

Herpes simplex virus (oral herpes)

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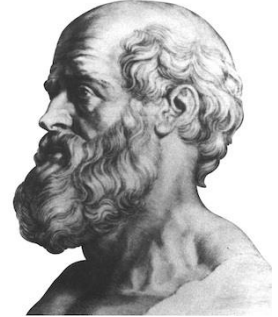
1. Introduction

1.1. History of the disease :

Herpes Virus Infections have been prevalent as early as ancient Greek times. Hippocrates is known to have described the cutaneous spreading of herpes simplex lesions and scholars of Greek civilization define **the greek word "herpes" to mean "to creep or crawl" in reference the spreading nature of the herpetic skin lesions.**

Herpes in Greece Herpes was first formally recognized by Hippocrates (460 to 370 BCE), who wrote about the symptoms of herpes lesions.

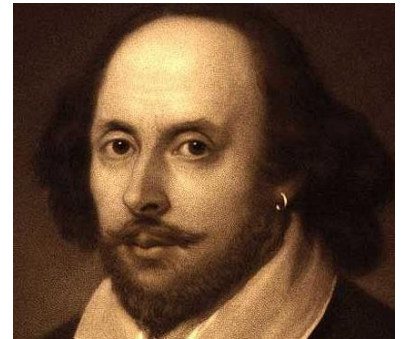
Herpes in Rome Later on, in Roman times, the Roman Emperor Tiberius tried to quell an oral herpes outbreak by banning kissing at public celebrations, events, and ceremonies. A Roman physician named Celsus developed a **treatment method** for herpes that involved **cauterizing open herpes lesions with a hot iron.**



Herpes and Shakespeare (1500's to 1600's)

It is believed that Shakespeare mentioned oral herpes in Romeo and Juliet:

*"O'er ladies" lips Which oft the angry Mab with blisters
plagues, Because their breaths with sweetmeats tainted
are. Act 1. Scene IV"*



Apparently, herpes was recognized but not well understood in Shakespeare's time. Eating sweetmeats (confections) will not give you oral herpes, nor will an imaginary fairy named Queen Mab.

Herpes in the 1800's

- In 1893, French scientist Emile Vidal proved through experimentation that herpes was transmitted from one person to another.
- In 1884 Louis Duhring, an American dermatologist, confirmed that herpes was different from eczema and pemphigus, which are non-contagious skin conditions.

- Two years later, in 1886, French doctors Charles-Paul Diday and Adrien Doyon published a full-length book about herpes called "The Genital Herpes."
- Viruses were discovered by Dmitri Ivanovski in Russia in 1893. Although Ivanovski was studying tobacco viruses, not herpes viruses, his research later became important for studying herpes.
- In 1896 German physician Paul Unna develops a way to differentiate herpes from syphilis under a microscope. This is important because previously it was not possible to identify the difference between herpes and syphilis since they often occurred concurrently.

Herpes in the 1900's

- 1913: Wilhelm Grater, a German ophthalmologist, is able to transmit the herpes virus from an infected person to the cornea of a rabbit and back again to a human . This is named the Grater test, which is used to diagnose herpes until the 1940's.
- In 1925 an American virologist, Ernest Goodpasture, proves that the herpes virus travels through the nerves, not the blood.
- In 1939, Frank LacFarlane Burnet, an Australian microbiologist, develop the theory of latency, or the fact that the herpes virus resides in the ganglions while there are no symptoms. In 1971 scientists Jack Stevens and Marjorie Cook prove it.
- A French scientist, Arnaud Tzanck develops cryto-diagnosis for herpes, which replaces the Grater test.
- In 1978, the first anti-viral drug, Acyclovir, that was safe, non-toxic, and effective is tested in humans. It was developed by Gertrude Elion, and three years later was available commercially.

1.2.Introduction of the virus:

Herpes simplex virus (HSV) commonly causes infections of the skin and mucous membranes. Sometimes it can cause more serious infections in other parts of the body. HSV is one of the most difficult viruses to control and has plagued mankind for thousands of years.



