MedChem401 Herpesviridae

Members of the herpesvirus family have been identified in more than 80 different animal species

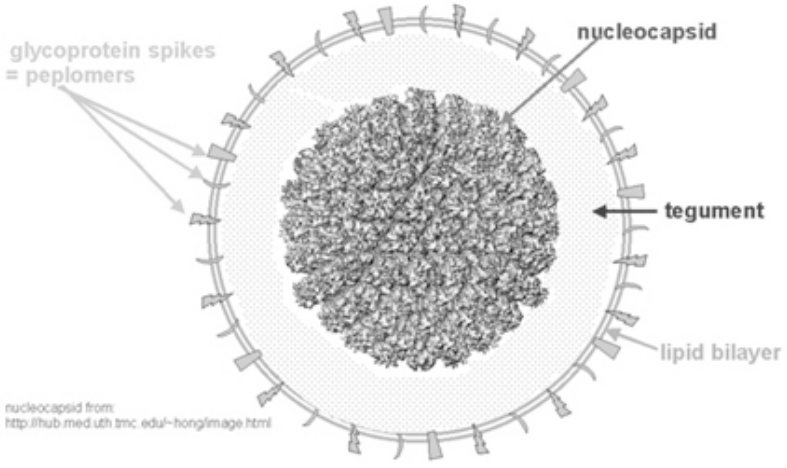
Eight have been identified as human pathogens

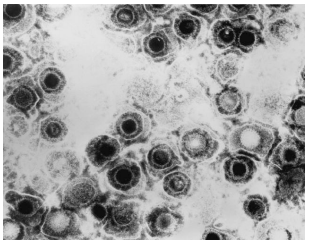
Herpes viruses are a leading cause of human viral disease, second only to influenza and cold viruses

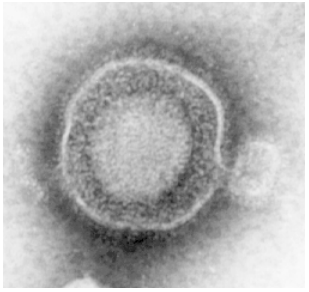
Herpes viruses infect most of the human population and persons living past middle age usually have antibodies to many of the human herpesviruses

Herpesviridae

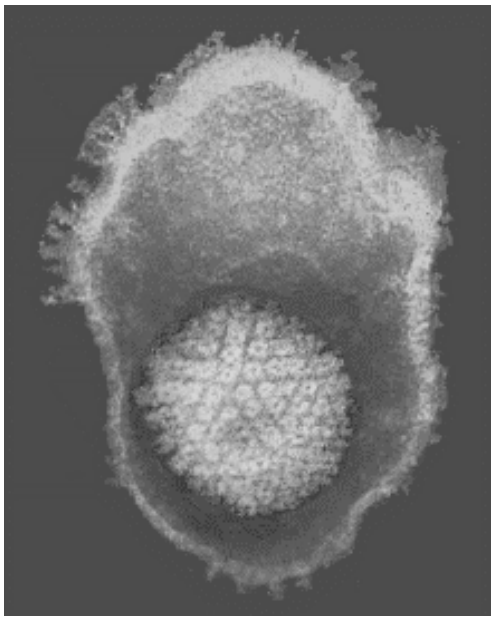
The Herpesviridae family comprises large, DNA-containing enveloped viruses

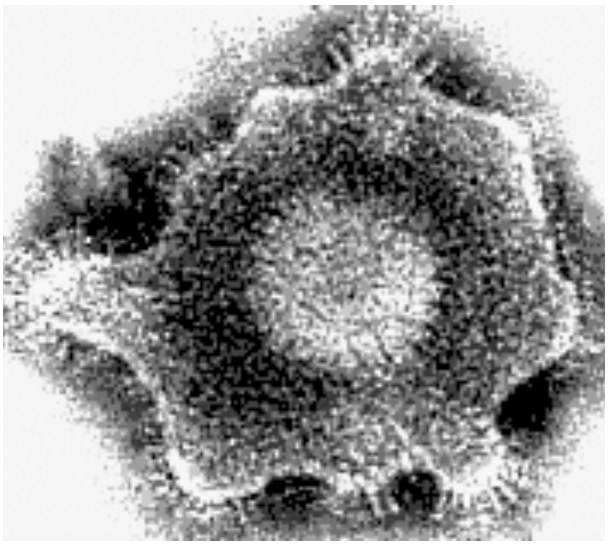






Herpesviridae





glycoprotein B (gpB) spikes visible in membrane

Herpesviridae

After the primary infection, herpesviruses establish latency in the infected host

