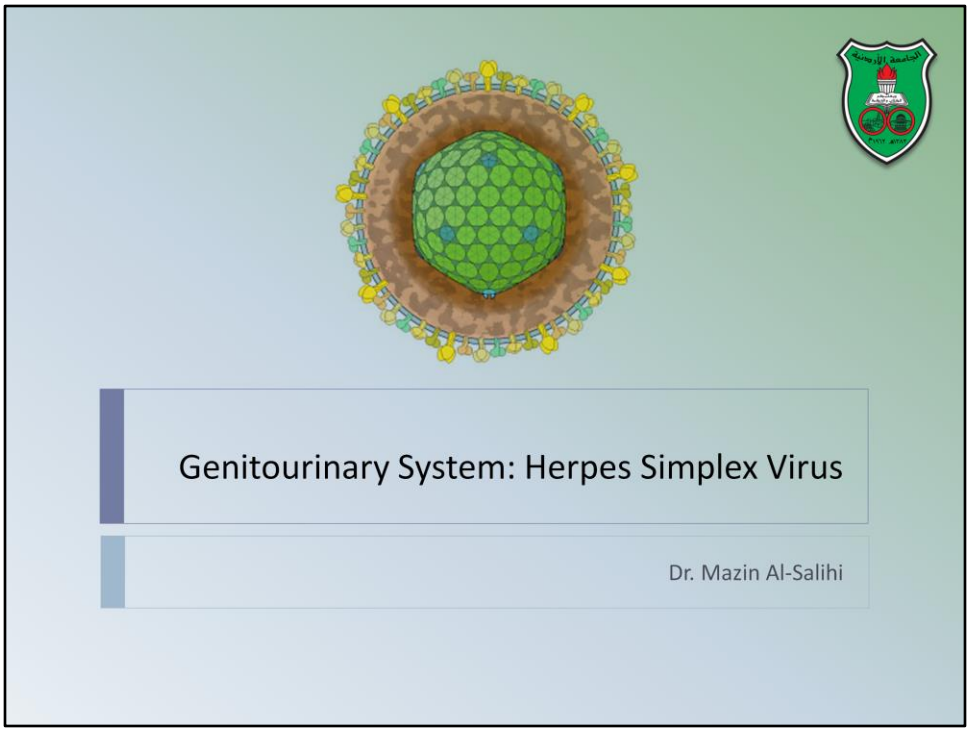
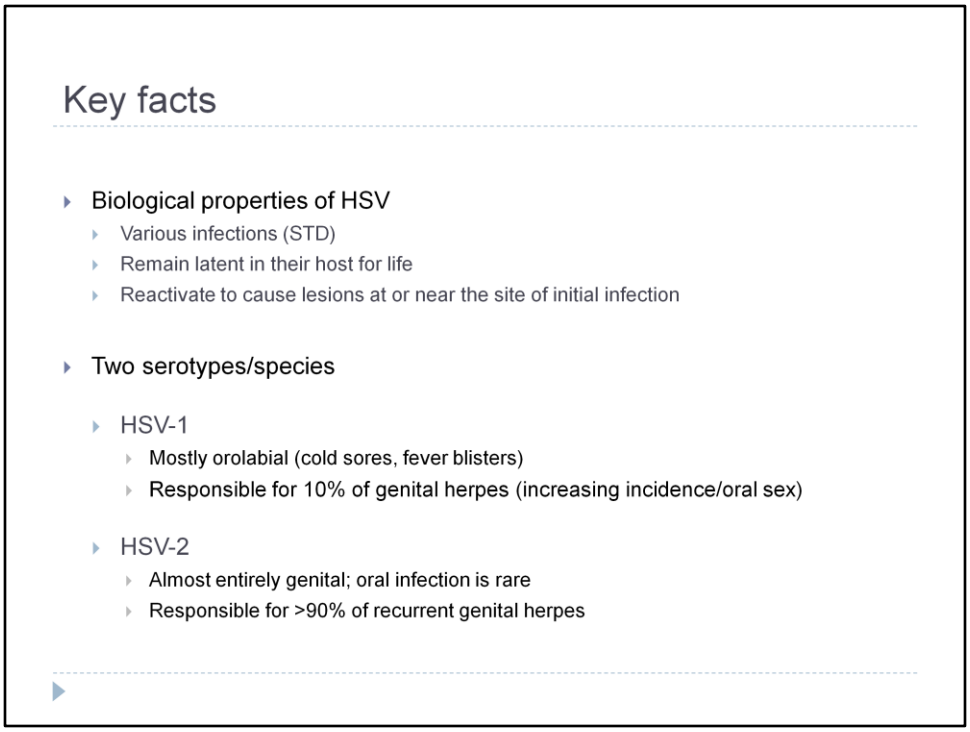


Descriptions of genital lesions that resemble those caused by HSV were described in a Sumerian tablet from the third millennium BC and in the Ebers Papyrus (c. 1500 BC).

"But of all such cases, the most formidable were those which took place about the pubes and genital organs. Such was the nature of these cases when attended with sores, and proceeding from an external cause; but the same things occurred in fevers, before fevers, and after fevers."
Hippocrates, "Of the Epidemics," 400 BC

Much later, according to the writings of John Astruc, physician to King Louis XIV, French prostitutes (*puellae publicae*) were under medical surveillance, Astruc and others studied their afflictions, and he was the first to describe *herpes genitalis.* A most enlightening description of recurrences of genital lesions was published by Unna in 1883. He wrote that herpes was "*so to say a vocational disease,*" recognized as being "*one of the most benign of affections both to the patient and her public.*" Shortly afterward, the first book dedicated to herpes—*Les Herpes Genitaux*—was published. In 1896, Fournier wrote about the diagnosis and treatment of genital herpes. His advice was "*For recurrent herpes the general treatment of arthritis* [by which he may have meant inlammation and pain] *may be necessary. As far as hygiene, forbid alcohol, tobacco, also wine fatigue, and sexual excesses*".



Mucocutaneous infection, retrograde spread along sensory nerves, latent infection in cranial nerve or dorsal spinal ganglia, mucocutaneous recurrences.