Herpes simplex is part of a group of other herpes viruses that include human herpes virus 8 (the cause of Kaposi's sarcoma) and herpes zoster

(the virus responsible for shingles and chicken pox). There are more than 80 types of herpes viruses. They differ in many ways, but the viruses share certain characteristics, **There are two forms of the herpes simplex virus:**

(1) Herpes simplex virus 1 (HSV-1)

occur in the oral cavity (mouth) and are not sexually transmitted

(2) Herpes simplex virus 2 (HSV-2)

attacks the genital area and is sexually transmitted

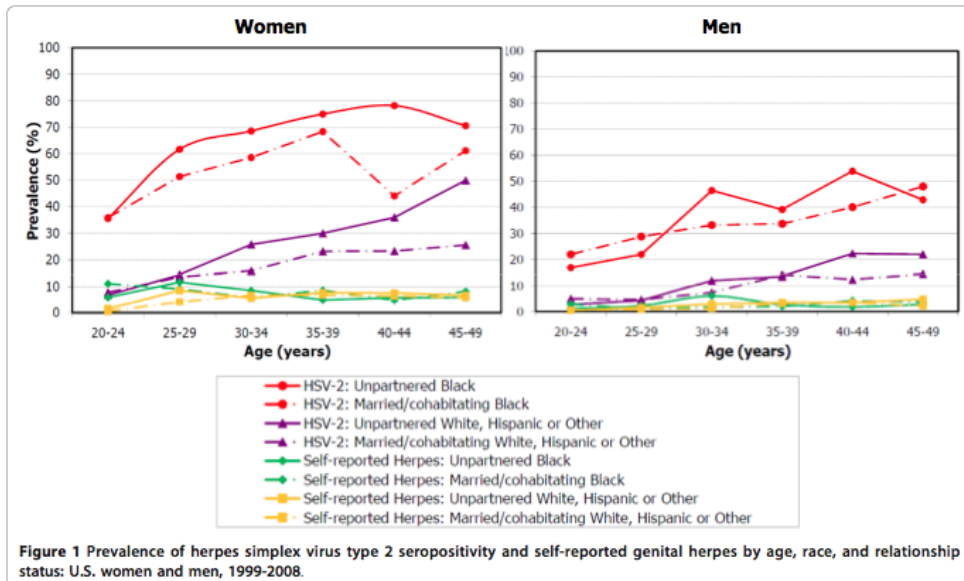
1.3. the distribution of this disease

The herpes simplex 1 genomes can be classified into six clades. Four of these occur in East Africa, one in East Asia and one in Europe and North America. This suggests **that the virus may have originated in East Africa**. The most recent common ancestor of the Eurasian strains appears to have evolved ~60,000 years ago. The East Asian HSV-1 isolates have an unusual pattern that is currently best explained by the two waves of migration responsible for the peopling of Japan.



1.4.epidemic

BY GENDER Herpes is more common in women than men, infecting approximately one out of four women, versus one out of five men. This difference in gender may be because male-to-female transmission is more efficient than transmission from females to males.



BY

REGION Herpes is common in all regions of the country and in both urban and rural areas. There are no significant differences in prevalence by geographic location.

BY AGE The percent of people infected with herpes increases with age because, once infected, people remain infected with this incurable disease throughout their lives. According to two national surveys between the 1970s and the 1990s, herpes increased fastest among white teens ages 12 to 19 years old. Herpes prevalence among white teens ages 12 to 19 years old in the 1990s was five times greater than the prevalence in the 1970s.

classification of the virus:

2.1 order

Herpesvirales,

2.2 family

Herpesviridae,

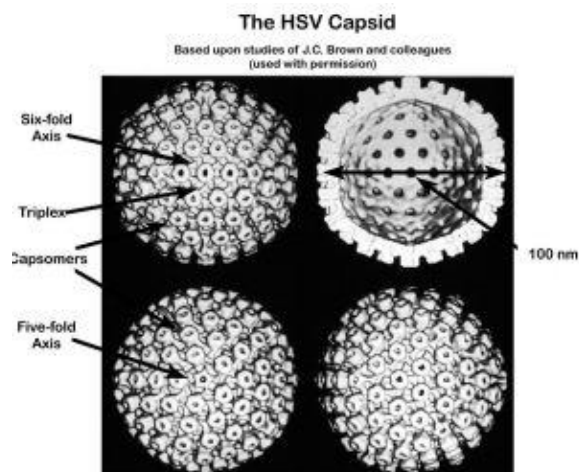
2.3 genus

Simplexvirus

2. structure and genome:

2.1. shape ,size and envelope

Herpesviruses have a unique four-layered structure: a core containing the large, double-stranded DNA genome is enclosed by an icosapentahedral capsid which is composed of capsomers and is considered to be relatively large for a virus, with virions ranging from 120 nm (nanometres) to 300 nm in size. The capsid is surrounded by an amorphous protein coat called the tegument. It is encased in a glycoprotein-bearing lipid bilayer envelope contains at least 8 glycoproteins. The matrix or tegument which contacts both the envelope and the capsid contains at least 15-20 proteins.



2.2.nucleic acid

The HSV-1 genome is a linear, double stranded DNA duplex 152,000 base pairs in length, and with a base composition of 67% G + C. The genome circularizes upon infection. Because the genome circularizes, the transcription and genetic map is conveniently shown as a circle

The HSV genome can be divided into six important regions:

- 1- one These are important in both **circularization of the viral DNA**, and in packaging the DNA in the virion.
- 2- Two which encode **regulatory protein and the promoter** .
- 3- The long unique region .It contains genes for **the DNA replication enzymes and the capsid proteins**.
- 4- Four encode protein witch is a very **powerful transcriptional activator**.
- 5- **the origins of replication**. region.very complicated replication complex-- very similar to that seen in the replication of phage T4.
- 6- Six which are glycoproteins important in **viral host range and response to host defense**.

3. Proteins (virulence factors):

3.1.Structural proteins and their function

HSV has an ability to cause the permanent infection in a patient's life by **replicating viral DNAs** and releasing them. Therefore:

HSV can turn off the immune system (interferon, natural killer cells, cytotoxic T cells, macrophages, etc.) by coating viruses with immunoglobulin

For example, gC (herpes glycoprotein) can bind the C3 protein, as well as gE and gI (herpes glycoproteins) can bind IgG through the Fc receptor of the immunoglobulin.

virus can also escape from humoral antibodies in extracellular space by moving directly from cell to cell . During the latency period, **nucleic acid of HSV finds a secure place in the nerves around the infected area**, so that it reduces the risk of losing or misplacing their daughter cells.

UL43	Membrane protein
UL49A	Envelope protein
VP5	Major capsid protein

Non-structural proteins

VP19C	Capsid assembly and DNA maturation
Terminase	Processing and packaging of DNA
DNA polymerase	DNA replication