Once a patient has become infected by herpes virus, the infection remains for life

Intermittently, the latent genome can become activated, in response to various stimulus, to produce infectious virions

Herpesviridae- Classification

Herpesviruses are classified into three groups based upon of tissue tropism, pathogenicity and behavior

α herpesviruses

- Fast replicating
- Variable host range
- Typically destroy host cell (lysis)
- Latency established in sensory ganglia

Herpes Simplex virus-1 and 2 (HSV-1/HSV-2)
Varicella-Zoster virus (VZV)

Herpesviridae- Classification

β herpesviruses

- Slowly replicating
- Restricted host range
- Infected cells enlarge (*cytomegalia*)
- Latency established in secretory glands, lymphoreticular cells, kidneys

Cytomegalovirus (CMV)
Human Herpesvirus-6 and 7 (HHV-6/HHV-7)

Herpesviridae- Classification

γ herpesviruses

- Replicate poorly
- Highly restricted host range
- Latency established in lymphoid tissue (T-cell or B-cell specific)

Epstein-Barr Virus (EBV), a B-cell transforming virus
Human Herpesvirus-8 (HHV-8, **KSHV**)

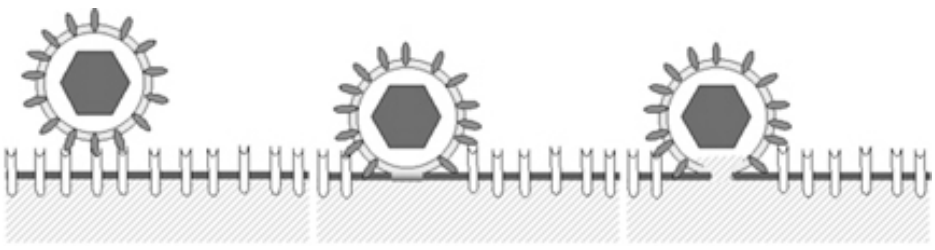
Herpesviridae- Replication

ADSORPTION

Envelope glycoproteins (e.g.- HSV proteins B and D) are required for binding and penetration

Cellular receptors recognized by the herpesviruses are unknown

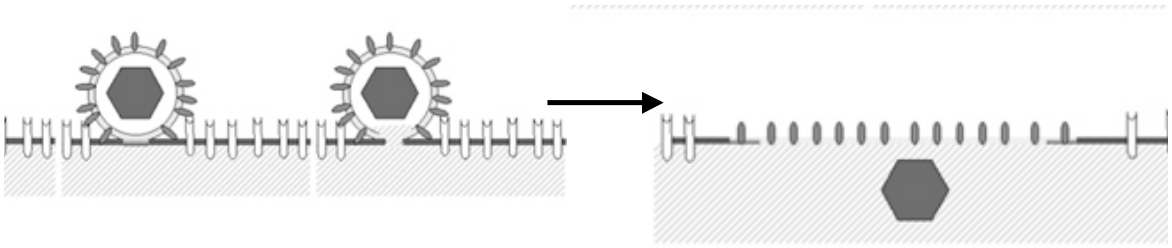
- EBV -> C3d complement receptor
- CMV -> Epidermal growth factor receptor
- HSV-1 -> Tumor necrosis factor receptor ??