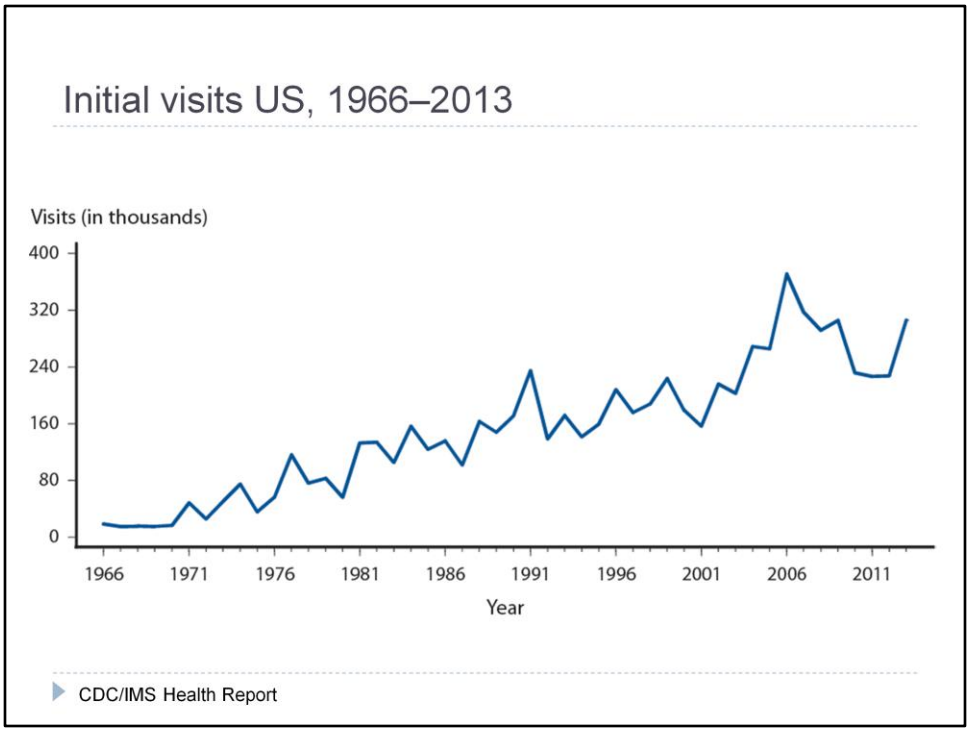
As with other STDs, the risk of infection is directly related to the number of sexual contacts. With women being more susceptible to acquiring genital HSV-2 than men. In addition, male circumcision has been shown to decrease the risk of acquisition of both HSV-2 and HIV.

As with HSV-1 infections of the mouth, HSV-2 unfortunately can be excreted in the absence of symptoms at the time of primary, initial, or recurrent infection. Shedding of virus occurs more frequently in the first year following genital infection than in subsequent years. Seropositive individuals with no history of lesions shed virus as frequently as those who are symptomatic. Asymptomatic shedding is the most significant
source for virus transmission.

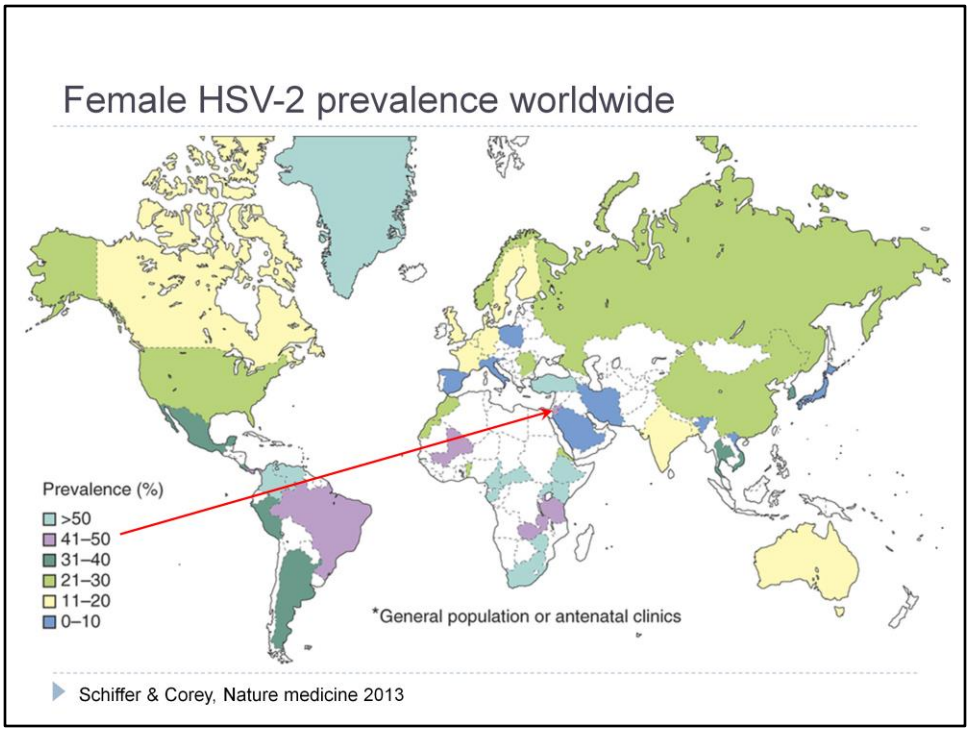
An individual with preexisting antibodies to one type of HSV (i.e., HSV-1 or HSV-2) can experience a first infection with the opposite virus type (i.e., HSV-2 or HSV-1, respectively) at a different site.

Because infections with HSV-2 are usually acquired through sexual contact, antibodies to this virus are rarely found before the onset of sexual activity.

Importantly, an ever-increasing proportion is attributable to HSV-1. The distinction in virus species is not insignificant; genital HSV-1 infections are usually both less severe clinically and less prone to recur. Sexual transmission of both viruses is the consequence of intimate contact, namely oral–genital or genital–genital.



