GENITAL HERPES DISEASES: AN OVERVIEW

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Summary

Genital herpes is an acute inflammatory disease of the genitalia caused by herpes simplex virus (HSV). There are two types of this virus: type 1 and type 2. Apart from genitals, the virus can infect the anus, buttocks, top of the thighs, mouth, lips or face. Primary genital herpes is usually self-limiting but may cause painful local or systemic disease in neonates and patients who are immunocompromised. Pregnant women who have an active herpes infection on their genitals or in their birth canal when they deliver may pass the infection to their newborn infant. Genital herpes passes through sexual contact and no condom can stop genital herpes and HPV (human papilloma virus) because their transmission is by skin-skin contact rather than semen, and the lesions are typically outside. The virus has also been linked with the development of cancer of the cervix, a disease which strikes 18000 women in North America each year. Diagnosis is possible through culture of fluid from a blister or open sore. The most accurate test called PCR is performed on fluid from a blister shows small amounts of DNA. The standard, effective and specific treatment for genital herpes is antiviral therapy with drugs like Valacyclovir and Acyclovir combined with analgesics like Aspirin or Paracetamol.

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Introduction

Genital herpes is a common virus infection caused by herpes simplex virus (HSV). There are two types of this virus: type 1 and 2. As well as the genitals, the virus can infect the anus, buttocks, top of the thighs, mouth, lips or face; infection on the lips or face results in facial herpes, which includes cold sores.[1] These infections have an essentially identical appearance when on external surfaces. It is an acute inflammatory disease of the genitalia. The prognosis varies, depending on the patient's age, the strength of his immune defenses, and the infection site.[2] Primary genital herpes is usually self-limiting but may cause painful local or systemic disease in neonates and patients who are immunocompromised (such as those with acquired immunodeficiency syndrome). Genital herpes is usually severe, resulting in complications and a high mortality.[3]

HISTORY [4, 5, 6]