Herpesviridae- Replication

PENETRATION

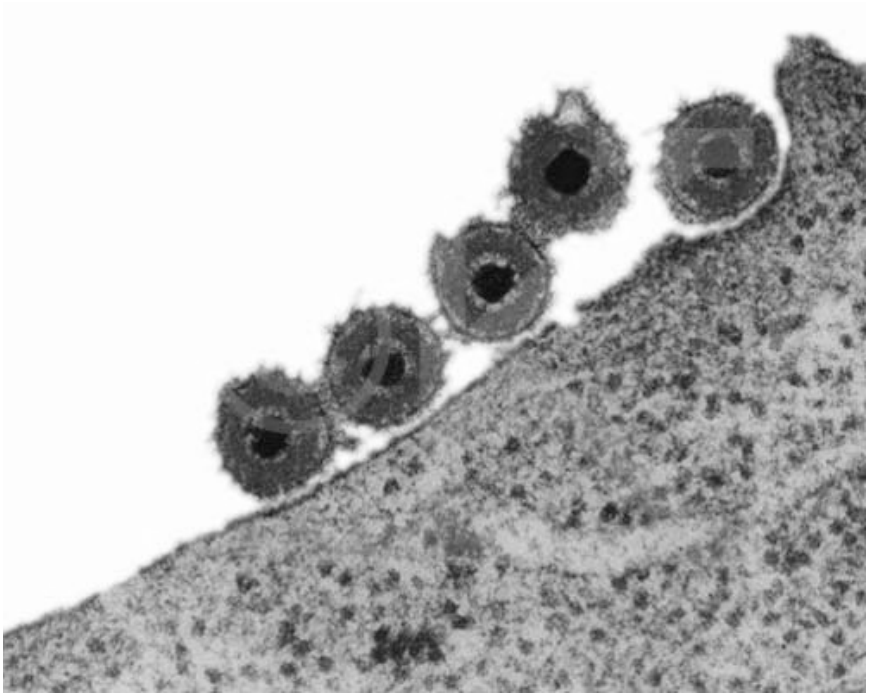
The nucleocapsid enters the cell by direct membrane fusion with the cell plasma membrane



