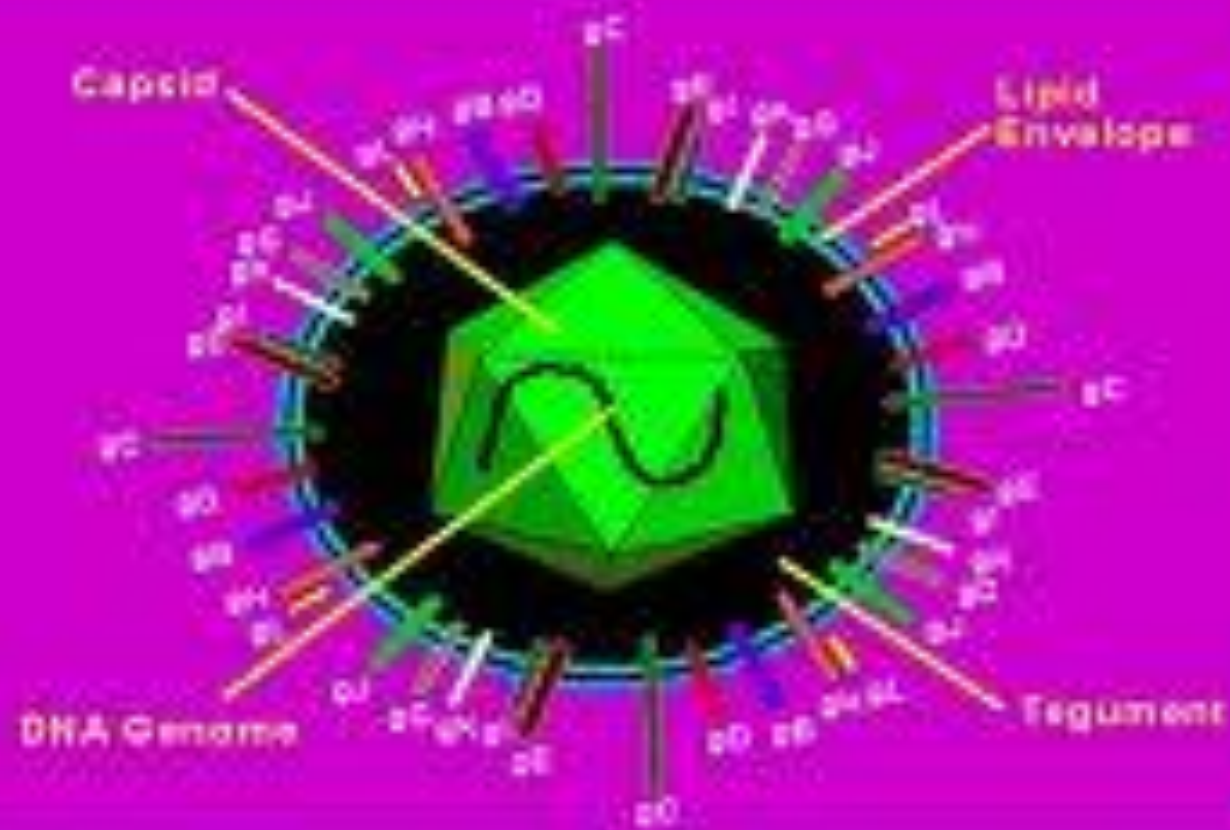


Herpes Simplex Virus

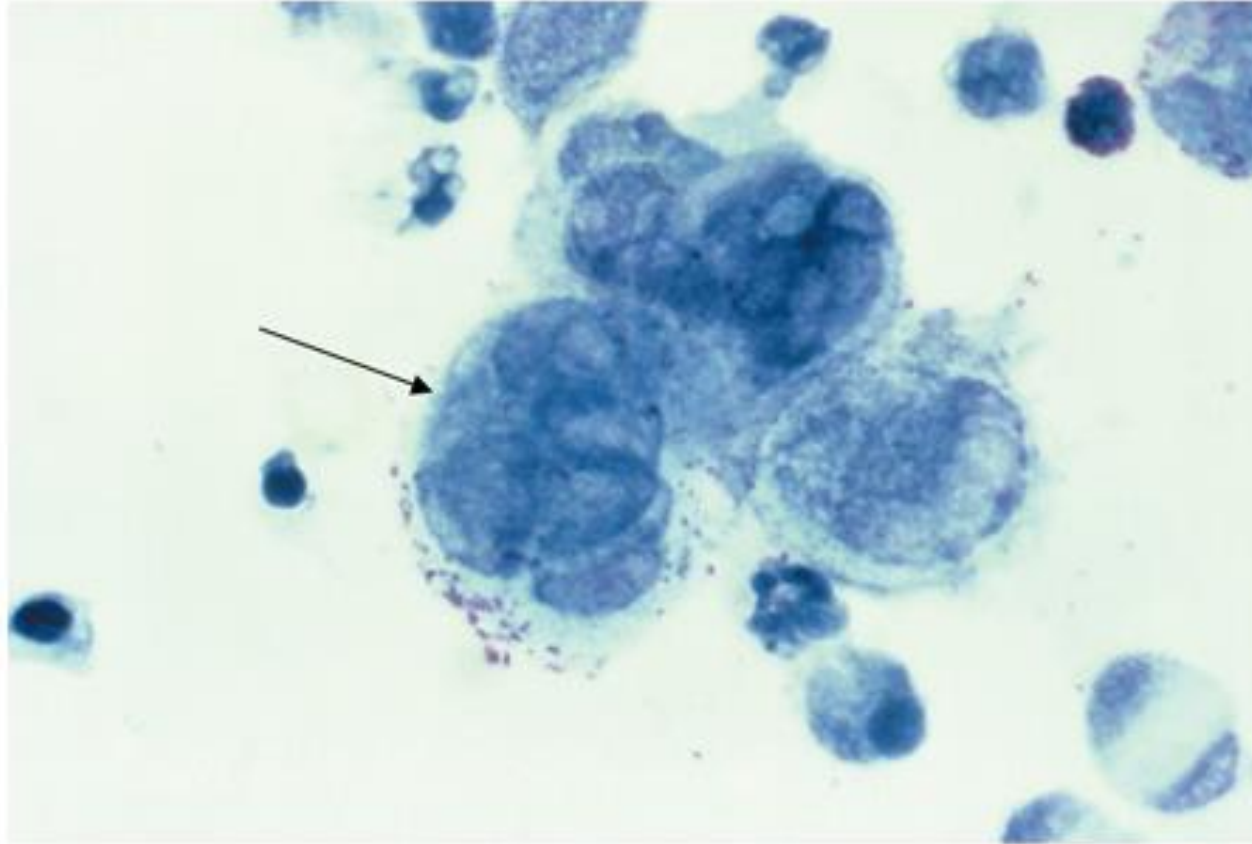


IMPORTANT FEATURES OF HERPES VIRUS 1 & 2 INFECTIONS

Virus	Primary infection	Usual Site of Latency	Recurrent Infection	Transmission
HSV1	Gingivo-stomatitis ¹	Cranial sensory ganglia	Herpes labialis, ² encephalitis, keratitis	Respiratory secretions & saliva
HSV2	Herpes genitalis, perinatal disseminated disease	Lumbar or sacral sensory ganglia	Herpes genitalis	Sexual contact, perinatal infection