4. Transmission

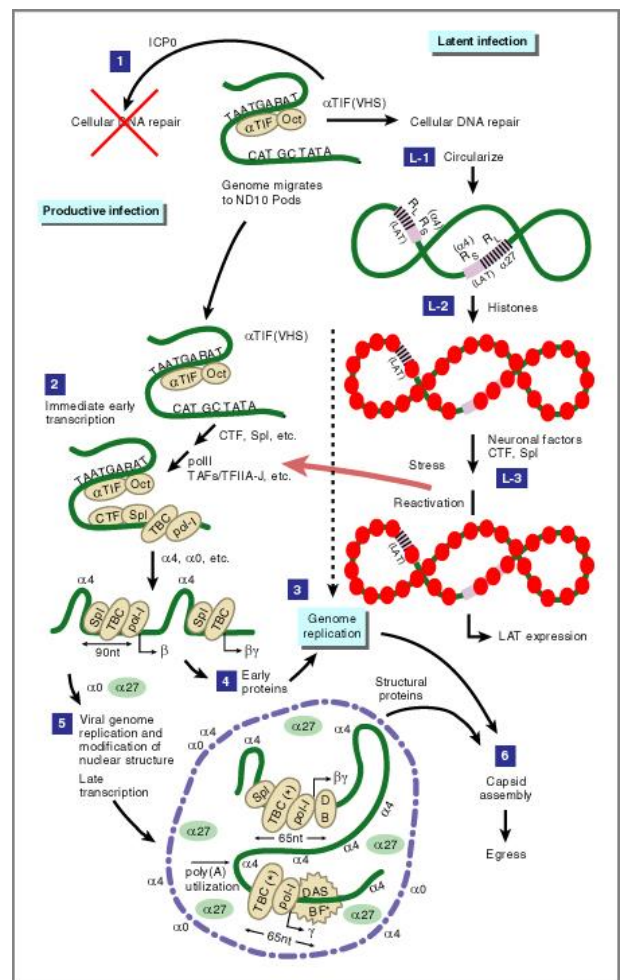
the herpes simplex viruses must get into the body **through broken skin or a mucous membrane**. Each virus can be carried in bodily fluids (saliva, semen, fluid in the female genital tract) or in fluid from herpes sores. Once the virus has **contact it begins to replicate**. However, at some point, it often begins to multiply again **without causing symptoms** (called asymptomatic shedding). **During shedding, the virus can infect other** people through exchange of bodily fluids.

Sometimes, infected people can transmit the virus and infect other parts of their own bodies. This process, known as autoinoculation

5. Penetration and the target organ

The target organ is the upper area of the body specially the face (mouth inside and outside and around the eye or in between them)

Upon infecting a cell, HSV is immediately faced with an important "decision", whether to proceed to **productive infection or whether to establish a latent infection**. viral DNA migrates to nuclear pods it is either circularized by cellular DNA repair enzymes acting on the "a" sequences or remains linear through the action of the immediate-early ICP0 protein, which inhibits cellular DNA repair.



Initial Steps in infection--**virus entry**

Virus entry requires sequential interaction between specific viral membrane glycoproteins and cellular receptors.

Upon entry the nucleocapsid is transported to the nuclear pores, where viral DNA is released into the nucleus. The viral genome is accompanied by the α -TIF protein which functions in enhancing immediate early viral transcription via cellular transcription factors.

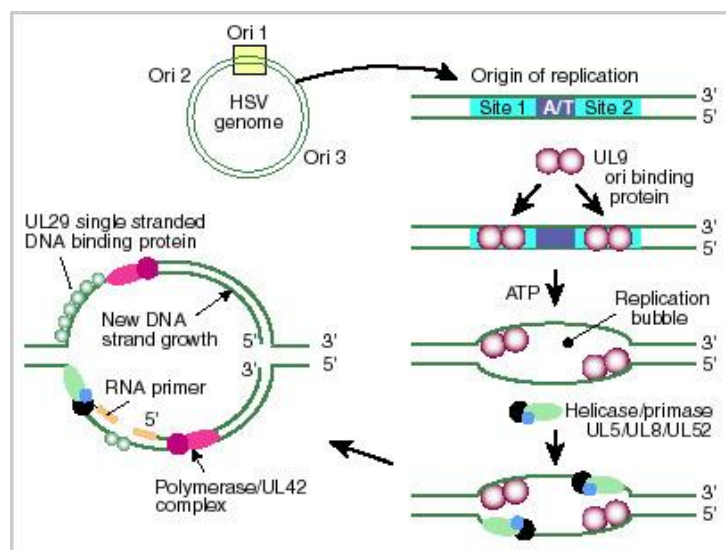
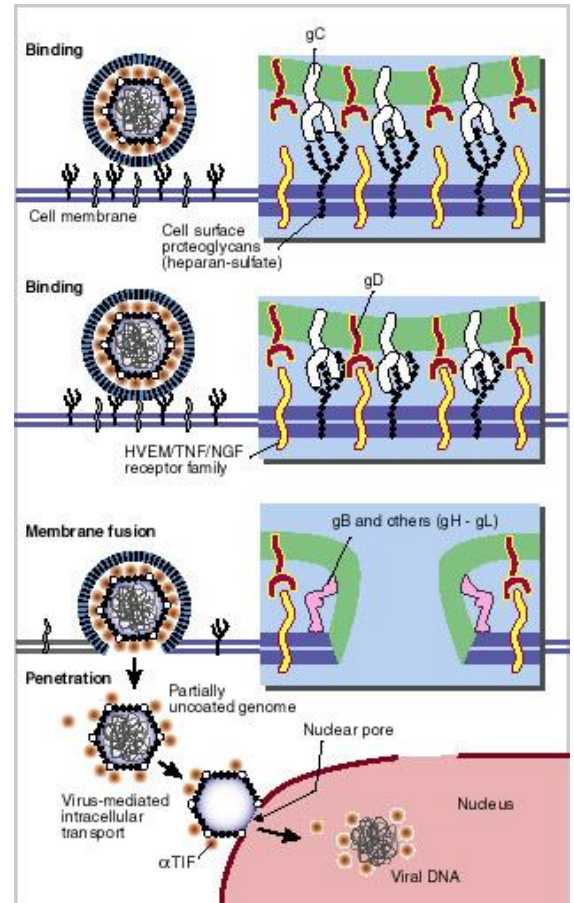
6. Replication cycle (the main site)