Capsids are transported to the nucleus

DNA passes into the nucleus, probably via nuclear pores

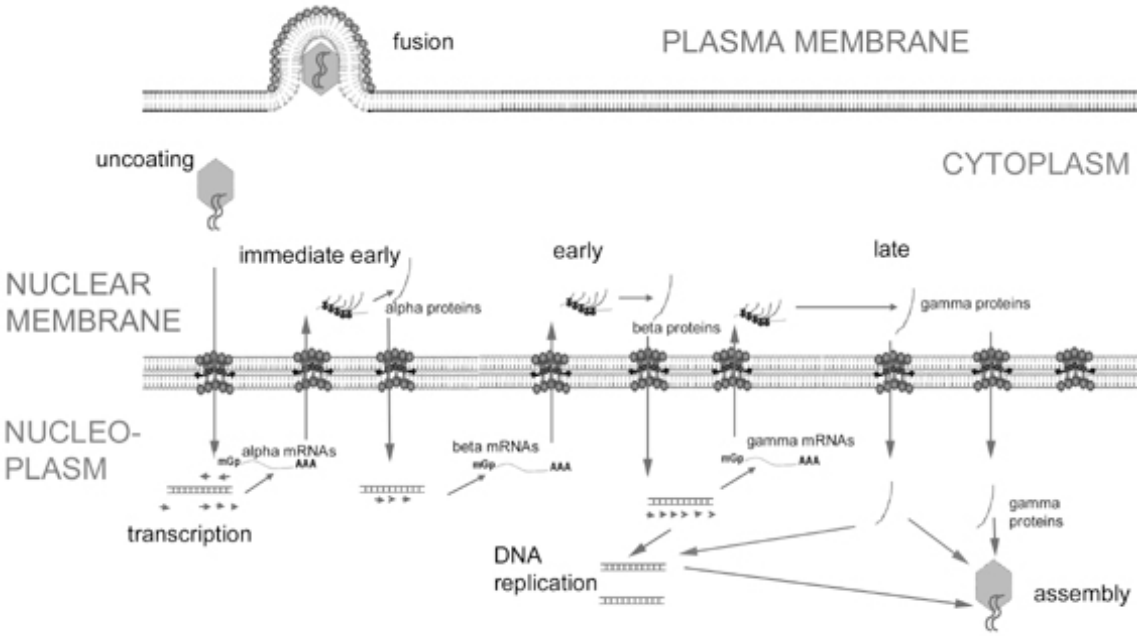
Herpesviridae- Replication



Adsorption and Penetration

Herpesviridae- Replication

Herpesvirus replication is a carefully regulated, multi-step process

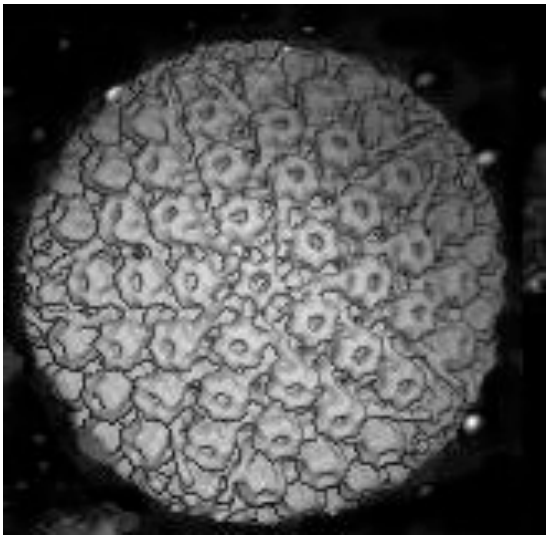


Herpesviridae- Replication

Virus Assembly

Assembly of the *nucleocasid* occurs in the nucleus

The nucleocapsid “buds” through intracellular membranes ultimately taking up tegument proteins beneath the envelope



Herpesviridae- Infection and Disease

Designation	Common Name	Subfamily	Associated Diseases
HHV-1	HSV-1	Alpha	Oral Herpes (cold sore), Genital Herpes
HHV-2	HSV-2	Alpha	Genital Herpes
HHV-3	VZV	Alpha	Chicken Pox, Shingles
HHV-4	EBV	Gamma	Mononucleosis, Lymphoma, Carcinoma
HHV-5	CMV	Beta	Mononucleosis, Retinitis, Transplant Rejection
HHV-6	HHV-6	Beta	Roseola infantum, Mononucleosis syndrome, Chronic fatigue syndrome, Multiple Sclerosis?
HHV-7	HHV-7	Beta	Roseola infantum?, Mononucleosis syndrome?
HHV-8	KSHV	Gamma	Kaposi's Sarcoma

Herpes Simplex Virus (HSV)

There are two types with very similar characteristics

- HSV-1 (HHV-1)
- HSV-2 (HHV-2)

The genome of HSV encodes a number of enzymes, including

- DNA-dependent DNA polymerase*
- Thymidine kinase*
- Ribonucleotide reductase
- Serine-protease
- Protease, RNase

Since these are viral enzymes, they represent reasonable targets for drug therapy

Herpes Simplex Virus (HSV)

The initial step of the interaction of virus with the cell is binding to heparan sulfate, which is found on many cell types