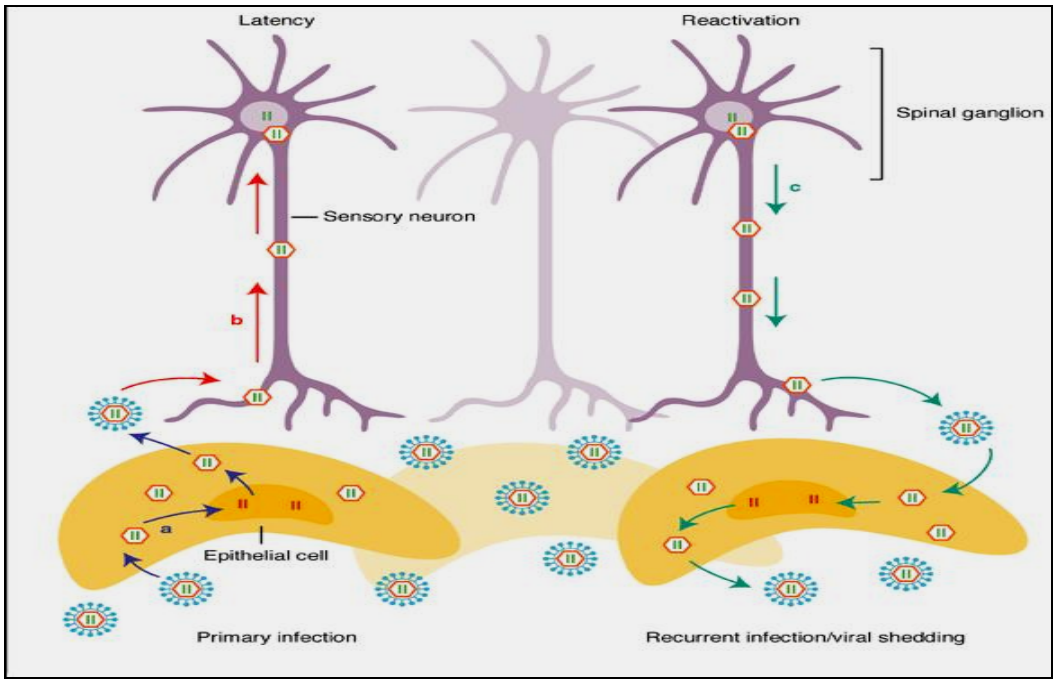
1976	Genital herpes, caused by herpes simplex virus type has been associated with cervical cancer, Dr. Alexander said. Cervical cancer is a rare genital herpes," Dr. Adams said, "is similar to that of fever blisters or cold sores, which are caused by herpes simplex virus type.
1981	Genital herpes are reported in the United States each year and the number is increasing. It is passed through sexual contact. The virus has also been linked with the development of cancer the cervix, a disease which strikes 18000 women in North America each year.
1982	Form of herpes and genital - simplex virus Infection, which causes an incurable sexually transmitted disease. But researchers say there is no proof the vaccine is beneficial for either Illness.
1985	Herpes simplex Type 2 is sexually transmitted and infects the genital area, resulting in painful fever blisters. The other two are Epstein-Barr virus, which causes a variety of infections, including mononucleosis, and cytomegalovirus, which has no symptoms.
1986	TALLAHASSEE What would be the first rewrite of Flor ida's venereal disease laws since 1919 was unanimously approved by the Senate Health and Rehabilitative Services People with such diseases as syphilis genital herpes, an AIDS related virus, Chlamydia and pelvic inflammatory.
1991	The proliferation of sex among unmarried heterosexuals has helped spawn outbreaks of herpes, genital warts and AIDS; 1.5 million abortions a year; thousands of teen-age mothers living wrecked lives.
1995	They're both herpes simplex virus. Classically, cold sores are type 1 and gential herpes is type 2. As far as symptoms and appearance, they are pretty much the same There is usually more of a problem with genital herpes and sometimes acyclovir is prescribed on a maintenance basis.
1997	In a single act of unprotected sex with an infected partner, a teen-age female has a 1 percent risk of acquiring HIV, a 30 percent risk of getting genital herpes and a 50 percent chance of contracting gonorrhea.
1998	FDA approved Glyde Dam Lollyes designed as a barrier for use while performing 'cunnilingus'. When properly used, it may help reduce the risk of catching or spreading many Sexually Transmitted diseases.
2002	Even genital herpes infection rates have remained flat in recent years. And most

	public health officials admit that much of the apparent. Widely used in foods such as ice cream and beer, carrageenan is believed to inhibit HIV and gential herpes from binding with target cells.
2003	A daily dose of the anti-viral drug valacyclovir can reduce transmission of genital herpes by 77 percent.
2006	Also, no condom can stop genital herpes and HPV (human papilloma virus) because their transmission is by skin-skin contact rather than semen, and the lesions are typically outside.