Seven enzymes are necessary and sufficient for viral DNA replication under all conditions:

DNA polymerase (UL30), DNA binding proteins (UL42 and UL29 or ICP8), ORI binding protein (UL9), and the helicase/primase complex (UL5, 8, and 52).

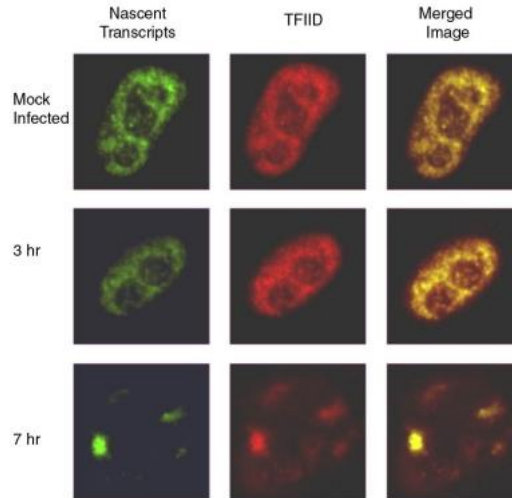
When sufficient levels of these proteins have accumulated within the infected cell, viral DNA replication ensues.

Other early proteins are involved in **increasing the deoxyribonucleotide pools** of the infected cells, while still others appear to function as **repair enzymes for the newly synthesized viral genomes**.