Thus, almost any human cell type can be infected by HSV

In many cells, such as endothelial cells and fibroblasts, infection is lytic

Neurons normally support a latent infection

If early and late proteins are made, the cell is set on a route to lysis

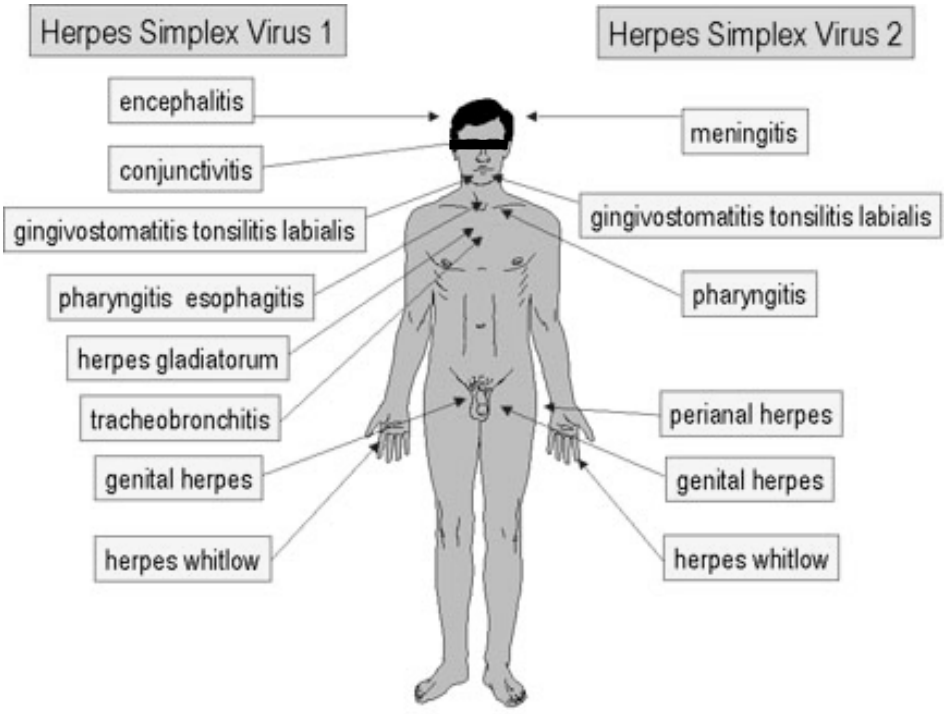
Herpes Simplex Virus (HSV)

HSV-1 and HSV-2 first infect cells of the mucoepithelia, or enter through wounds

The site of the initial infection depends on the way in which the patient acquires the virus

- HSV-1 above the waist
- HSV-2 below the waist

HSV- Pathology



HSV- Pathology

The virus replicates in the epithelial tissue yielding a characteristic “fever blister” or “cold sore”

The fluid in this blister is full of infectious virus

The blister ulcerates and forms a crusted lesion that heals without a scar

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HSV- Pathology

Interferon and natural killer cells are important in limiting the initial infection

Antibodies are directed against viral glycoproteins

The virus can also spread from one cell to another without entering the extracellular space

This means that cell-mediated responses are vital in controlling herpes infections; cytotoxic T cells and macrophages kill infected cells

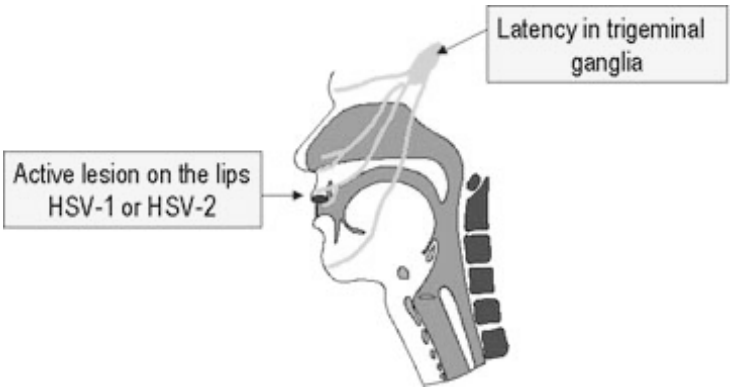
HSV- Latency

HSV also infects neurons that innervate the epithelial tissue

The virus travels along the neuron (retrograde transport)

- •oral mucosa -> trigeminal ganglia
- •genital mucosa -> sacral ganglia

A latent infection is established in the nervous tissue



HSV- Reactivation

Several agents may trigger recurrence

- •stress
- •exposure to strong sunlight
- •fever

The virus can travels back down the nerve axon and arrives at the mucosa that was initially infected

Vesicles containing infectious virus are formed on the muscosa and the virus spreads

Recurrent infections are usually less pronounced than the primary infection and resolve more rapidly

HSV Infections

Oral Herpes

Both HSV-1 and HSV-2

Genital Herpes

Primarily HSV-2 (10% cases HSV-1)
Involve a transient viremia (fever, myalgia, glandular inflammation in the groin area)
Secondary infections are frequently less severe

Herpes Keratitis

An infection of the eye
Primarily HSV-1
Sometimes recurrent
Leading cause of corneal blindness in the US

HSV Infections

Herpes gladiatorum

Contracted by wrestlers
Spreads by direct contact from skin lesions
Usually appears in the head and neck region
Also seen in other contact sports such as rugby (Herpes Rugbeiorum, or scrum pox)