History of Genital herpes

LIFE CYCLE

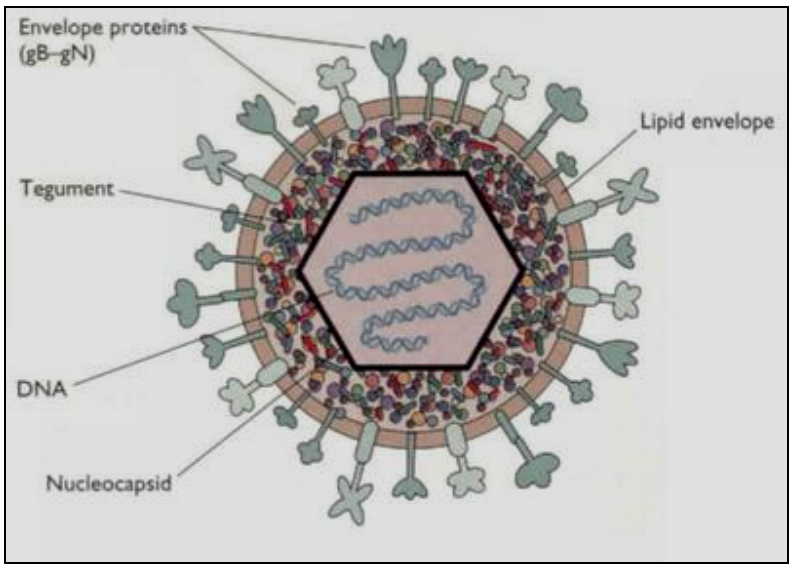
HSV infects its host through both lytic and latent infection, and replication of HSV occurs within 15 hours after infection. In the lytic cycle, HSV infects epithelial cells located in the mucosa, replicates, and causes epithelial cell death. [7] HSV-1 most frequently invades oral and ocular epithelial cells while HSV-2 infects the genital areas, but both strains have the ability to cause infection in either area of the body. In order to infect epithelial cells, glycoproteins (namely gB, gC, and gD) on the surface of HSV fuse with entry receptors on the host cell membrane. One study demonstrated that when the virion lacks gC, the virus loses some function in binding to host cells, and the infectivity of the virus is decreased by a factor of 10. Also, gC-negative virions did bound to host cells required much more time to penetrate the host cell compared to controls.[8] gD has also been found to be necessary for fusion between the host cell membrane and the virus envelop and for entry of viral particles into the host cell. There are three known types of entry receptors located on the host cell that bind to HSV during cell infection and fusion. [9] This receptor is expressed at high levels on NK-T cells and naïve CD8+ cells and at weaker levels on CD4+ cells and dendritic cells. The third receptors are nectin-1 and nectin-2, which are members of the immunoglobulin superfamily, and these receptors are expressed in epithelial cells, fibroblasts, and neurons. HSV-1 and 2 both bind to HVEM and nectin-1, while HSV-1 also uses heparin sulfate and HSV-2 uses nectin-2.[10]



Life cycle of HSV

GENOMIC STRUCTURE

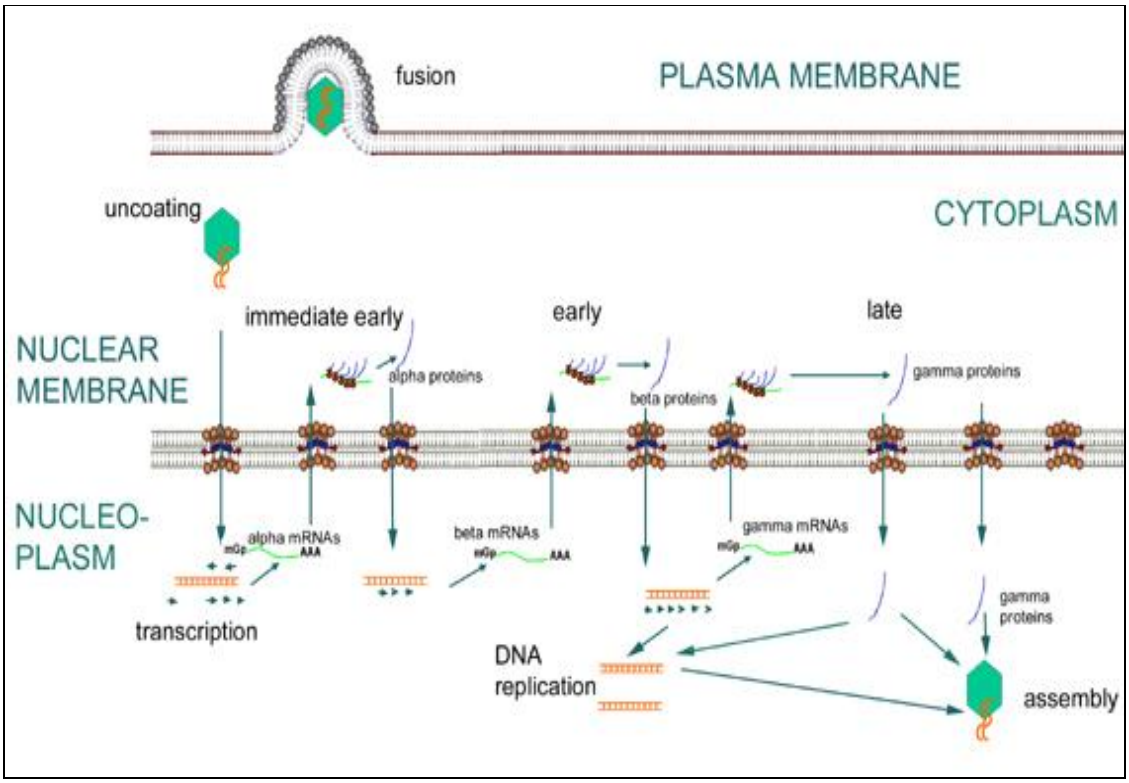
Herpes Simplex Virus Type (HSV) is a double stranded DNA virus that belongs to *Herpesviridae* family. It contains three main structural components. [11] A central core holds the viral DNA; an inner core is surrounded by an envelope that is made of viral glycoproteins and host cell membranes, and a capsid.[12] The tegument is located between the capsid and the envelope and various proteins that are delivered into the infected cell upon cell fusion. [13]