Four herpesviruses, namely herpes HSV 1 & 2, VZV, & CMV, induce the formation of **multinucleated giant cells**, which can be seen microscopically in the lesions.

Herpes
simplex
type-2



Multinucleated giant cells in Tzanck smear. Arrow points to a multinucleated giant cell with approximately eight nuclei.

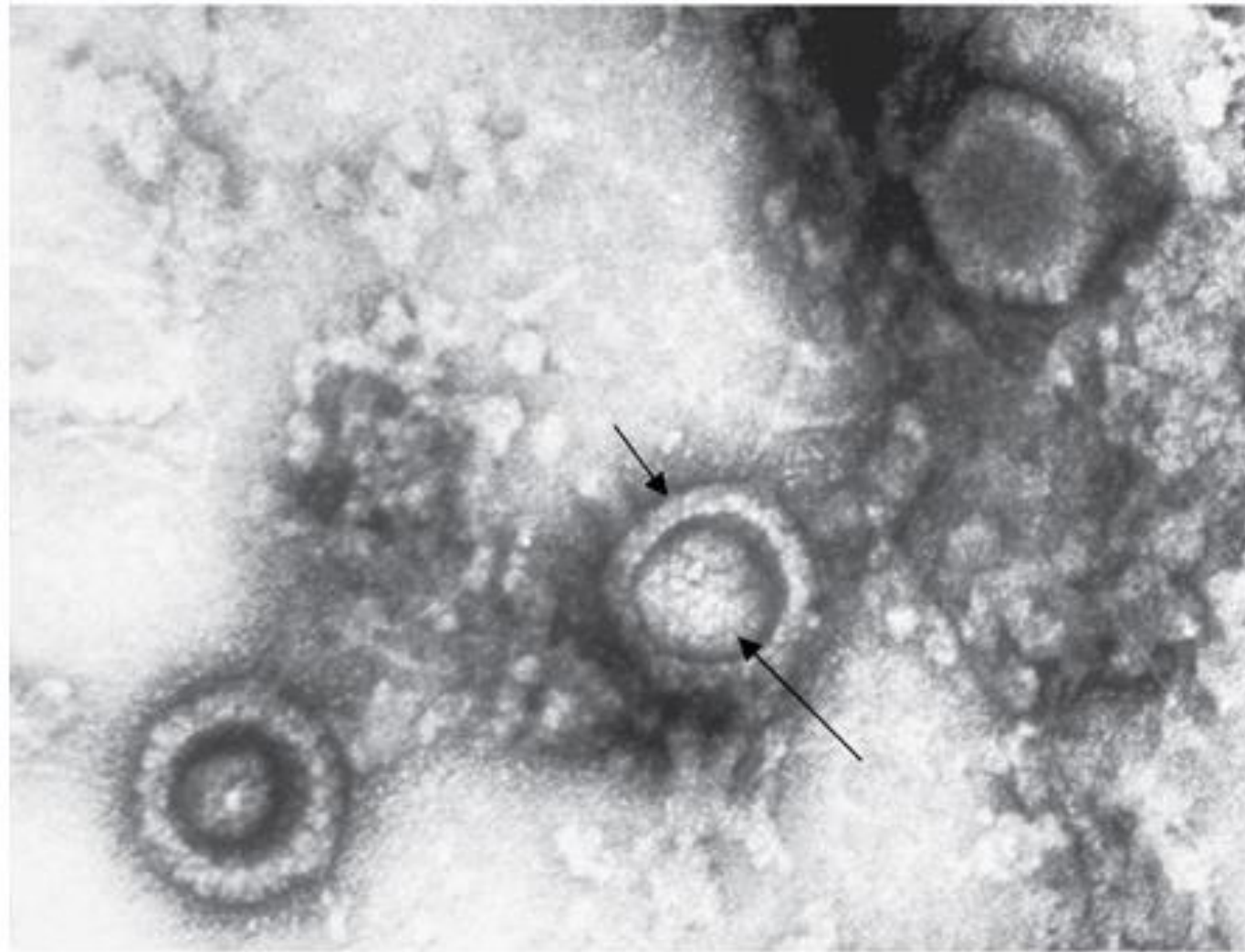
HSV1



HSV2



Herpes simplex virus



Electron micrograph. 3 HSV virions are visible.
Short arrow points to the envelope of an HSV virion.
Long arrow points to the nucleocapsid of the virion.
Dark area between the inner nucleocapsid and the outer envelope is the tegument