Widespread in sexually active adults

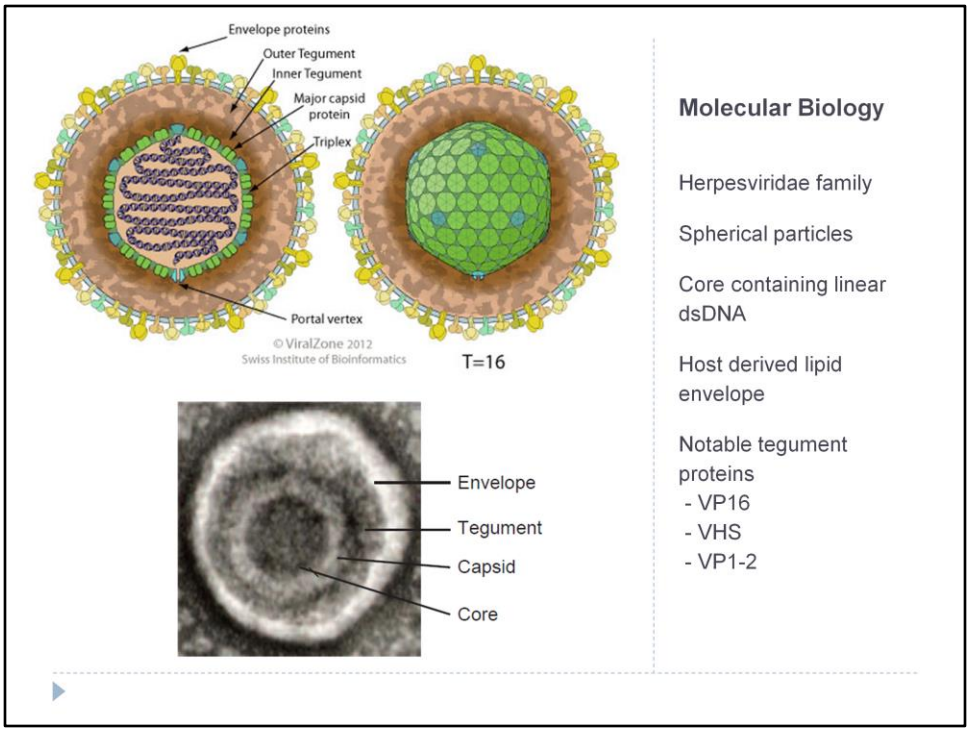


The paper the above review cites regarding Jordanian numbers:

Seroepidemiologic study of herpes simplex virus type 2 and cytomegalovirus among young adults in northern Jordan. (Jul 2000)
Abuharfeil N1, Meqdam MM.

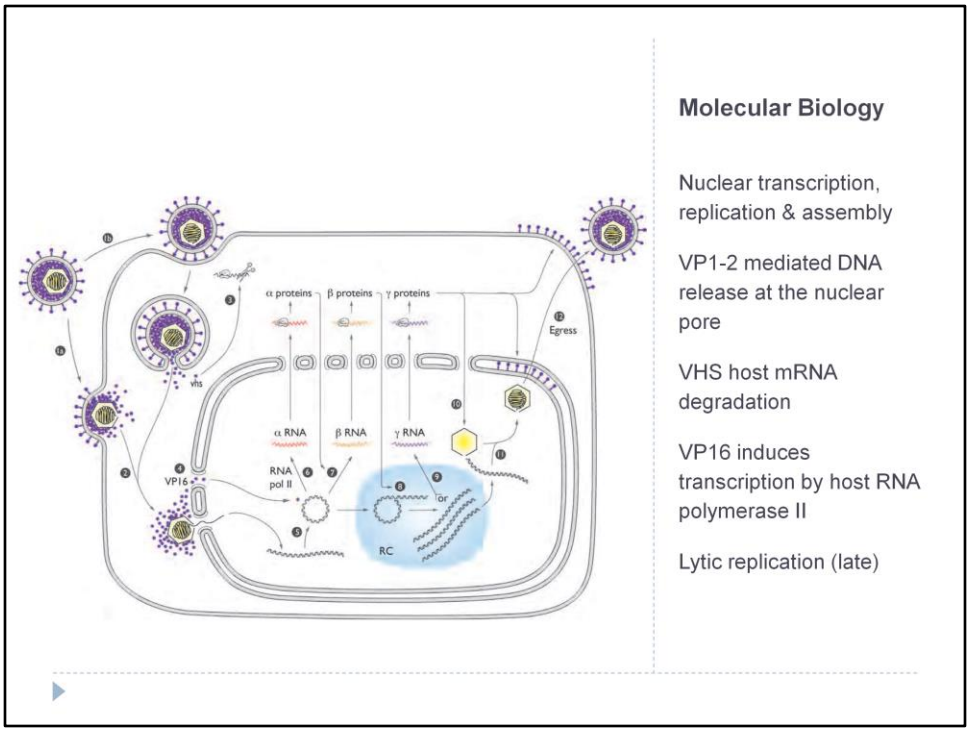
Author information
1Department of Applied Biology, Faculty of Science, Jordan University of Science and Technology, Irbid, Jordan.

Abstract
Blood samples were randomly collected from 360 males and 390 females among apparently healthy university students aged 18-24 years and tested for herpes virus type 2 (HSV-2) and cytomegalovirus (CMV) antibodies. The prevalence of HSV-2 seropositivity was 52.8% for males and 41.5% for females as detected by ELISA.



The space between the undersurface of the envelope and the surface of the capsid, designated as the tegument is comprised of at least 18 viral proteins. The most notable of the proteins associated with the tegument are the VP16 virion transactivator protein (early gene activation as well as viral assembly); the virion host shutoff (VHS) protein, which was reported to have the ability to spread cell to cell (causes degradation of host messenger RNAs); and a very large protein (VP1–2), which plays a role in DNA release at the nuclear pore during viral entry. (See next slide)

The envelope consists of a host derived lipid bilayer with viral glycoproteins embedded in it.



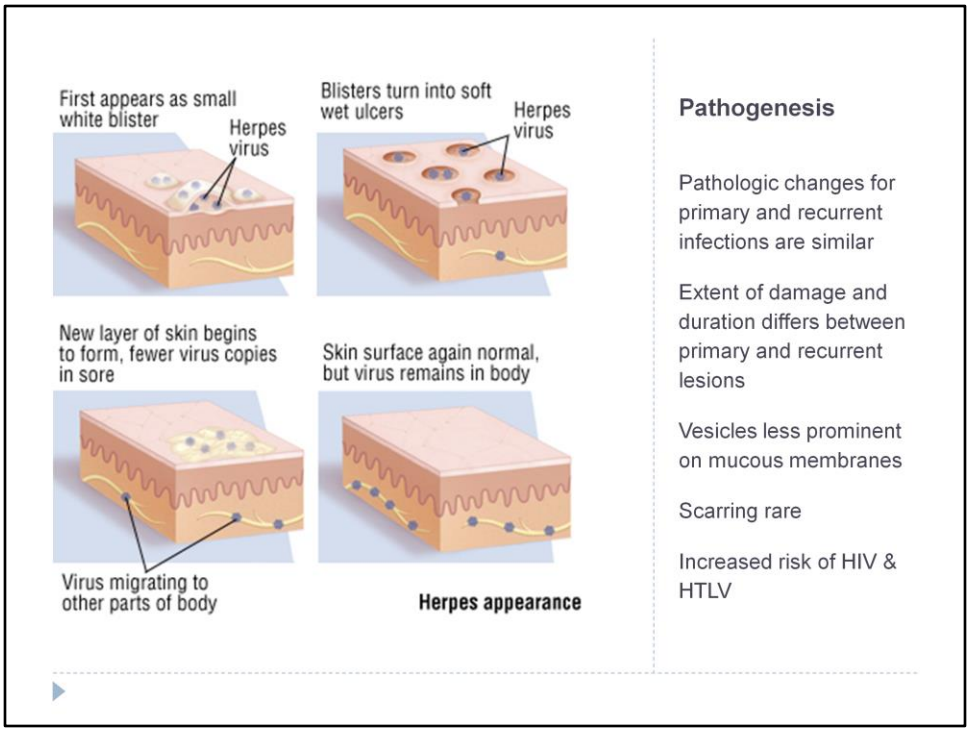
All genes are transcribed by the host RNA polymerase II. There are three temporal classes of genes: immediate-early (alpha), early (beta) and late (gamma). The immediate-early genes are transcribed immediately after infection to take control of cell defense and to activate early genes. These encode the proteins necessary for the viral DNA replication. The late genes mostly encode structural proteins. Latent genes can stop the replicative process at the early step.