Structure of HSV

GENES

The HSV genome encodes for over 80 proteins. There are three classes of viral genes that are transcribed and translated in a specific order, including the immediate early (IE; α), early (E; β), and late (L; γ) genes. Immediate early genes (such as α-TIF) are transcribed and translated first.[14] Four (ICP0, ICP4, ICP22, and ICP27) of these five proteins from the IE genes serve as regulatory proteins that initiate transcription of early genes by the host cell's RNA polymerase. ICP4, however, is the main regulatory protein of HSV. [15] Early genes serve to down regulate immediate early gene expression and up regulate the third set of genes in infection, called late genes. Late genes down regulate early gene expression and are structural proteins.[16] After the late phase of infection; a viral capsid is formed in the nucleus that contains viral DNA. The capsid buds through the nuclear membrane and leaves the cell through the Golgi complex. During this process, the virus acquires its tegument and envelop, and the host cell dies as virus is released. HSV is then retrograde transported along axons to the cell body of neurons to establish a latent infection. This transport is accomplished by dyne in and dynactin, which move HSV capsid along microtubules.[17]



Replication of HSV

MECHANISM

Herpes is contracted through direct contact with an active lesion or body fluid of an infected person.[18] Herpes transmission occurs between discordant partners; a person with a history of infection (HSV seropositive) can pass the virus to an HSV seronegative person.[19] The only way to contract Herpes simplex virus 2 is through direct skin-to-skin contact with an infected individual. To infect a new individual, HSV travels through tiny breaks in the skin or mucous membranes in the mouth or genital areas. Even microscopic abrasions on mucous membranes are sufficient to allow viral entry.HSV asymptomatic shedding occurs at some time in most individuals infected with herpes.[20] It can occur more than a week before or after a symptomatic recurrence in 50% of cases.[21] Concurrent infection with HIV increases the frequency and duration of asymptomatic shedding. There are indications that some individuals may have much lower patterns of shedding, but evidence supporting this is not fully verified; no significant differences are seen in the frequency of asymptomatic shedding when comparing persons with one to twelve annual recurrences to those who have no recurrences.[22] Antibodies that develop following an initial infection with a type of HSV prevents reinfection with the same virus type a person with a history of orofacial infection caused by HSV-1 cannot contract herpes whitlow or a genital infection caused by HSV-1. In a monogamous couple, a seronegative female runs a greater than 30% per year risk of contracting an HSV infection from a seropositive male partner.[23]

SIGNS AND SYMPTOMS

Many people with HSV-2 infection never have sores, or they have very mild symptoms that they do not even notice or mistake for insect bites or another skin condition.[24]

If signs and symptoms do occur during the first outbreak, they can be quite severe. This first outbreak usually happens within 2 weeks of being infected.