IMPORTANT DIFFERENCES BETWEEN THE DISEASES CAUSED BY HSV-1 & 2

Site	Disease Caused by HSV-1	Disease Caused by HSV-2
Skin	Vesicular lesions above the waist	Vesicular lesions below the waist
Mouth	Gingivo-stomatitis	Rare
Eye	Kerato-conjunctivitis	Rare
CNS	Encephalitis (temporal lobe)	Meningitis
Neonate	Rare ¹	Skin lesions, encephalitis, & disseminated infection ²
Dissemination to viscera in immunocompromised patients	Yes	Rare

¹Infection acquired after birth from HSV-1–infected person.

²Infection acquired during passage through birth canal

TRANSMISSION

- ❖ HSV-1 is transmitted primarily in saliva, whereas HSV-2 is transmitted by sexual contact.
- ❖ HSV-1 infections occur mainly on the face, whereas HSV-2 lesions occur in the genital area.
- ❖ However, oral–genital sexual practices can result in HSV-1 infections of the genitals & HSV-2 lesions in the oral cavity (this occurs in about 10–20% of cases).
- ❖ Although transmission occurs most often when active lesions are present, asymptomatic shedding of both HSV-1 & HSV-2 does occur & plays an important role in transmission.

EPIDEMIOLOGY

- ❖ The number of HSV-2 infections has markedly increased in recent years, whereas that of HSV-1 infections has not.
- ❖ Roughly 80% of people in the USA are infected with HSV-1 & 40% have recurrent herpes labialis.
- ❖ Most primary infections by HSV-1 occur in childhood, as evidenced by the early appearance of antibodies.
- ❖ In contrast, antibody to HSV-2 does not appear until the age of sexual activity.

PATHOGENESIS

- ❖ The virus replicates in the skin or mucous membrane at the initial site of infection, then
- ❖ Migrates up the neuron by retrograde axonal flow & becomes latent in the sensory ganglion cells.
- ❖ HSV-1 becomes latent in the trigeminal ganglia, whereas HSV-2 becomes latent in the lumbar & sacral ganglia.
- ❖ During latency, most—if not all—viral DNA is located in the cytoplasm rather than integrated into nuclear DNA.
- ❖ The virus can be reactivated from the latent state by a variety of inducers, at which time it migrates down the neuron & replicates in the skin, causing lesions.

PATHOGENESIS

- ☐ **The typical skin lesion is a vesicle that contains serous fluid filled with virus particles & cell debris.**
- ☐ **When the vesicle ruptures, virus is liberated & can be transmitted to other individuals.**
- ☐ **Multinucleated giant cells are typically found at the base of herpesvirus lesions.**

IMMUNITY

Immunity is type-specific, but some cross-protection exists.

Immunity is incomplete, & both re-infection & reactivation occur in the presence of circulating IgG.

CMI is important in limiting herpesviruses, because its suppression often results in

Reactivation

Spread

Severe disease.

CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Genital Herpes

Is characterized by painful vesicular lesions of the male & female genitals & anal area.

The lesions are more severe & protracted in primary disease than in recurrences.

Primary infections are associated with fever & inguinal adenopathy.

Asymptomatic infections occur in both men (in the prostate or urethra) & women (in the cervix) & can be a source of infection of other individuals.

Many infections are asymptomatic, i.e., many people have antibody to HSV-2 but have no history of disease.

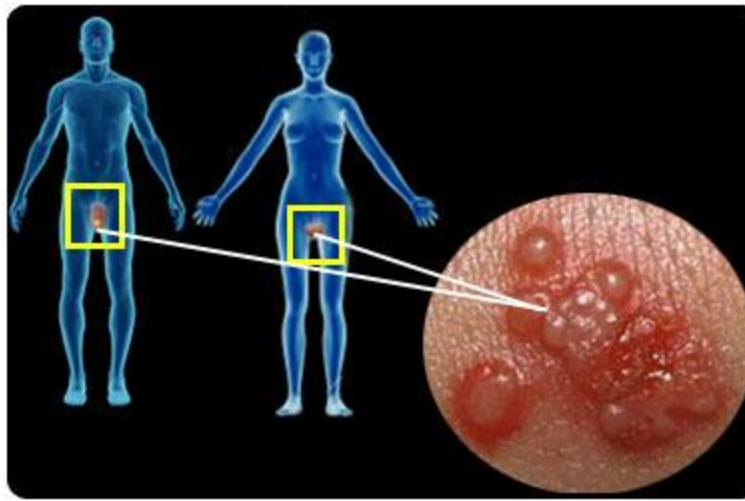


Photo courtesy of CDC - Dr. Mark Fleming & Dr. Anne Chen

Genital Herpes



CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Neonatal Herpes

Originates chiefly from contact with vesicular lesions within the birth canal.

In some cases, although there are no visible lesions, HSV-2 is shed into the birth canal (asymptomatic shedding) & can infect the child during birth.

Neonatal herpes varies from severe disease (e.g., disseminated lesions or encephalitis) to milder local lesions (skin, eye, mouth) to asymptomatic infection.

Neonatal disease may be prevented by performing cesarean section on women with either active lesions or positive viral cultures.

Mother with
active herpes infection
(although active infection
may not be apparent)



Blisters due to
congenital
herpes



CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Both HSV-1 & HSV-2 can cause severe neonatal infections acquired after birth from carriers handling the child.