1: The virus binds to the cell plasma membrane and the virion envelope fuses with the plasma membrane (1a) or the virus enters by endocytosis (1b), releasing the capsid and tegument proteins into the cytoplasm. **2:** The capsid is transported to the nuclear pore, where the viral DNA is released into the nucleus. **3:** The *vhs* protein causes degradation of host messenger RNAs (mRNAs). **4:** VP16 localizes into the nucleus. **5:** The viral DNA circularizes. **6:** It is then transcribed by host RNA polymerase II to give first the α mRNAs. α gene transcription is stimulated by the VP16 tegument protein. Five of the six immediate-early proteins act to regulate viral gene expression in the nucleus. **7:** α proteins transactivate β gene transcription. **8:** The β proteins are involved in replicating the viral DNA molecule. **9:** Viral DNA synthesis stimulates γ gene expression. **10:** The γ proteins are involved in assembling the capsid in the nucleus and modifying the membranes for virion formation. **11:** DNA is encapsidated in the capsid. **12:** The filled capsid buds through the inner membrane to form an enveloped virion, and the virion exits from the cell

Cell lysis is a very late aspect of HSV infection. There are at least three proposed pathways that the virus can egress from the cell (beyond the scope of this lecture)

The fundamental strategies of the host defenses to this invasion are threefold. First, the cytoplasmic organelles and cytosol contain an abundance of pattern recognition sensors capable of detecting virion components prior to *de novo* synthesis of viral gene products. The signal transduction pathways converge to activate in a cell type–dependent manner the antiviral gene products that include IFN-a/b and proinflammatory cytokines. Second, there are attempts to shut off the synthesis of viral genes both at the point of entry of viral DNA into the virus nucleus and immediately after the onset of synthesis of viral DNA. Third, there is an attempt to commit suicide to preclude the synthesis and dissemination of the virus in the body.

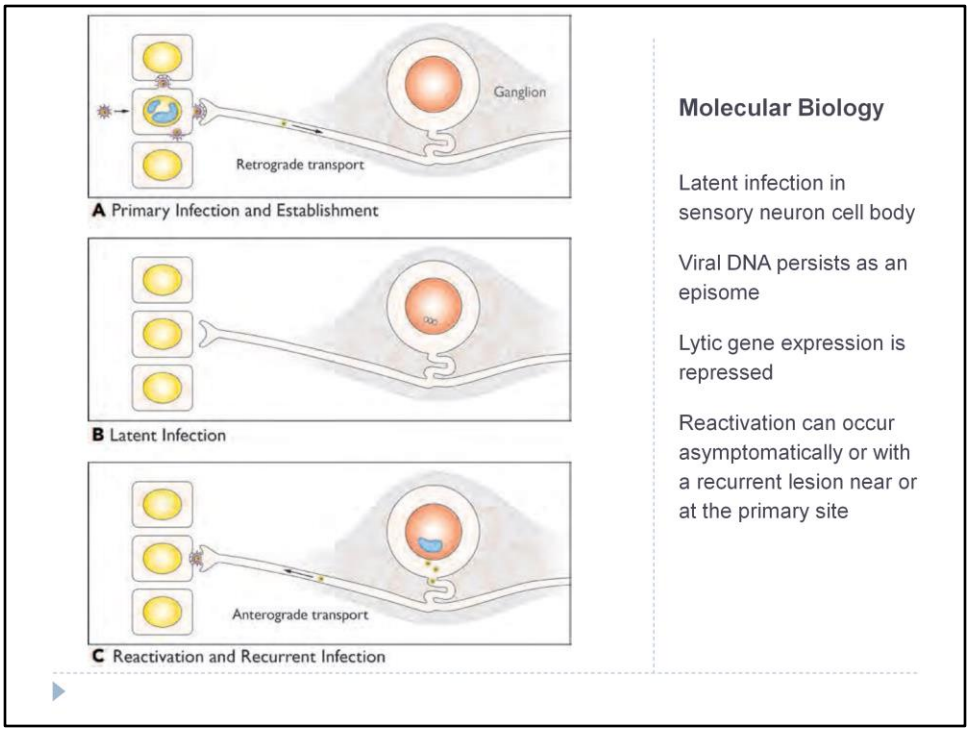
The strategy employed by the virus is to preempt any response on the part of the cell to the presence of the virus or its components. Some preemptive strikes are carried out by virion components brought into the cell during infection or made after infection. A key component of the strategy is to block any potential response by multiple mechanisms expressed by different gene products. On the basis of the number of functions directed to suppress a specific host response, the synthesis of IFN and of IFN-dependent host gene products emerge as the major targets. This is partly achieved through VHS mediated host mRNA degradation.



After acquisition of HSV infection at a mucocutaneous site, macules and papules appear, followed by vesicles, pustules, and ulcers. The pathologic changes induced by HSV replication are similar for both primary and recurrent infection but vary in the extent. Recurrent HSV-2 infection, like HSV-1, can be either symptomatic or asymptomatic. A recurrence is associated with a shorter duration of viral shedding and fewer lesions.

Pathology is a combination of virus-mediated cell death and associated inflammation. With cell lysis, clear (referred to as vesicular) fluid containing virus appears between the epidermis and dermal layer. The vesicular fluid contains cell debris, inflammatory cells, and, often, multinucleated giant cells. In dermal substructures, there is an intense inflammatory response, usually in the corium of the skin. With healing, the vesicular fluid becomes pustular with the recruitment of inflammatory cells and then it scabs. Scarring is uncommon but has been noted in some patients with frequent recurrences. When mucous membranes are involved, vesicles are less likely to be prominent. Instead, shallow ulcers are more common because the vesicles rapidly rupture as a result of the very thin cornified epithelium.

HSV-2 infection, by the nature of being an ulcerative disease, is associated with increased risk of acquisition of both human immunodeiciency virus type 1 (HIV-1) and human T-cell lymphotropic virus type 1 (HTLV-1).