Generalized or whole-body (systemic) symptoms may include:

- Decreased appetite
- Fever
- General sick feeling (Malaise)
- Muscle aches in the lower back, buttocks, thighs, or knees

Genital symptoms include the appearance of small, painful blisters filled with clear or straw-colored fluid.[25] They are usually found:

- In women: on the outer vaginal lips (labia), vagina, cervix, around the anus, and on the thighs or buttocks
- In men: on the penis, scrotum, around the anus, on the thighs or buttocks
- In both sexes: on the tongue, mouth, eyes, gums, lips, fingers, and other parts of the body
- Before the blisters appear, the person may feel the skin tingling, burning, itching, or have pain at the site where the blisters will appear
- When the blisters break, they leave shallow ulcers that are very painful. These ulcers eventually crust over and slowly heal over 7 - 14 days or more.[26]

Other symptoms that may occur include:

- Enlarged and tender lymph nodes in the groin during an outbreak
- Painful urination
- Women may have vaginal discharge or, occasionally, be unable to empty the bladder and require a urinary catheter

A second outbreak can appear weeks or months after the first. It is almost always less severe and shorter than the first outbreak. Over time, the number of outbreaks tends to decrease.[27]

Once a person is infected, however, the virus hides within nerve cells and remains in the body. The virus can remain "asleep" (dormant) for a long period of time (this is called latency).

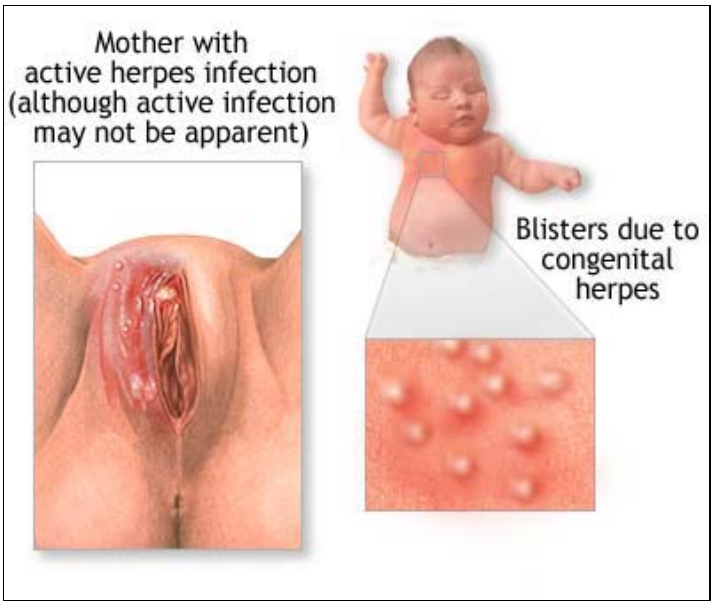
The infection can flare-up or reactivate at any time. Events that can trigger latent infection to become active and bring on an outbreak include:

- Fatigue
- Genital irritation
- Menstruation
- Physical or emotional stress
- Trauma

Attacks can recur as seldom as once per year, or so often that the symptoms seem continuous. Recurrent infections in men are generally milder and shorter than those in women.[28, 29]

SITES OF INFECTION

- In women, the genital areas most commonly affected are the vulva and the entrance to the vagina. Sores can also sometimes develop on the cervix.[30]
- In men, sores are most common on the glans (end of the penis), the foreskin and shaft of the penis. Sometimes sores can develop on the testicles. Less commonly, both men and woman can experience sores around the anus, on the buttocks and tops of the thighs.[31]



Site of infection in Mother

DIAGONOSIS

Tests can be done on skin sores or blisters to diagnose herpes. These tests are most often done when someone has a first outbreak and when a pregnant woman develops genital herpes symptoms.

- Culture of fluid from a blister or open sore may be positive for herpes simplex virus. The herpes simplex virus can be seen in the culture in 2-3 days. It is most useful during the first outbreak.
- A test called PCR performed on fluid from a blister shows small amounts of DNA. It is the most accurate test to tell whether the herpes virus is present in the blister.
- Blood tests check for antibody levels to the herpes virus. These blood tests can identify whether someone has ever been infected with the herpes virus, even between outbreaks. It may be positive even if they've never had an outbreak. [32, 33,34, 35, 36]

TRANSMISSION OF THE INFECTION

Persons with herpes can be infectious both when symptoms of a herpes outbreak are present and also when there are no symptoms. People who experience an episode of herpes, either facial or genital, should consider themselves infectious from the start of the episode to the healing of the last ulcer.[37] Facial herpes lesions (e.g. cold sores) are also a source of transmission through the practice of oral sex.