Despite their association with neonatal infections, neither HSV-1 nor HSV-2 causes congenital abnormalities significantly.

CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Serious neonatal infection is more likely to occur when the mother is experiencing a primary herpes infection than a recurrent infection for two reasons:

- (1) the amount of virus produced during a primary infection is greater than during a secondary infection**
- (2) mothers who have been previously infected can pass IgG across the placenta, which can protect the neonate from serious disseminated infection.**

Aseptic meningitis

Caused by HSV-2 is usually a mild, self-limited disease with few sequelae.

CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Erythema multiforme

- ❖ Both HSV-1 & HSV-2 infections are associated with erythema multiforme.
- ❖ The lesions are typically macular or papular & occur symmetrically on the trunk, hands, & feet.
- ❖ The rash is thought to be an immune-mediated reaction to the presence of HSV antigens.
- ❖ Acyclovir is useful in preventing recurrent episodes of erythema multiforme, probably by reducing the amount of HSV antigens.

Erythema Multiforme

Central red area surrounded
by a ring of normal skin
outside of which is a red ring

("target" or
"bull's eye"
lesion).



CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Erythema multiforme

Many drugs, especially

- Sulfonamides among the antimicrobial drugs, commonly cause erythema multiforme.

Other prominent infectious causes include

- *Mycoplasma pneumoniae*
- Viruses such as HBV & HCV

CLINICAL FINDINGS

HSV-2 CAUSES PRIMARY & RECURRENT

Stevens-Johnson syndrome

Erythema multiforme major, also known as Stevens-Johnson syndrome, is characterized by

- ❖ Fever
- ❖ Erosive oral lesions
- ❖ Extensive desquamating skin lesions.

M. pneumoniae infection is the most common infectious cause of Stevens-Johnson syndrome.



Stevens-Johnson syndrome

LABORATORY DIAGNOSIS

- 1. Cell culture**
- 2. Tzanck smear**
- 3. Polymerase Chain Reaction (PCR) assay**
- 4. Serologic tests such as the neutralization test**

LABORATORY DIAGNOSIS

Cell culture

A diagnostic procedure is isolation of the virus from the lesion by growth in cell culture.

The typical cytopathic effect occurs in 1 to 3 days, after which the virus is identified by:

- Fluorescent antibody staining of the infected cells or by
- Detecting virus-specific glycoproteins in ELISAs.

LABORATORY DIAGNOSIS

Tzanck smear

Cells from the base of the vesicle are stained with Giemsa stain.

The presence of multinucleated giant cells suggests herpesvirus infection.

LABORATORY DIAGNOSIS

Polymerase Chain Reaction (PCR) assay

A rapid diagnosis of **encephalitis** can be made by detecting HSV-1 DNA in the spinal fluid by using a PCR assay, but virus is rarely recovered from the spinal fluid.

Diagnosis of **neonatal herpes infection** typically involves the use of:

- Viral cultures or
- PCR assay.

PCR is the most sensitive test for HSV diagnosis.

LABORATORY DIAGNOSIS

Serologic tests such as the neutralization test

Can be used in the diagnosis of **primary infections** because a significant rise in antibody titer is readily observed. However,

They are of no use in the diagnosis of recurrent infections because many adults already have circulating antibodies & recurrences rarely cause a rise in antibody titer.

TREATMENT

1. **Acyclovir (Zovirax)**
2. **Valacyclovir (Valtrex)**
3. **Famciclovir (Famvir)**
4. **Penciclovir (a derivative of acyclovir) or**
5. **Docosanol (a long-chain saturated alcohol)**
6. **Trifluridine (Viroptic)**
7. **Foscarnet**

TREATMENT

Acyclovir (Zovirax)

Is the treatment of choice for

- Encephalitis & systemic disease caused by HSV-1.
- Primary & recurrent genital herpes; it shortens the duration of the lesions & reduces the extent of shedding of the virus.
- Neonatal infections caused by HSV-2.

Valacyclovir (Valtrex) & famciclovir (Famvir)

Used in the treatment of genital herpes & in the suppression of recurrences.

TREATMENT

**Penciclovir (a derivative of acyclovir) or docosanol
(a long-chain saturated alcohol)**

**Used to treat recurrences of orolabial HSV-1 infections
in immunocompetent adults.**

Trifluridine (Viroptic)

Topical use for HSV-1 eye infections

TREATMENT

Foscarnet

Used for mutants of HSV-1 resistant to acyclovir.

No drug treatment of the primary infection prevents recurrences.

Drugs have no effect on the latent state, but prophylactic, long-term administration of acyclovir, valacyclovir, or famciclovir can suppress clinical recurrences.

PREVENTION

Avoiding contact with the vesicular lesion or ulcer.

Cesarean section is recommended for women who are at term & who have genital lesions or positive viral cultures.

Circumcision reduces the risk of infection by HSV-2.

Vaccine formed of purified HSV glycoproteins given before the primary infection



**MOST PEOPLE WITH GENITAL HERPES DON'T
KNOW IT.**

☐ True

☐ False

TRUE

About 16% of people aged 14-49 in the U.S. are infected with the herpes simplex virus-2 (HSV-2) that causes genital herpes, but as many as 81% of them had not received the diagnosis.

HOW MANY PEOPLE IN THE U.S. ARE ESTIMATED TO HAVE GENITAL HERPES?

1 million

10 million

30 million

45 million

HOW MANY PEOPLE IN THE U.S. ARE ESTIMATED TO HAVE GENITAL HERPES?

45 million

Genital herpes is very common, infecting at least 45 million people aged 12 and older in the United States.