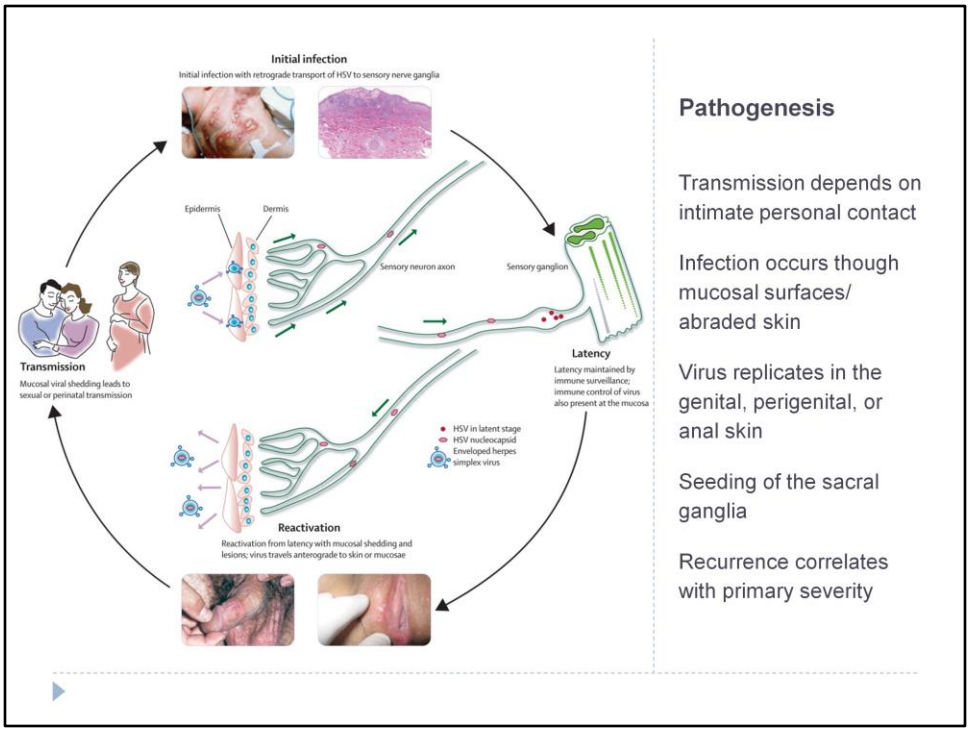


A: HSV is introduced onto a mucosal surface or a break in the skin, and it replicates productively in epithelial cells at the site of inoculation and spreads through the tissue. Virus enters sensory neuron axons and is transported to the cell body in a ganglion. **B:** HSV establishes a latent infection in the neuronal cell nucleus. Viral DNA is circular and assembled in chromatin. **C:** Upon neuronal damage or activation, the virus reactivates and undergoes at least a limited productive cycle. Capsids are transported by anterograde transport to the axonal termini, and virions are released. Reactivated virus causes a recurrent infection of the mucosal tissue, causing the shedding of virus.

CD8+ T cells have been shown to play an essential role in control of HSV replication in the nervous system and in controlling viral replication in the ganglia during acute times of infection. IFN-γ can also block viral gene expression and replication.

In humans, latent virus is reactivated after local stimuli such as injury to tissues innervated by neurons harboring latent virus, or by systemic stimuli such as physical or emotional stress, hyperthermia, exposure to UV light, menstruation, and hormonal imbalance, which may reactivate virus simultaneously in neurons of various ganglia (e.g., trigeminal and sacral). A modest amount of evidence and the most plausible common denominator is that injury or stimulation of cells innervated by dorsal root neurons harboring latent virus is a common trigger of recrudescence of lesions caused by reactivated virus.

No replicating virus can be detected in the sensory ganglia during latent infection. However, the ability of sensitive PCR tests to measure HSV
DNA in genital secretions has led to the detection of frequent viral DNA shedding in the genital tract of both asymptomatic and symptomatic individuals. This frequent shedding has led to questions about whether HSV latent infection is actually a low level chronic infection producing constant shedding of virus rather than a true latent infection.

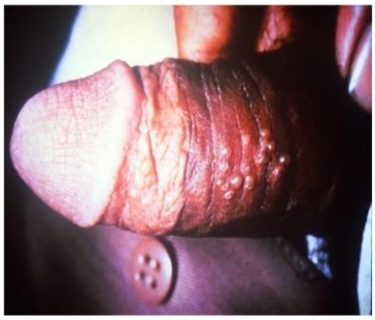


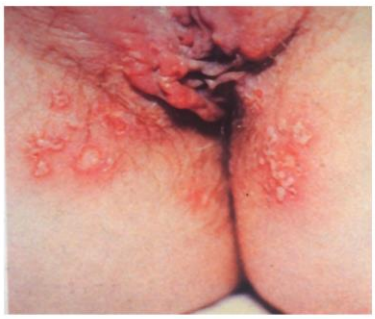
HSV is transmitted when the virus comes into contact with a mucosal surface or broken skin of a susceptible host. Such transmission requires direct contact with an infected person, because the virus is readily inactivated at room temperature, particularly if dried.

Accumulated clinical experience suggests that after primary infection, replication of virus at the portal of entry, usually oral or genital mucosa, results in infection of sensory nerve endings; virus is transported to dorsal root ganglia. Rarely, replication can sometimes lead to disease and
can infrequently result in life threatening CNS infections.

Primary infection can spread beyond the dorsal root ganglia, thereby becoming systemic. Multiorgan disease is encountered in disseminated neonatal HSV infection, visceral organ disease of pregnancy, and, rarely, in immunosuppressed patients.

The more severe the primary infection, as reflected by the size, number, and extent of lesions, the more likely it is that recurrences will ensue.





Clinical Features (Primary/initial)

Wide range of manifestations from asymptomatic to life threatening

First episode patients typically have locally painful vesicular lesions (frequently bilateral)

Itching prodrome

Local complications of dysuria, discharge

Mild systemic manifestations

As mentioned earlier, both HSV-1 and HSV-2 can cause genital or oral infection, and both can produce primary or recurrent mucocutaneous lesions that are clinically indistinguishable. The manifestations of HSV infection vary considerably, depending on whether the infection is primary or recurrent. HSV disease ranges from the usual case of mild illness, nondiscernible in most individuals, to sporadic, severe, and life-threatening disease in a few infants, children, and adults.