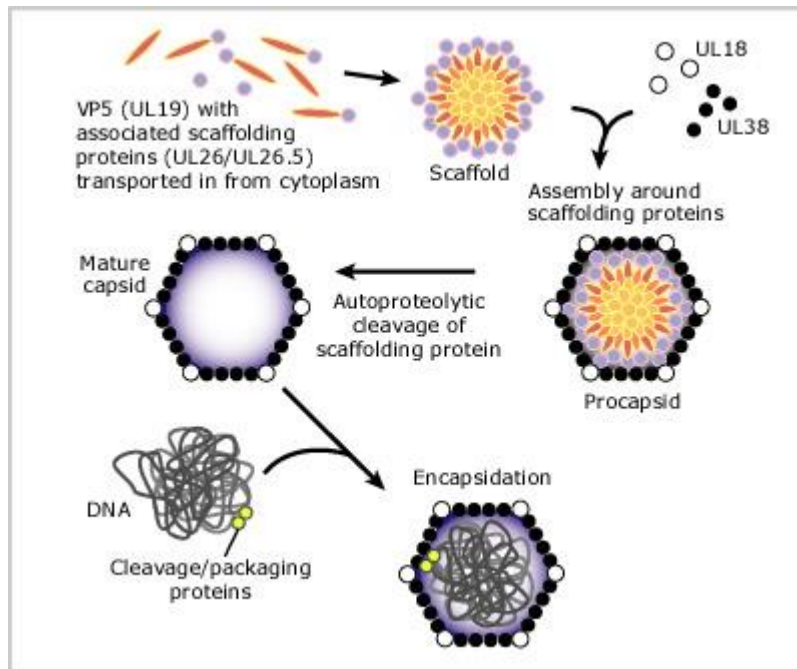


Genome replication and late gene expression

The vegetative **replication of viral DNA** represents a critical and central event in the viral replication cycle. High levels of DNA replication irreversibly commit a cell to **producing virus**, which eventually results in **cell destruction**.



7. Assembly and egression

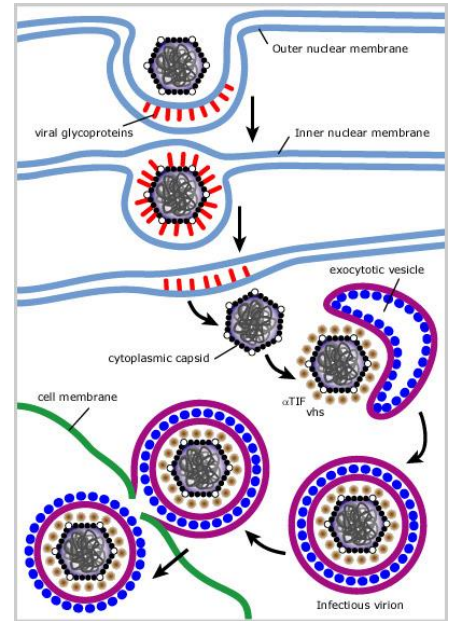


More than 30 HSV-1 gene products are structural components of the virion

HSV capsids assemble around viral scaffolding proteins **in the nucleus**, and then other viral proteins interact with replicated viral DNA to allow DNA encapsidation. The **full capsids** presumably associate with tegument (matrix) proteins **near the nuclear membrane**.

Virus Envelopment and Release

The **viral membrane formation is by a double envelopment process**. **Mature capsids bud through the inner nuclear membrane that contains viral glycoproteins**. In the early maturation process in the nucleus, capsids appear to be surrounded by **the primary tegument protein**, and this directs the budding through **the inner nuclear membrane**. These primarily enveloped capsids **bud through the outer nuclear membrane where the primary envelope is lost**. The **cytoplasmic capsids** then **associate** with the numerous **tegument proteins** of the mature virion, which interact to help **final envelopment**. then **bud into exocytotic vesicles**,



8. Symptoms

It usually affects the lips. In some primary attacks, the mucous membranes in the mouth. A herpes infection may occur on the **cheeks or in the nose**, but facial herpes is **very uncommon**.

If the primary (initial) oral infection causes symptoms, they can be **very painful, particularly in small children**.



- **Blisters on the lips or tongue.**
- **The blisters, painful open sores, develop a yellowish membrane and disappear within 3 - 14 days.**
- **Increased salivation and bad breath.**
- **Rarely, the infection may be accompanied by difficulty in swallowing, chills, muscle pain, or hearing loss.**

9. Diagnosis and cytopathic effect

The herpes simplex virus is usually identifiable by its characteristic lesion: A thin-walled blister on an inflamed base of skin. many patients who carry the

virus do not have visible genital or oral lesions. Laboratory tests are needed to confirm a herpes diagnosis. These tests include:

- *Virologic* tests (viral culture of the lesion)
- *Serologic* tests (blood tests that detect antibodies)

Virologic Tests

Viral culture tests are made by taking a fluid sample, or culture, from the lesions as early as possible, ideally within the first 3 days of the outbreak. The viruses, if present, will reproduce in the culture but may take 1 - 10 days to do so. If infection is severe, testing technology can shorten this period to 24 hours, but speeding up the test may make the results less accurate. Viral cultures are very accurate if lesions are still in the clear blister stage, but they do not work as well for older ulcerated sores, recurrent lesions, or latency. At these stages the virus may not be active enough to reproduce sufficiently to produce a visible culture.