**GENITAL HERPES CAUSED BY HSV-2 IS
FOUND MORE FREQUENTLY IN WOMEN
THAN IN MEN.**

☐ True

☐ False

**GENITAL HERPES CAUSED BY HSV-2 IS FOUND
MORE FREQUENTLY IN WOMEN THAN IN MEN.**

True

About one in five women between the ages of 14 and 49 have genital herpes caused by HSV-2, while about one in nine men in that same age range are infected.

**YOU CAN GET GENITAL HERPES FROM A
TOILET SEAT.**

☐ True

☐ False

**YOU CAN GET GENITAL HERPES FROM A
TOILET SEAT.**

False

As with other sexually transmitted diseases, herpes can be spread by close contact or sexual activity. It is highly unlikely to be spread by a toilet seat or other objects.

YOU CAN GET GENITAL HERPES FROM SOMEONE WHO DOESN'T HAVE VISIBLE SORES.

☐ True

☐ False

YOU CAN GET GENITAL HERPES FROM SOMEONE WHO DOESN'T HAVE VISIBLE SORES.

True

Genital herpes can be transmitted even if the infected partner has no symptoms or visible signs or doesn't know he or she is infected.

WASHING THE GENITAL AREA BEFORE AND AFTER SEX CAN HELP PREVENT THE TRANSMISSION OF GENITAL HERPES.

☐ True

☐ False

WASHING THE GENITAL AREA BEFORE AND AFTER SEX CAN HELP PREVENT THE TRANSMISSION OF GENITAL HERPES.

False

Washing the genital area doesn't help prevent any sexually transmitted disease (STD), including genital herpes.

The best way to prevent any STD is to abstain from sex or engage in sex only with someone you know is not infected.

Condoms are not guaranteed to prevent infection, but research has shown that they provide some protection.

**A PREGNANT WOMAN CAN GIVE HERPES TO HER
UNBORN BABY.**

☐ **True**

☐ **False**

A PREGNANT WOMAN CAN GIVE HERPES TO HER UNBORN BABY.

True

The estimated number of pregnant women infected with HSV-2 is 880,000.

Most transmission to newborns occurs during vaginal delivery.

If a woman had genital herpes before getting pregnant, her baby may be infected but the chance is very low -- less than 1%.

However, the risk of infecting the baby is much higher (25% to 50%) when a woman is newly infected late in pregnancy.

If pregnant women think infected, she has to tell her doctor right away.

Women with genital herpes are examined carefully for any symptoms before giving birth.

If sores or signs that an outbreak is coming are present at the time of delivery, the baby may be delivered by cesarean section (C-section).

A BLOOD TEST CAN DETERMINE IF SOMEONE HAS GENITAL HERPES.

☐ True

☐ False

A BLOOD TEST CAN DETERMINE IF SOMEONE HAS GENITAL HERPES.

True

To find out if you have genital herpes, a doctor can take a sample from a sore and test it in the laboratory.

There is also a blood test that looks for antibodies to the virus that your immune system would have made.

HSV-2 almost always infects the genitals, so if antibodies to HSV-2 are detected in your blood, you probably have genital herpes.

A blood test that shows antibodies to HSV-1 means you could have genital or oral herpes. That's because oral herpes, typically caused by HSV-1, can be spread to the genitals during oral sex.

NEW OR INITIAL GENITAL HERPES INFECTIONS

- a) Tend to be the most severe**
- b) May produce fever and flu-like symptoms**
- c) Can cause genital itching, burning, and painful genital blisters**
- d) All of the above**

NEW OR INITIAL GENITAL HERPES INFECTIONS

- a) All of the above**

WHEN DO THE SORES ASSOCIATED WITH GENITAL HERPES TYPICALLY HEAL AFTER THE FIRST OUTBREAK?

- a) Within a week
- b) Within one to two weeks
- c) Within two to four weeks
- d) Within five to six weeks

WHEN DO THE SORES ASSOCIATED WITH GENITAL HERPES TYPICALLY HEAL AFTER THE FIRST OUTBREAK?

- a) Within two to four weeks**

The classic symptom of genital herpes is small fluid-filled blisters that break, forming painful sores that crust and heal. These may appear four to seven days after the initial virus transmission.

**GENITAL HERPES OUTBREAKS INCREASE IN
FREQUENCY OVER TIME.**

☐ **True**

☐ **False**

**GENITAL HERPES OUTBREAKS INCREASE IN
FREQUENCY OVER TIME.**

False

Genital herpes typically causes several outbreaks (four or five) within a year of the first outbreak, with fewer and less severe outbreaks over time.

WHICH OF THESE IS NOT A COMMONLY REPORTED TRIGGER OF A GENITAL HERPES OUTBREAK?

- a) Vigorous sex**
- b) Stress**
- c) Surgery**
- d) Perspiration**

WHICH OF THESE IS NOT A COMMONLY REPORTED TRIGGER OF A GENITAL HERPES OUTBREAK?

a) Perspiration

Some commonly reported triggers for genital herpes outbreaks include stress, illness, surgery, vigorous sex, diet, and menstrual periods.

Molluscum Contagiosum Virus

Molluscum Contagiosum Virus

Molluscum contagiosum virus (MCV) is a member of the poxvirus family but is quite distinct from smallpox & vaccinia viruses.

MOLLUSCUM CONTAGIOSUM VIRUS (MCV)

- ☐ The lesion of molluscum contagiosum is a small (2–5 mm.)
- ☐ Flesh-colored papule on the skin or mucous membrane that is painless, nonpruritic, & not inflamed.
- ☐ The lesions have a characteristic cup-shaped (umbilicated) crater with a white core.
- ☐ The inclusion body contains progeny MCV.
- ☐ Note that these lesions are different from warts, which are caused by papillomavirus, a member of the papovavirus family.



**Painless, hard lumps over the skin surface.
The condition mainly affects children.**

MOLLUSCUM CONTAGIOSUM VIRUS (MCV)

TRANSMISSION

MCV is transmitted by close personal contact, including sexually.