Primary infection with HSV-2 often is mildly symptomatic. In persons experiencing their first episode, locally painful vesicular lesions are often accompanied by dysuria, urethral discharge, local lymph node enlargement and tenderness, and systemic manifestations, such as fever, muscle aches, and headache. HSV is actively shed during this period and continues to be shed until the mucosal lesions have completely healed
(typically 3 weeks). Signs and symptoms may last for several weeks during the primary phase of disease. Complications of primary genital herpetic infection have included sacral radiculomyelitis, which can lead to urinary retention, neuralgias, and meningoencephalitis. In immunocompetent adults, herpes genitalis generally is not life-threatening. However, HSV does pose a major threat to immunosuppressed patients, in whom fatal, disseminated disease may develop.

Nonprimary but initial genital infection (i.e., occurring in an individual with pre-existing antibody) is less severe symptomatically and heals more quickly than primary

infection. The duration of disease is approximately 2 weeks. The number of lesions, severity of pain, and likelihood of complications are significantly decreased.

In males, the lesions may occur on the glans, on the penile shaft, on the inner thigh, buttocks, or anus. Primary perianal and anal HSV-2 infections, as well as associated proctitis, are common in male homosexuals.

In females, lesions may occur on the cervix, on or near the pubis, labia, clitoris, vulva, buttocks, or anus.

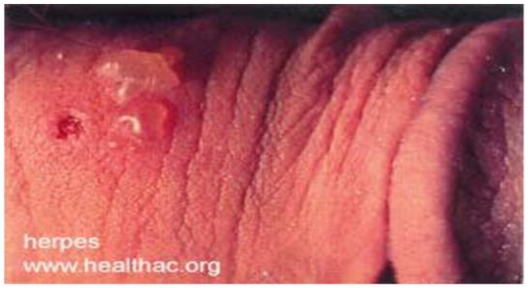
Complications

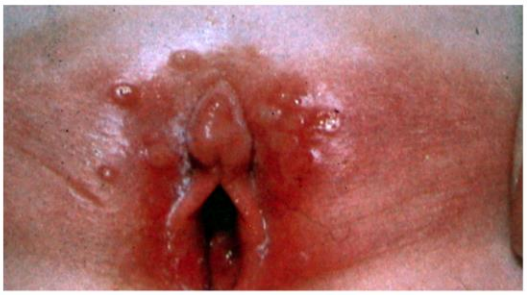
Physiological

- Aseptic meningitis
  - More common in primary than recurrent infection
  - Generally no neurological sequelae
- Rare complications include:
  - Stomatitis and pharyngitis
  - Radicular pain, sacral parathesias
  - Transverse myelitis
  - Autonomic dysfunction

Psychological

- A diagnosis of genital herpes can induce negative feelings related to the condition. Though these feelings lessen over time, they can include:
  - Depression
  - Fear of rejection
  - Feeling isolated
  - Fear of disclosure/discovery
  - Self-destructive tendencies





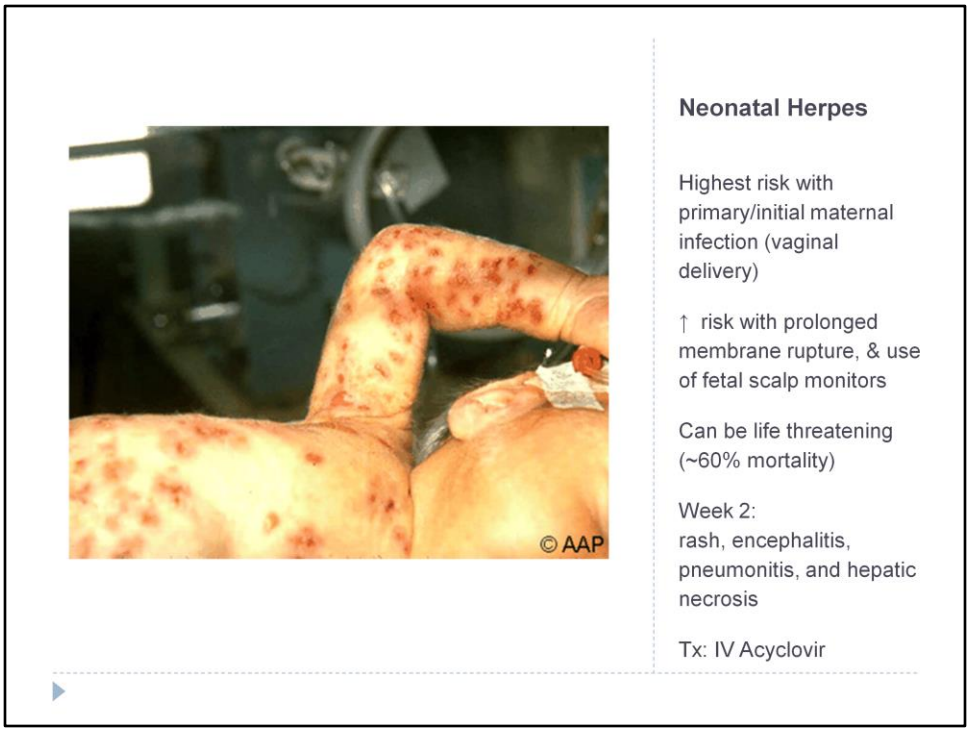
Clinical Features (Recurrent)

- Mildest form
- Shorter duration (7-10 days)
- Fewer lesions
- Systemic & neurologic manifestations are uncommon
- Lymphadenopathy is uncommon
- Recurrence depends on serotype and can vary widely

Recurrent genital herpes is the mildest form of disease. With recurrent genital herpetic infection, a limited number of vesicles, usually three to five, appear on the shaft of the penis of the male or as simply a vulvar irritation in the female. The duration of disease is approximately 7 to 10 days and parallels that encountered with recurrent HSV labialis. Neurologic or systemic complications are uncommon with recurrent disease; however, paresthesias and dysathesias can occur.

The extent of viral replication is different for recurrent infection as compared with primary infection. Virus is shed for an average of only 2 to 5 days and at lower concentrations.