Polymerase chain reaction (PCR) tests are much more accurate than viral cultures,

An older type of virologic testing, the Tzanck smear test, uses scrapings from herpes lesions. The scrapings are stained and examined under a microscope. The test is quick but accurate only 50 - 70% of the time. It cannot distinguish between virus types or between herpes simplex and herpes zoster. The Tzanck test is not reliable for providing a conclusive diagnosis of herpes infection and is not recommended by the CDC.

Serologic Tests

Serologic (blood) tests can identify antibodies that are specific for either herpes virus simplex 1 (HSV-1) or herpes virus simplex 2 (HSV-2). When the herpes virus infects someone, their body's immune system produces specific antibodies to fight off the infection. If a blood test detects antibodies to herpes, it's evidence that you have been infected with the virus, even if the virus is in a non-active (dormant) state. The presence of antibodies to herpes also indicates that you are a carrier of the virus and might transmit it to others.

Serologic tests are most accurate when performed 12 - 16 weeks after exposure to the virus.

10. Control the virus and prevention

Unfortunately, once you get the herpes virus you are stuck with it. There is as of now no cure for the virus, but there are many ways of controlling and treating it with and without medications. To help control the frequency of

outbreaks one needs to lead a healthy life. Outbreaks can occur from poor diet, stress, anger, or even too much sun exposure

To reduce the chance of acquiring HSV-1, avoid touching saliva, skin, or mucous membranes of people who have HSV-1 lesions. Prevention of genital HSV may be accomplished by latex condoms, but protection is never 100%. Spermicides do not protect against HSV. Some clinicians recommend using dental dams (small latex squares) during oral sex, but like condoms, they are not 100% protective

11. Treatment

11.1. Vaccines

Severe infection may require treatment with an antiviral agent. Oral antiviral drugs include

- acyclovir (Zovirax),
- valacyclovir (Valtrex),
- famciclovir (Famvir),

These drugs may stop viral replication in the skin but do not eliminate HSV from the body or prevent later outbreaks (HSV reactivation)

11.2. Medication

Treatment includes medication for fever and taking plenty of fluids.

- A topical anesthetic such as viscous lidocaine (Dilocaine, Nervocaine, Xylocaine, Zilactin-L) may be prescribed to relieve pain associated with oral blisters and lesions.
- Oral or IV medication does exist for HSV but is not recommended for people with a normal immune system. It is used only for people with weakened immune systems,

12. Host immune defense

Interferon and humoral, mucosal, and cellular immunity are important defenses. Herpes simplex virus infections are more severe in immunocompromised hosts.

13. Genetics (gene mutation)

The UL28 protein of herpes simplex virus type 1 (HSV-1) is one of seven viral proteins required for the cleavage and packaging of viral DNA. Previous results indicated that UL28 interacts with UL15 and UL33 to form a protein complex

(terminase) that is presumed to cleave concatemeric DNA into genome lengths. In order to define the functional domains of UL28 that are important for DNA cleavage/packaging, we constructed a series of HSV-1 mutants with linker insertion and nonsense mutations in UL28. Insertions that blocked DNA cleavage and packaging were found to be located in two regions of UL28: the first between amino acids 200 to 400 and the second between amino acids 600 to 740 .

14.Recent discoveries

Herpes infected humans before they were human

Date:June 10, 2014

Source:University of California, San Diego Health Sciences

Summary:

Researchers have identified the evolutionary origins of human herpes simplex virus (HSV) -1 and -2, reporting that the former infected hominids before their evolutionary split from chimpanzees 6 million years ago while the latter jumped from ancient chimpanzees to ancestors of modern humans - Homo erectus -- approximately 1.6 million years ago.

15. References:

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