The disease is quite common in children, in whom lesions often occur around the eyes & on the trunk.

Adults often have lesions in the genital area.

The lesions can be widespread in patients with reduced cellular immunity.

In immunocompetent patients, the lesions are self-limited but may last for months.

MOLLUSCUM CONTAGIOSUM VIRUS (MCV)

DIAGNOSIS

The diagnosis is typically made clinically

The virus is not isolated in the clinical laboratory, & antibody titers are not helpful.

MOLLUSCUM CONTAGIOSUM VIRUS (MCV)

TREATMENT

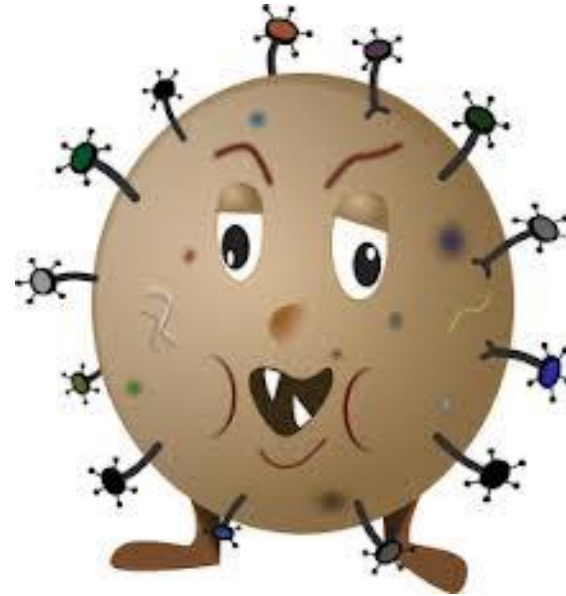
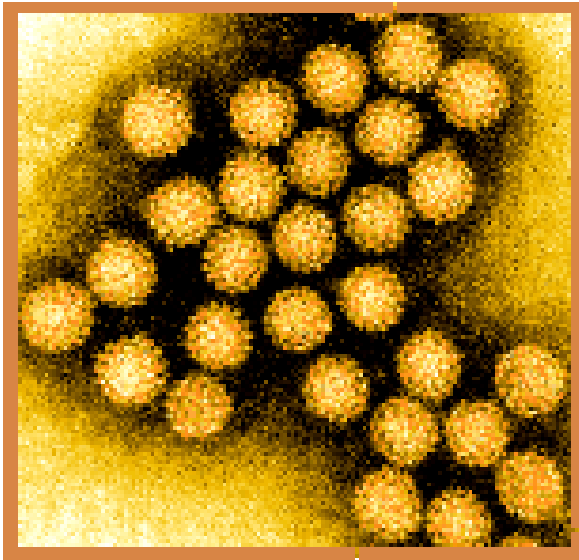
Removal of the lesions by curettage or with liquid nitrogen is often effective.

There is no established antiviral therapy, but cidofovir may be useful in the treatment of the extensive lesions that occur in immunocompromised patients.

In AIDS patients, antiretroviral therapy may restore sufficient immunity to cause the lesions to resolve.

There is no vaccine.

2. Human Papillomaviruses HPV



DISEASES

- ◉ Some HPV types, especially types 16 and 18, cause carcinoma of the cervix & penis.

IMPORTANT PROPERTIES

- ◉ HPV are nonenveloped viruses with double-stranded circular DNA & an icosahedral nucleocapsid.
- ◉ Two of the early genes, E6 & E7, are implicated in carcinogenesis.
- ◉ Inactivation of the p53 and RB proteins is an important step in the process by which a normal cell becomes a cancer cell.

IMPORTANT PROPERTIES

- ◉ There are at least 100 papillomaviruses, classified primarily based on DNA restriction fragment analysis.
- ◉ Skin warts are caused primarily by HPV-1 through HPV-4
- ◉ Genital warts are usually caused by HPV-6 & HPV-11.
- ◉ Approximately 30 types of HPV infect the genital tract.

TRANSMISSION

- ◉ HPV are transmitted primarily by skin-to-skin contact & by genital contact.
- ◉ HPV transmitted from an infected mother to the neonate during childbirth causes:
warts in the mouth & in the respiratory tract, especially on the larynx, of the infant.
- ◉ Many species of animals are infected with their own types of papillomaviruses, but these viruses are not an important source of human infection.

EPIDEMIOLOGY

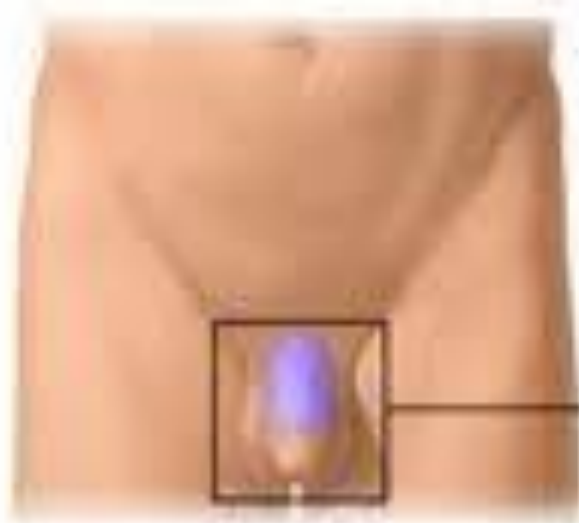
- ◉ Genital warts are among the most common STDs.
- ◉ Skin warts are more common in children & young adults & tend to regress in older adults.