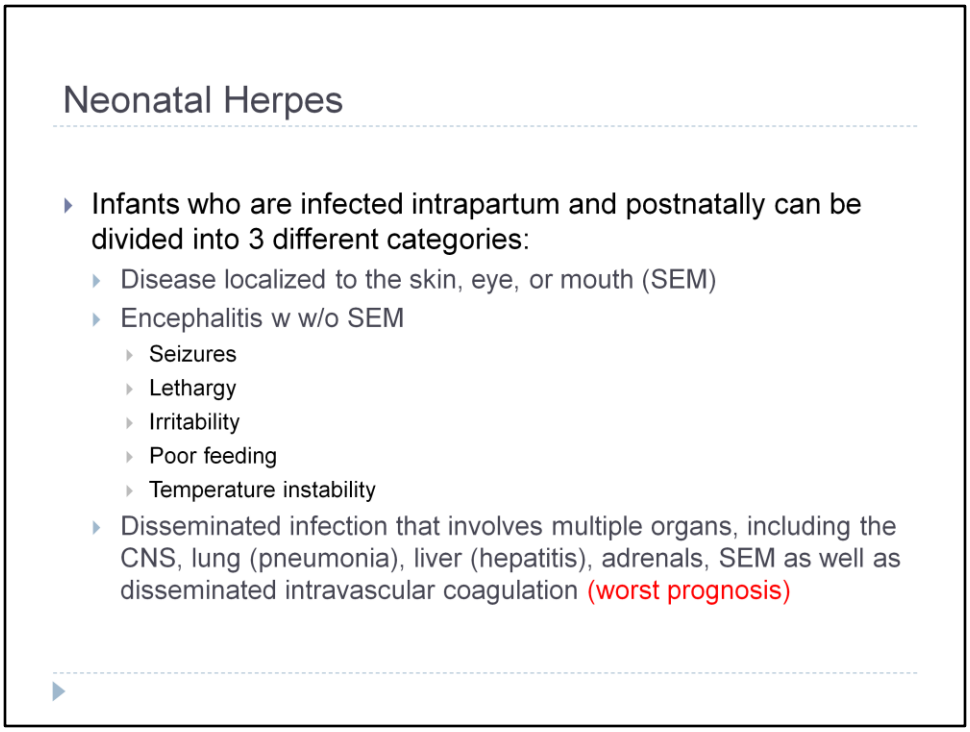
Some individuals experience their first-episode genital infection years after an asymptomatic or atypical primary infection. In such circumstances, disease can be as severe as true primary infection.



Also life-threatening is *neonatal herpes infection,* which occurs in about half of infants delivered vaginally of mothers suffering from either primary or recurrent genital HSV infection. The viral infection is acquired during passage through the birth canal. Its incidence has risen in parallel with the rise in genital HSV infection. *The manifestations of neonatal herpes, which typically develop during the second week of life, include rash, encephalitis, pneumonitis, and hepatic necrosis.* Approximately 60% of affected infants die of the disease, with significant morbidity occurring in about half of the survivors.

At least four factors influence transmission of infection from mother to fetus. First, the major risk to the fetus is maternal primary or initial genital HSV infection. If a pregnant woman experiences initial or primary genital infection in the last trimester of gestation, the likelihood of transmission to the fetus is between 30% and 50%. On the other hand, recurrent maternal infection is associated with a rate of transmission of 3% or less. Primary infection is associated with (a) larger quantities of virus replicating in the genital tract and (b) a period of viral excretion that may persist for an average of 3 weeks. Second, transplacental maternal neutralizing and antibody-dependent cell-mediated cytotoxic antibodies appear to have at least an ameliorative effect on acquisition of infection and disease presentation. Third, prolonged rupture of membranes (>6 hours) increases the risk of acquisition of virus. Fourth, certain forms of medical intervention in the labor and delivery suites may increase the risk of neonatal HSV infection, including the use of fetal scalp monitors.

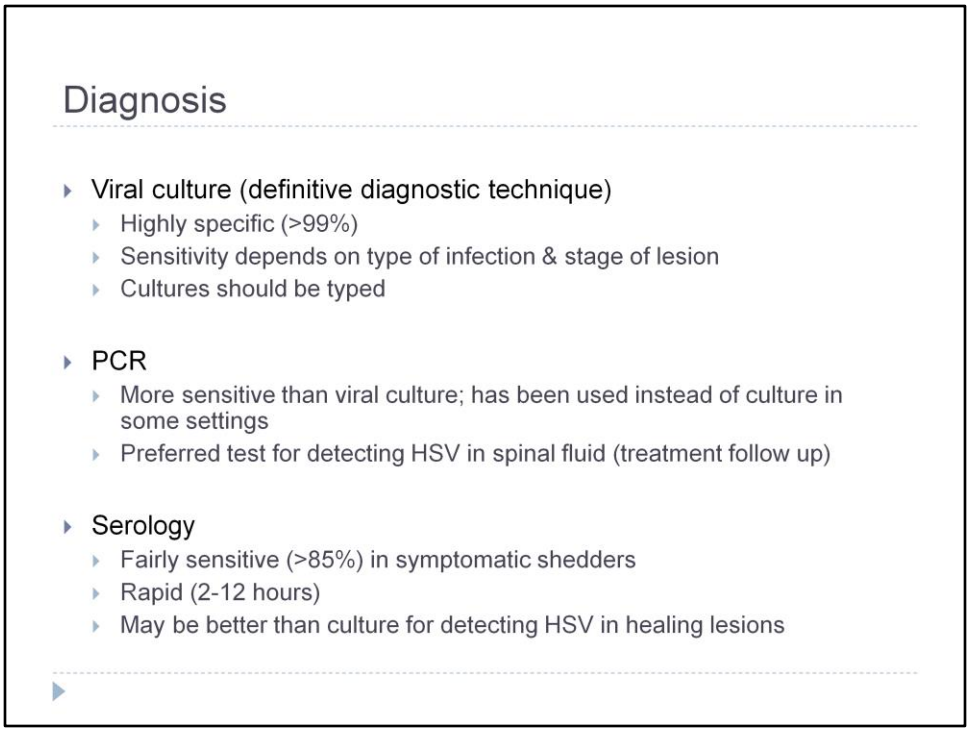
The baby may also be infected from other sources such as oral lesions from the mother or a herpetic whitlow in a nurse.



Factors that predict a poor outcome include disseminated intravascular coagulopathy and prematurity for those babies with disseminated
neonatal herpes, whereas for those with encephalitis seizures and prematurity predict a poor neurologic outcome.