Consequently, oral sex should be avoided if one partner has a facial herpes attack. Infectious virus can still be present in people with no obvious lesions, during periods of asymptomatic virus shedding. Asymptomatic virus shedding cannot be predicted but is known to occur on at least 5% of days. Occasionally, one partner in a long-term relationship may develop symptoms of herpes for the first time. Often this is due to one or both of the partners being carriers of HSV and not knowing it.[38] The sudden appearance of herpes does not necessarily imply recent transmission from someone outside the relationship.[39] By avoiding sex when the signs of herpes are present, and by using condoms with sexual partners between outbreaks, the chance of passing on herpes may be reduced.[40]

PREVENTION

The best way to avoid getting genital herpes is to avoid all sexual contact, including oral sex. Next best is being in a long-term, mutually monogamous relationship with someone who has been tested and is not, and never has been, infected with herpes.[41]

Condoms remain the best way to protect against catching genital herpes during sexual activity with someone who is infected. Using a condom correctly and consistently will help prevent the spread of the disease.

- Only latex condoms will work to prevent infection. Animal membrane (sheepskin) condoms won't work because the virus can go right through them.
- The female condom has been tested and shown to reduce the risk of transmitting herpes, as well.
- A latex condom should be used during ALL sexual contact, even if the infected person does not have any sores or blisters at that time.
- In addition, people with genital herpes who don't have any current symptoms should tell their partner that they have the disease.

- Vaccines against herpes have been developed but are still experimental.[42, 43, 44]

TREATMENT

Genital herpes is manageable. Over the years, a number of treatments offering effective relief from symptoms of genital herpes have been developed.

Simple treatments for the relief of discomfort: [45, 46, 47]

The following non-specific treatments can alleviate the pain and discomfort of genital sores.

- SALT BATHS, used to wash the genital area, can clean, soothe and dry the sores. Use 1 teaspoon of salt in 600 ml of water or a handful in a shallow bath.
- PAIN RELIEVERS include simple analgesics (such as aspirin and paracetamol), ice (which can be soothing if applied directly to the sores) and creams with an anaesthetic component. Creams, however, can slow down drying and should therefore be used sparingly and only for pain relief. In addition, topical creams have limited value on moist mucosal surfaces, particularly in women.
- LOOSE UNDERCLOTHES, preferably cotton (not nylon), can help minimize discomfort and allow healing.

For anyone experiencing extreme pain when urinating, the process can be less painful when done in a cool bath. And it is important to remember to drink plenty of fluids as this dilutes the urine.

Antiviral Therapy

The standard, effective and specific treatment for genital herpes is antiviral therapy, which is usually in tablet form.[48] Antiviral drugs stop HSV from replicating in the body. The treatment only works while you are taking the drug, and cannot prevent future outbreaks once you stop taking it.[49]

Antiviral treatments can:

- Shorten the duration of a genital herpes outbreak and help speed healing
- Reduce the number of outbreaks suffered - or prevent them completely. [50, 51]

Antiviral medications can be used in two ways:

1. To treat outbreaks as they happen - this is known as 'episodic' treatment. With episodic treatment, the aim is to shorten the time each outbreak lasts and to relieve symptoms. If you are coping well and your outbreaks are not too frequent, you and your doctor may agree that episodic treatment is the most appropriate option.[52]

2. To prevent or delay recurrent outbreaks - this is known as 'suppressive' therapy. If your recurrent outbreaks are frequent or severe - or if you find them particularly bothersome - your doctor may recommend that you take oral antiviral medication every day to help prevent outbreaks happening. Suppressive therapy is taken continuously, e.g. daily, for months or even years.[53]

Oral antiviral medication is only available by prescription. If you are taking 'episodic' therapy then the earlier treatment starts after symptoms of an outbreak first appear, the more effective it will be. So see your doctor and ask him/her to prescribe treatment in advance that you can self-initiate immediately you detect the early symptoms of a herpes episode.[54]