HSV Encephalitis

Typically HSV-1
Most common cause of sporoadic viral encephalitis
Relatively rare (1000 cases/yr)

HSV- Treatment

Nucleoside Analogs

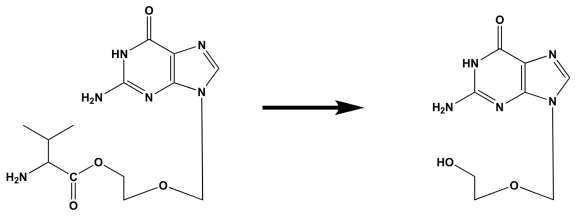
Acyclovir (Zovirax®)
Valacyclovir (Valtrex®; L-valyl ester of acyclovir)
Famciclovir (Famvir®; diacetyl ester of 6-deoxy penciclovir)

All suffer from the appearance of resistant HSV mutants

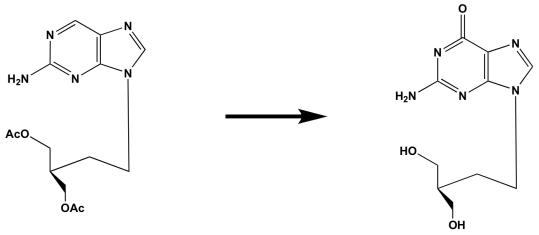
Fortunately, the mutant strains are less virulent

The drugs are ineffective against latent virus

Nucleoside Analogs

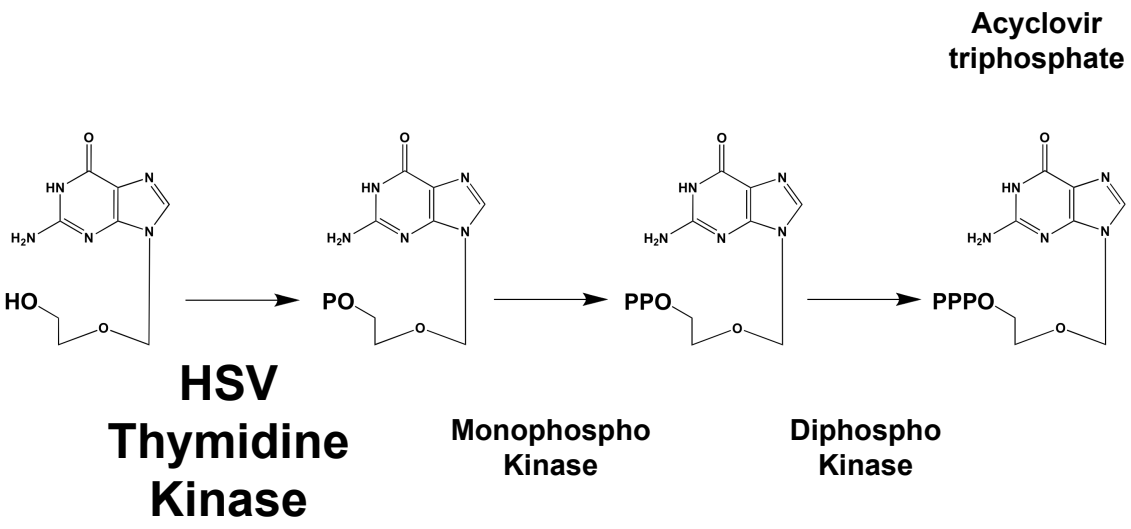


Valacyclovir **Acyclovir**



Famciclovir **Penciclovir**

Nucleoside Analogs- MOA



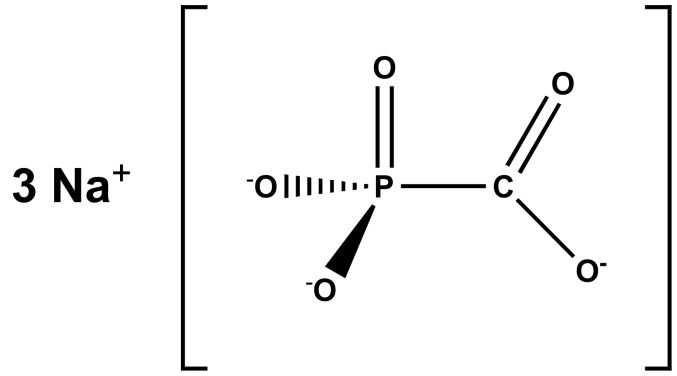
Nucleoside Analogs- MOA

Acyclovir triphosphate is a competitive inhibitor of viral DNA polymerase

Acyclovir triphosphate is incorporated into viral DNA and acts as a chain terminator

What are the requirements for DNA synthesis by DNA polymerase enzymes?