PATHOGENESIS & IMMUNITY

- ◉ HPV infect squamous epithelial cells & induce within those cells a **characteristic cytoplasmic vacuole**.
- ◉ These **vacuolated cells, called koilocytes**, are the hallmark of infection by these viruses.
- ◉ Most warts are benign & do not progress to malignancy.
- ◉ However, HPV infection is associated with carcinoma of the uterine cervix & penis.

PATHOGENESIS & IMMUNITY

- ◉ Both CMI & antibody are induced by viral infection & are involved in the spontaneous regression of warts.
- ◉ Immunosuppressed patients, e.g., AIDS patients, have more extensive warts, & women infected with HIV have a very high rate of carcinoma of the cervix.



Genital warts:
Found on shaft of penis (male),
vagina, vulva, cervix (female)
and around anus

CLINICAL FINDINGS

Genital warts are caused primarily by
HPV-6 & HPV-11.



CLINICAL FINDINGS

Genital warts are caused primarily by
HPV-6 & HPV-11



CLINICAL FINDINGS

**Genital Condylomata acuminata are caused by
HPV-6 & HPV-11**



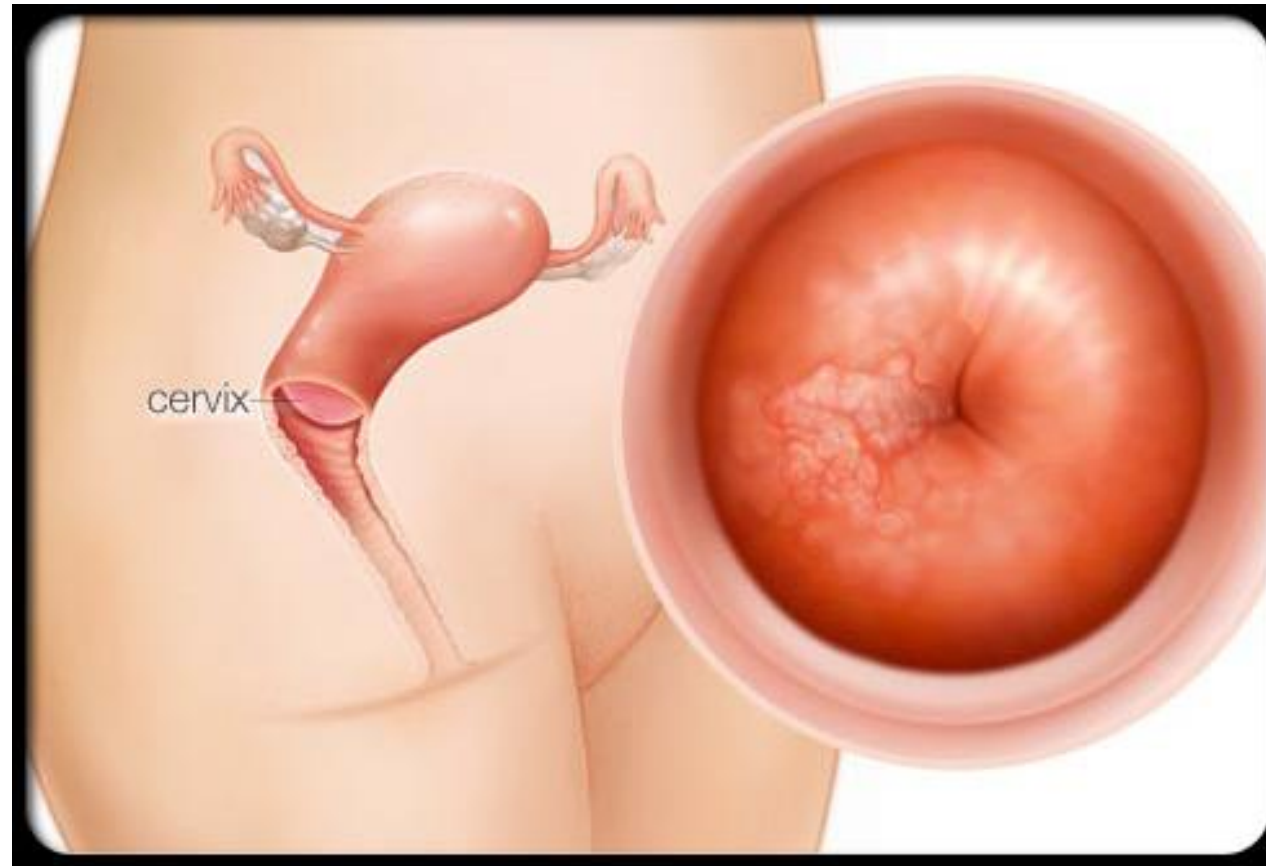


Will my
genital warts turn
into cancer?

No. But we should
also check for other
types of HPV.