Specific Antiviral Therapies

Valaciclovir

When used as episodic treatment, valaciclovir helps the sores heal faster, and shortens the period of pain during the outbreak. Valaciclovir also cuts down the time during which the virus is detected on genital skin surfaces (virus shedding) - a time when the disease can be passed on to a sexual partner.[55] If you take valaciclovir as soon as you notice the first signs of an outbreak such as tingling, itching or redness you may be able to completely prevent the development of painful blisters. In clinical tests, valaciclovir prevented the development of painful blisters and ulcers in one third more patients who took the drug within 24 hours of noticing the first symptoms of the outbreak, compared to those who took a dummy (placebo).[56] Valaciclovir is taken twice a day when used as episodic treatment. In many countries, valaciclovir can be used as 'suppressive' treatment. Clinical trials have proved it to prevent or delay up to 85% of herpes outbreaks. For suppressive treatment, you only need to take valaciclovir once a day or possibly twice a day if outbreaks are very frequent.[57]

Side effects with valaciclovir are usually mild and may include headache or nausea.

Aciclovir
When aciclovir is taken as episodic treatment, it can reduce the severity of outbreaks of genital herpes and shorten their duration, in a similar way to valaciclovir. Like valaciclovir, aciclovir also shortens the time during which the herpes virus is detected on skin surfaces. As episodic treatment; aciclovir should be taken five times a day. Aciclovir can also be used as suppressive treatment to help reduce the number of outbreaks. If you take aciclovir as suppressive treatment, you will need to take tablets two, three or four times a day.[58]

The side effects of aciclovir are usually mild. They include nausea and diarrhoea.

Famciclovir
Famciclovir has been shown to reduce the time that outbreaks last when used as episodic treatment. The severity of pain with outbreaks is also decreased. Like valaciclovir and aciclovir, famciclovir also shortens the period during which virus is detected on genital surfaces.[59] Famciclovir is taken three times a day, when it is used as episodic treatment for the initial genital herpes episode, or two times a day to treat recurrent outbreaks. Famciclovir is approved in some countries for daily use as suppressive therapy (your doctor will be able to advise you if this is the case in your country). When it is used in this way, it has been shown in clinical trials to increase the time between outbreaks. For suppressive therapy, famciclovir is taken two times every day.[60]

The side-effects of famciclovir are generally mild with headache and nausea being reported.

SIDE EFFECTS [61, 62]

Possible side effects from herpes medications include:

- Fatigue
- Headache
- Nausea and vomiting
- Rash
- Seizures
- Tremor

Complications:
Pregnant women who have an active herpes infection on their genitals or in their birth canal when they deliver may pass the infection to their newborn infant. [63]

- The risk of passing the infection to the baby is highest if the mom first becomes infected with herpes during pregnancy. Babies of women who become infected during pregnancy are at risk for premature birth. The baby may develop brain infection (meningitis, encephalitis), chronic skin infection, severe developmental delays, or death.
- The risk for severe infection in the baby is lower in recurrent outbreaks, with the highest risk in women experiencing an outbreak at the time of delivery.
- Women with a history of herpes but who only have occasional or no outbreaks transmit the infection to their babies.

Some people may develop severe herpes infections that involve the brain, eyes, esophagus, liver, spinal cord, or lungs. These complications often develop in people who have a weakened immune system, AIDS, are undergoing chemotherapy or radiation therapy, or who take high doses of cortisone.

Someone with an active herpes infection who has sexual contact with someone who is HIV positive is more likely to contract HIV infection themselves.[64]

Conclusion

Genital herpes is a painful viral disease with variable symptoms including small, painful blisters filled with clear or straw-colored fluid with generalized fatigue, genital irritation, decreased appetite, fever, and malaise, muscle aches in the lower back, buttocks, thighs, or knees. The virus has also been linked with the development of cancer of the cervix. The best way to avoid getting genital herpes is to avoid all sexual contact, including oral sex. Next best is being in a long-term, mutually monogamous relationship with someone who has been tested and is not, and never has been, infected with herpes. Using a latex condom correctly and consistently will help prevent the spread of the disease. The female condom has been tested and shown to reduce the risk of transmitting herpes, as well. Vaccines against herpes have been developed but are still experimental. Antivirals like Valacyclovir and Acyclovir are capable of controlling the spread as well as completely abolish the symptoms.

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