 genomes are terminally redundant.

The genome encodes about 75 proteins that are differentially expressed.

First the early proteins are synthesized to activate the transcription of middle and late genes.
Middle genes are responsible for the DNA replication while Late genes are mostly structural proteins.

During neuronal latency, the genome becomes circular and transcribed few RNAs, including two LAT RNAS (2 kb and 1.5 kb) and 8 miRNAs. Several of the miRNAs produced plays a role in the inhibition of Immediate early protein ICP0, ICP4 and ICP34.5 expression inhibition.

Replication Cycle



Koujah, Lulia & Suryawanshi, Rahul & Shukla, Deepak. (2019). Pathological processes activated by herpes simplex virus-1 (HSV-1) infection in the cornea. Cellular and Molecular Life Sciences. 76. 10.1007/s00018-018-2938-1.

Mode of transmission:

- Direct contact with lesion fluid or saliva
- Sexual transmission; genital herpes
- Perinatal route; child gets Herpes during birth from infected mother
- Congenital transmission; it is rare
- **Pathogenesis:**
- Virus enter through skin and mucus membrane and multiply locally
- Virion interacts with specific cell surface receptor through its glycoprotein spike
- HSV1 and HSV2 have several cell surface receptor, they uses one of them for entry in host cell
- Binding of glycoprotein trigger fusion of viral envelope with host cell membrane and this fusion causes the release of nucleo-capsid into cytoplasm and is transported to nucleus.
- In the nucleus of host cell, virus replication occur immediately. At first Viral gene will be transcribed leading to synthesis of virus protein, replication of virus genome and assembly of progeny viruses.
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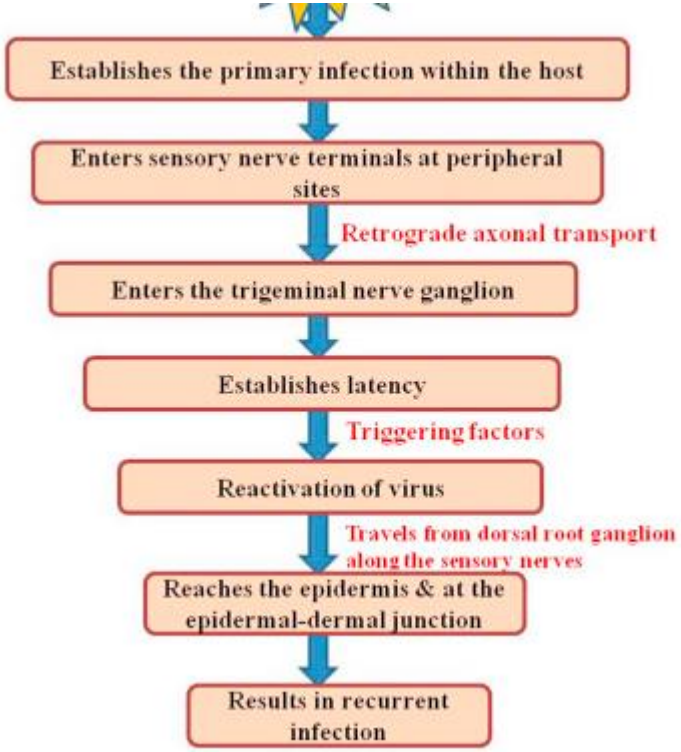
Pathogenesis



1. Primary infection:

•HSV1 infection are usually limited to oropharynx and transmitted by respiratory droplet or saliva whereas HSV2 infection usually transmits by genital route.

•Primary infection of Herpes results in vesicle formation under the layer of keratinized squamous epithelium cell. The vesicle is filled with fluid which contains multinucleated giant cells and eosinophilic intranuclear inclusions bodies along with inflammatory cell and cellular debris

•After primary infection, the virus invades local nerve ending and travel from retrograde intra axonal flow to sensory root ganglia where they further multiply.

•The virus settle within neuron in sensory ganglia (trigeminal ganglia in case of HSV1 and sacral ganglia in case of HSV2) and remain latent.

2. Latent infection:

•During latency no viral particles are produced. Also the latent infection does not causes any demonstrable damage in neuron.

•This latency phase may be reactivated periodically in some individuals causing recurrent oral and genial lesion.

3. Recurrence herpes:

•Various stimulus such as physical or emotional stress, trauma, fever, sunlight, certain food, menstrual cycle in female etc can induce recurrence of latent infection.

Clinical Symptoms

1. Cutaneous or skin infection:

2. Mucosal or Oropharyngeal infection:

3. Ophthalmic or eye infection:

4. Nervous system infection:

Herpes encephalitis; caused by HSV-1

5. Visceral herpes:

Herpes esophagitis

6. Genital herpes:

It is mostly caused by HSV-2

7. Congenital herpes:

Neonatal herpes is caused by HSV-2, and it is manifested as infection of eye, mouth, skin and more commonly a disseminated infection with multiple organ involvement.

Mortality rate is high and survivors may have neurological disabilities.

Laboratory diagnosis:

1. Specimens:

Saliva, vesicle fluids, conjunctival fluids, corneal scrapping, skin swab and CSF.

Depends upon site of infection

2. Microscopy:

Tzanck smear preparation: Smear is prepared from lesion and stained with 1% aqueous solution of toluidine blue for 15 seconds. Multinucleated giant cells are visualized in positive smear.

Giemsa stain can also be used to see inclusion bodies.

3. Electron microscope

4. Virus Culture:

Primary human embryonic kidney **cell line culture**, Hela cell, Human amnion, Hep2

Cytopathic effect should be visualized within 1-3 days

5. Serology:

ELISA, neutralization test, Complement fixation test (CFT), Immunofluorescent test

7. Molecular diagnosis:

PCR, DNA probe

Treatment:

- Acyclovir; orally or parenterally
- Ganciclovir, Viderabine, Famiciclovir; orally
- Idoxuvidine; topically in eye and skin infection

Vaccine trials

- Unsuccessful HSV Vaccine till now
- The first in human, fully enrolled Phase 1/2 trial of Moderna mRNA-1608 is designed to test safety and immunogenicity and to establish a proof-of-concept of clinical benefit in adults 18 to 55 years of age with recurrent HSV-2 genital herpes. The randomized 1:1:1:1, observer-blind, controlled study is fully enrolled with 300 participants in the U.S.

- Varicella-Zoster virus (VZV)

- Herpes zoster, also known as shingles, is caused by reactivation of latent VZV, the same virus that causes chickenpox. Declining immunity in older adults decreases immunity against VZV, allowing reactivation of the virus from latently infected neurons, causing painful and itchy lesions. Herpes Zoster occurs in one out of three adults in the U.S. in their lifetime and the incidence increases at 50 years of age. There is potential to reach a growing and underserved patient population.

- Moderna's VZV vaccine candidate mRNA-1468 has initial data available from a Phase 1/2 trial, which was designed to test safety and immunogenicity in healthy adults 50 years of age and older in the U.S. The randomized 1:1:1:1:1, observer-blind, active-controlled study of mRNA-1468 elicited strong antigen-specific T cell responses at one month after the second dose and was generally well tolerated. Results of the first interim analysis support the further clinical development of mRNA-1468 for the prevention of shingles. Additional results from the ongoing Phase 1/2 study will be available later this year, including persistence data. The Company is planning for a pivotal Phase 3 trial.