CLINICAL FINDINGS

Carcinoma of the uterine cervix are associated
with infection by
HPV-16 & HPV-18



CLINICAL FINDINGS

Carcinoma the penis, are associated with
infection by
HPV-16 & HPV-18



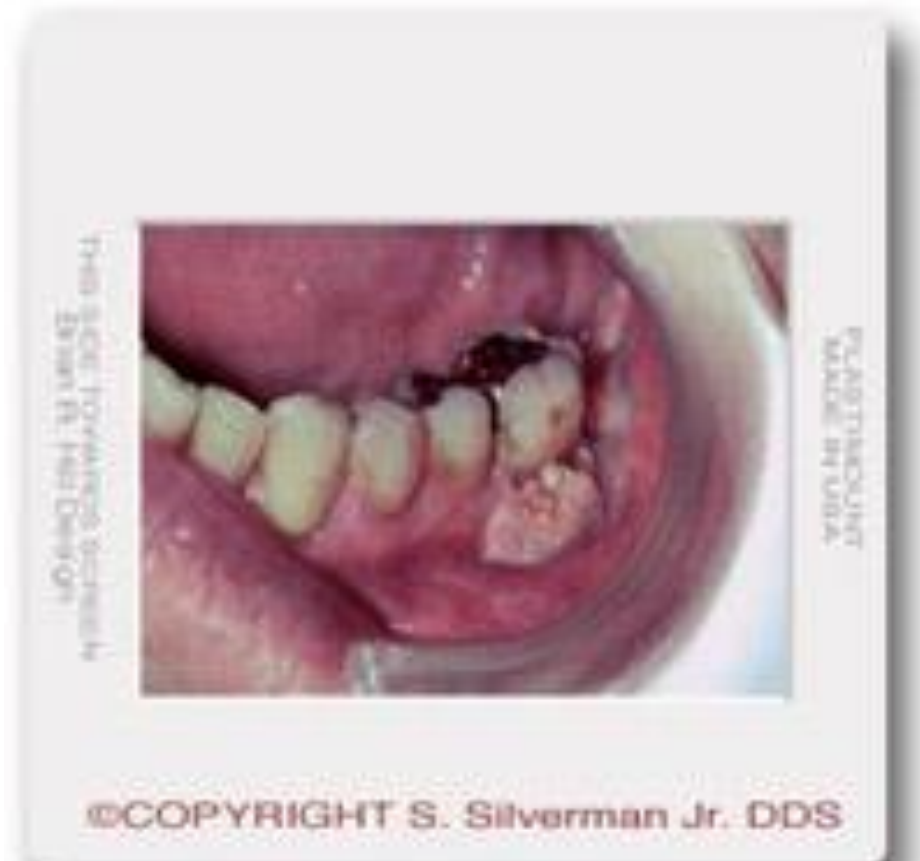
CLINICAL FINDINGS

**Carcinoma of the anus are associated with
infection by
HPV-16 & HPV-18**



CLINICAL FINDINGS

Oral cancers are associated with infection by
HPV-16



CLINICAL FINDINGS

- ◉ **HPV-6 & HPV-11** also cause respiratory tract papillomas, especially laryngeal papillomas, in young children.
- ◉ Occult premalignant lesions of the cervix & penis can be revealed by applying acetic acid to the tissue.

LABORATORY DIAGNOSIS

- ◉ **Used tests**
- ◉ Infections are usually diagnosed clinically.
- ◉ The presence of **koilocytes** in the lesions indicates HPV infection.
- ◉ DNA hybridization tests to detect the presence of viral DNA are commercially available.
- ◉ **Not used test**
- ◉ Tests based on the detection of antibodies in a patient's serum or on the isolation of the virus from a patient's tissue

TREATMENT

- ◉ The usual treatment for genital warts is podophyllin
- ◉ Alpha interferon is also effective & is better at preventing recurrences than are non-antiviral treatments.
- ◉ Liquid nitrogen is commonly used for skin warts.
- ◉ Plantar warts can be removed surgically or treated with salicylic acid topically.
- ◉ Cidofovir may be useful in the treatment of severe HPV infections.

PREVENTION

◉ HPV vaccines

- ◉ The FDA approved a recombinant vaccine against four types of HPV in 2006.
- ◉ The vaccine, called Gardasil, contains the capsid proteins of types
 - 6 & 11, which cause genital warts, &
 - 16 & 18 are the two most common causes of cervical carcinoma.

HPV VACCINES

- ◉ **Cervarix and Gardasil**
- ◉ Both are very effective against HPV types 16 & 18, which cause most cervical cancers.
- ◉ Both are very safe.
- ◉ Both are made with very small parts of the HPV
- ◉ Gardasil also protects against HPV types 6 & 11. These HPV types cause most genital warts in females & males.

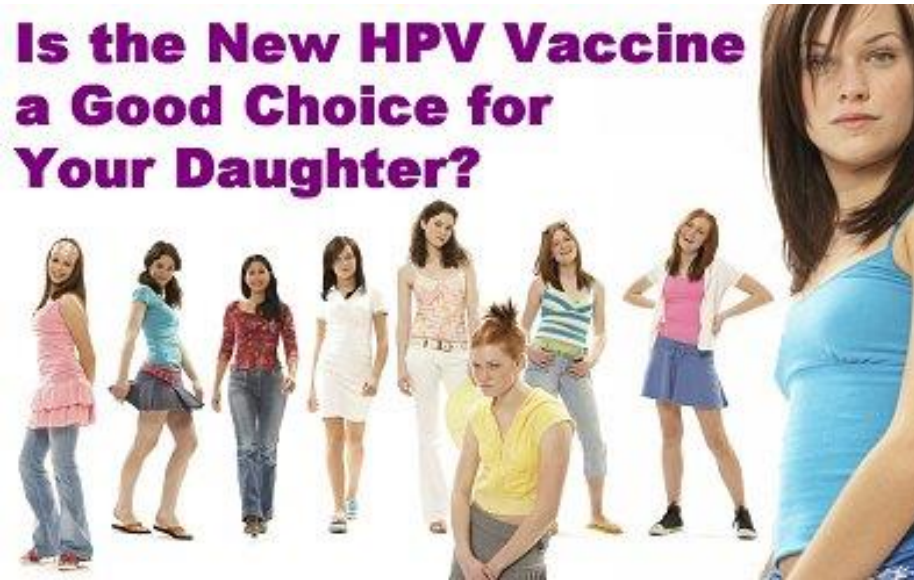


HPV VACCINES

- ◉ Cervarix and Gardasil
- ◉ The second dose be given one to two months after the first, and
- ◉ The third dose be given six months after the first dose.

RECOMMENDATIONS FOR HPV VACCINE

- It is approved for use in female patients between the ages of 9 & 26 years.



Pregnant women are not included in the recommendations for HPV vaccines