Foscarnet



Analog of Inorganic Pyrophosphate
Binds to phosphate binding site in DNAP

Varicella-Zoster Virus (VZV)

Initial infection usually in childhood with Varicella virus (HHV-3)
-> ***Chicken Pox***

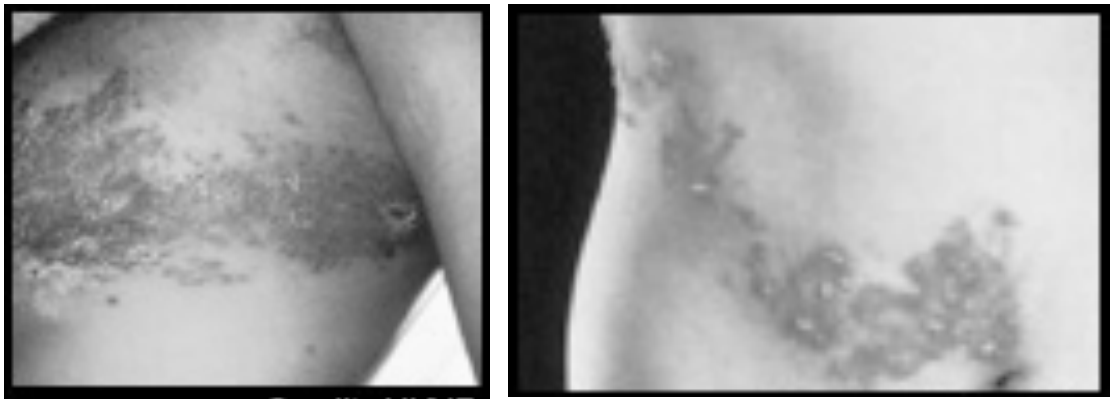
It is spread by respiratory aerosols or direct contact with lesions

The virus establishes latency within the dorsal root ganglia

Years or decades later, the virus (Herpes zoster) may reactivate -> ***Shingles***

Varicella-Zoster Virus (VZV)

Zoster means girdle, from the characteristic rash that forms a belt around the thorax



Rash along dermatomes

VZV- Pathology

Trigeminal nerve reactivation

- uveitis, keratitis, conjunctivitis

Cranial nerve reactivation

- **Bells palsy:** a condition that causes the facial muscles to weaken or become paralyzed. It's caused by trauma to the 7th cranial nerve and is not permanent.

- **Ramsay-Hunt syndrome:** virus spread to facial nerves. Characterized by intense ear pain, a rash around the ear, mouth, face, neck, and scalp, and paralysis of facial nerves. Symptoms may include hearing loss, vertigo, and tinnitus.

VZV- Pathology

Post-herpetic neuralgia: chronic burning or itching pain; hyperesthesia (increased sensitivity to touch)

Acyclovir, valacyclovir, and famciclovir are approved for the treatment of VZV

Epstein Barr Virus (EBV)

EBV (HHV-4) is responsible for **infectious mononucleosis**

The primary infection is often asymptomatic, but the patient may shed infectious virus for many years

Some patients develop symptoms after 1-2 months

- malaise
- lymphadenopathy
- tonsillitis
- enlarged spleen and liver
- fever
- occasional rash

The severity of disease often depends on age, but usually resolves in 1 to 4 weeks

EBV may be transmitted by blood transfusion

Epstein Barr Virus (EBV)

The virus uses the C3d complement receptor for entry and thus infects only a small number of cell types

- •oro- and naso-pharynx
- •B lymphocytes

Lytic Infection

The ZEBRA protein is expressed in epithelial cells
This transcription factor promotes the expression of early genes -> active virus replication and lytic infection

Epstein Barr Virus (EBV)

Latency

B lymphocytes are only semi-permissive for replication and EBV infection is often latent

The infected B-lymphocyte contains a few ***episomes***

Only a few genes are expressed from the episome, including two membrane proteins that are ***oncogenic***

- •Burkitts lymphoma
- •nasal pharyngeal carcinoma

In addition:

- •infectious mononucleosis?
- •chronic fatigue syndrome?