Congenital infection

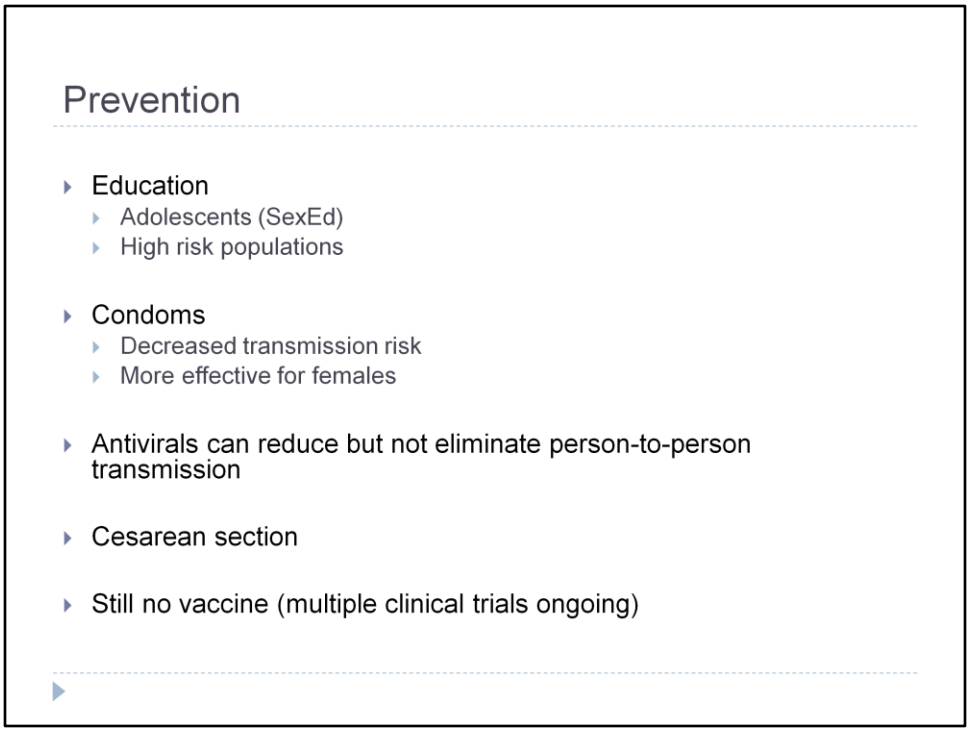
In utero infection can occur as a consequence of either transplacental or ascending infection. The incidence has been estimated to be 1 in 200,000 deliveries. Placental necrosis and inclusions in the trophoblast can occur. Intrauterine infection is characterized by the triad of skin vesicles or skin scarring, eye disease (chorioretinitis or microphthalmia), and the far more severe manifestations of microcephaly or hydranencephaly.



Every effort should be made to confirm infection by viral isolation or PCR detection of viral DNA. Virus isolation is a definitive diagnostic method; however, PCR detection of viral DNA has gained increased acceptance even for routine skin infections, replacing culture in most laboratories. PCR evaluation of cerebrospinal fluid can be used to follow therapeutic outcome in patients with HSV encephalitis. Persistence of HSV DNA in the cerebrospinal fluid of newborns with HSV encephalitis at the completion of antiviral therapy predicts poor neurologic outcome.

Cytopathologic detection of evidence of infection is less rewarding. These methods have a sensitivity of only approximately 60% to 70% in babies, and slightly higher in adults, and therefore should not be the sole diagnostic determinant of infection. The demonstration of intranuclear inclusions and multinucleated giant cells are indicative, but not diagnostic, of HSV infection. Electron microscopic assays have limited use.

Serologic diagnosis of HSV infection is clinically valuable in the counselling of patients regarding genital herpes provided that the assays are type specific.



Because of the increased awareness of genital herpes and neonatal herpes and its association with increased risk of acquisition of HIV, every effort should be made to prevent HSV-2 infections. Until a vaccine is proven efficacious, educational efforts must be developed for adolescents
and those at greatest risk. The use of condoms should be promoted, as use significantly decreases the probability of acquiring genital HSV infection. Condoms are more effective in the prevention of infection of females than males. Valacyclovir has been demonstrated to decrease but not totally prevent person-to person transmission of genital herpes in discordant couples.

Surgical abdominal delivery is associated with the decreased transmission of infection when membranes are ruptured less than 4 hours; however, cesarean section has not been proven efficacious when membranes are ruptured for longer periods of time.

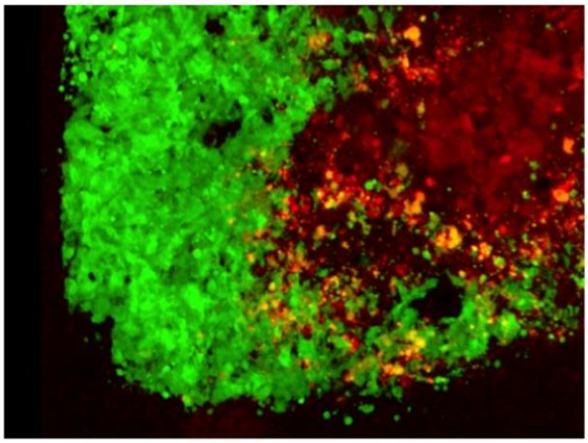
Treatment

- No cure (erradication/prevent recurrence)
- Non-prescription analgesics can reduce pain and fever during initial attacks

Infection	Drugs	Adult dosage[a]
Genital		
First episode	Acyclovir	400 mg PO tid or 200 mg PO 5×/d × 7–10 d[b]
	Famciclovir	250 mg PO tid × 7–10 d
	Valacyclovir	1 g PO bid × 7–10 d
Episodic treatment of recurrences	Acyclovir	800 mg tid or 400 mg PO tid × 3–5 d
	Famciclovir	125 mg PO bid × 5 d
	Valacyclovir	500 mg PO bid × 3 d
Suppression of recurrences	Acyclovir	400 mg PO bid
	Famciclovir	250 mg PO bid
	Valacyclovir	500 mg or 1 g PO 1×/d
Encephalitis	Acyclovir	10–15 mg/kg IV q8h × 14–21 d
Neonatal	Acyclovir	20 mg/kg IV q8h × 14–21 d

Today, acyclovir and its prodrug valacyclovir, as well as the prodrug of penciclovir, famciclovir, are the most useful and widely used therapeutics
for the treatment of HSV infections. Both valacyclovir and famciclovir have a distinct advantage over acyclovir. Specifically, the oral bioavailability of acyclovir following valacyclovir administration allows for improved pharmacokinetics. The same case is also made of plasma levels of penciclovir following famciclovir administration.

Although these medications significantly reduce the frequency of recurrences, and therefore the probability of reactivation, periodic excretion of virus still occurs during suppressive therapy and can result in person-to-person transmission of infection.



Stem cells loaded with cancer-killing herpes virus attack a brain tumor cell. Tumor cells in green. oHSV-loaded stem cells in red. oHSV-infected tumor cells in yellow. (Credit: Khalid Shah/MGH)

Special topic

ONCOLYTIC HERPES SIMPLEX VIRUS THERAPY

Engineered virus with reduced neurovirulence

Multiple trials at various stages

For the most part engineered HSV has been safe in humans

Some trials are promising with clear efficacy

http://hsci.harvard.edu/news/herpes-loaded-stem-cells-used-kill-brain-tumors

Genetically engineered HSVs have mainly been assessed for the treatment of human glioblastoma multiforme.

Engineered HSV constructs have been proven consistently safe when administered intracranially to humans at high doses. With some constructs, suggestions of efficacy are apparent. Likely, no one construct or approach will cure all tumors. Future work will need to improve replication competence without sacrificing safety & improved delivery.