Cytomegalovirus (CMV)

CMV (HHV-5) derives its name from the fact that it can form multinucleated cells (syncytia)

Some cells such as macrophages and fibroblasts support a productive infection

Other cells such as T lymphocytes and stromal cells of the bone marrow set up latent infection

The virus is spread via most secretions, particularly saliva, urine, vaginal secretions and semen

CMV may also be spread by blood transfusion and organ transplant

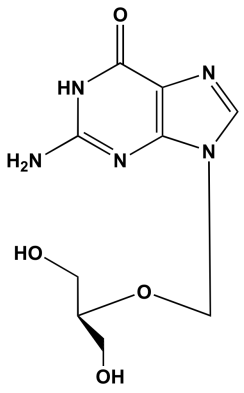
CMV causes no symptoms in children and mild disease in adults

CMV

The virus elicits both humoral and cell-mediated immunity but the infection is not cleared

The virus may reactivate, particularly in cases of immunosuppression

- Organ transplant patients
- Immunosuppressive disease
  (**CMV-retinitis** occurs in up to 15% of all AIDS patients; also pneumonia, colitis, esophagitis and encephalitis)

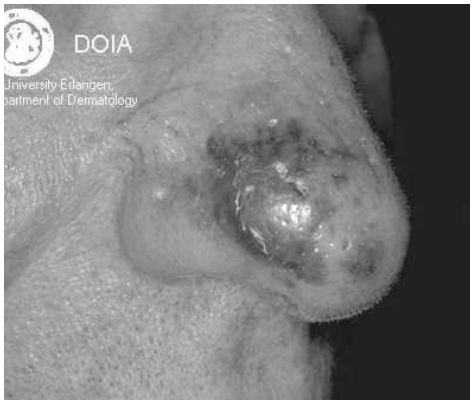


Gancyclovir may be used, especially to treat retinitis in the immunosuppressed

Human Herpesvirus 8

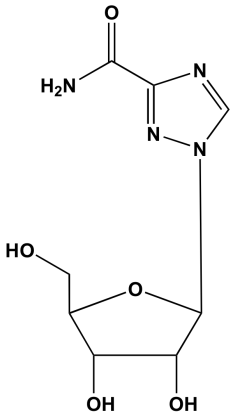
Human Herpesvirus 8 (HHV-8) , or **Kaposi Sarcoma Herpes Virus** (KSHV), is associated with the development of Kaposi's Sarcoma in AIDS patients.

Kaposi's sarcoma is a type of cancer that affects men and is rarely seen in women.



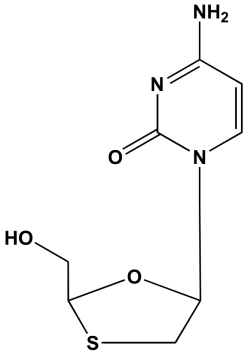
Although KS mainly affects the skin, the mouth, and the lymph nodes, it can also involve the bowels and lungs.

HHV 8 is sexually transmitted.



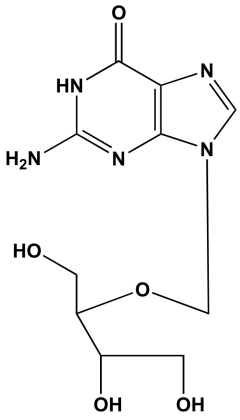
Ribavirin

Phosphorylated
Interferes with RNA synthesis/



Lamivudine

Phosphorylated
Inhibits hepatitis B DNAP
Inhibits HIV RT



Vidarabine

Phosphorylated
Opthalmic Ointment