HERPESVIRIDAE (1)

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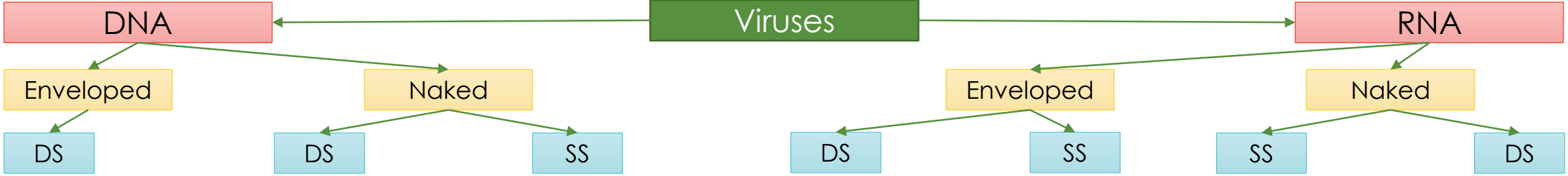


Herpesviridae (Ic)

Herpes simplex virus 1&2

Adenoviridae (Ic)

Adenovirus

Parvoviridae (Ic)

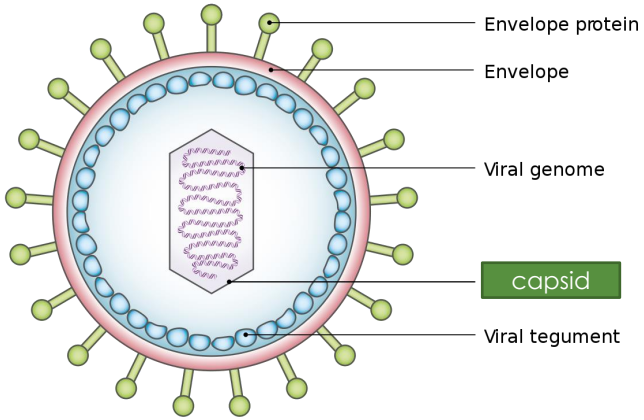
Parvovirus B19

Bocaviruses

Guidelines:
SS: single stranded
DS: Double stranded
Ic: Ichosahedral capsid
He: Helical capsid
Co: Complex capsid

Herpesviridae (1)

1- Structure & composition

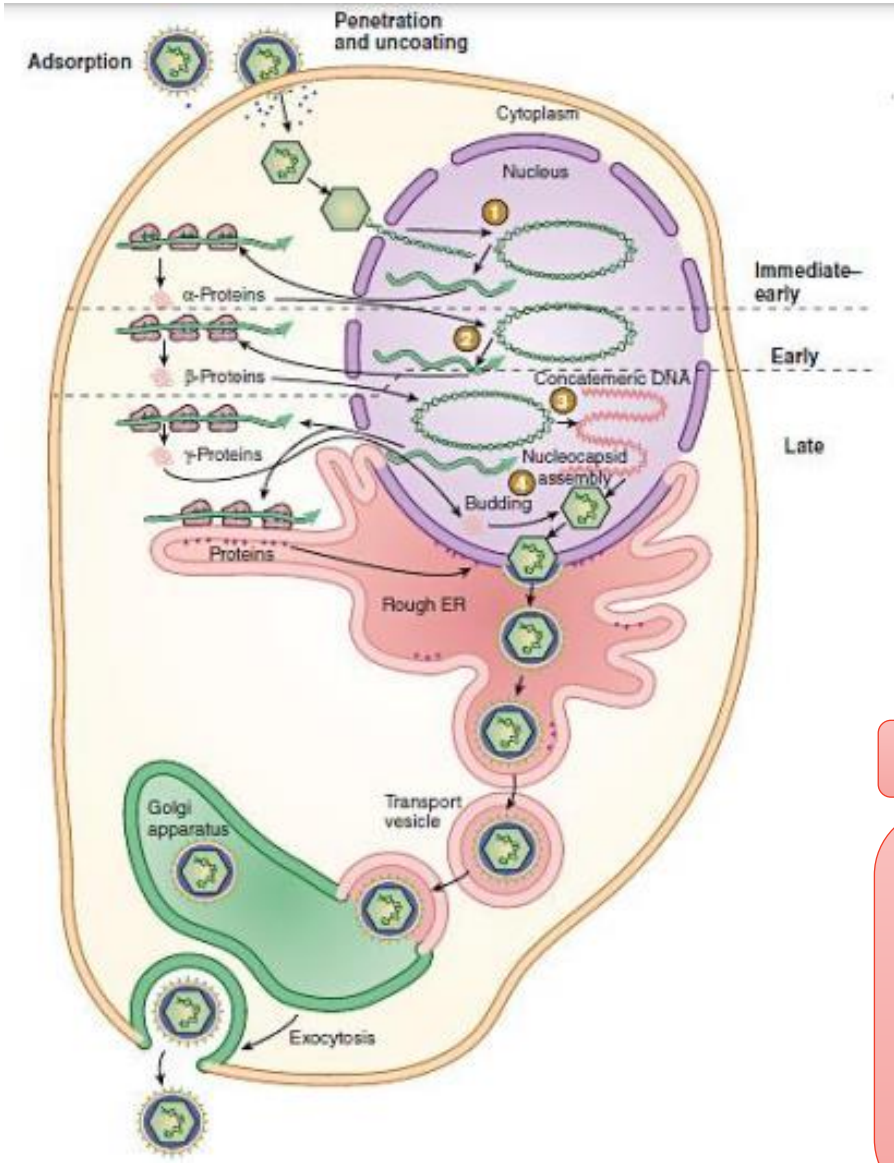


Subfamily ("-herpesvirinae")	Examples: Official Name ("Human Herpesvirus")	Examples: Common Name
Alpha	1	Herpes simplex virus type 1
	2	Herpes simplex virus type 2
	3	Varicella-zoster virus
Beta	5	Cytomegalovirus
	6	Human herpesvirus 6
	7	Human herpesvirus 7
Gamma	4	Epstein-Barr virus
	8	Kaposi sarcoma-associated herpesvirus

2- General features

- Different members are indistingushable by electron microscopy
- Latent viruses
- Some cause cancer

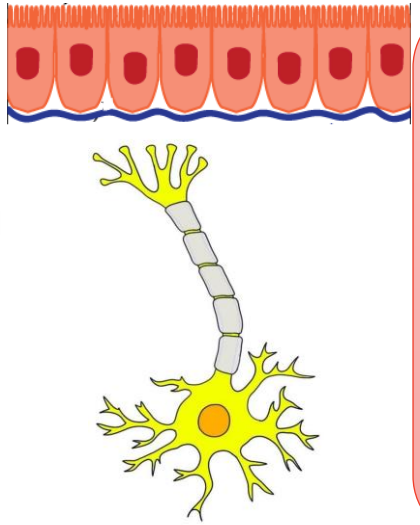
3- Replication



4- Herpesvirus Simplex Viruses - Overview

- Fast replication/ a subfamily / kill infected cells

5- Pathogenesis



- Replicate at site of entry
- Move to the nerve and establish latency
- When immune is suppressed its activated again
- May cause viremia

6- Clinical manifestations

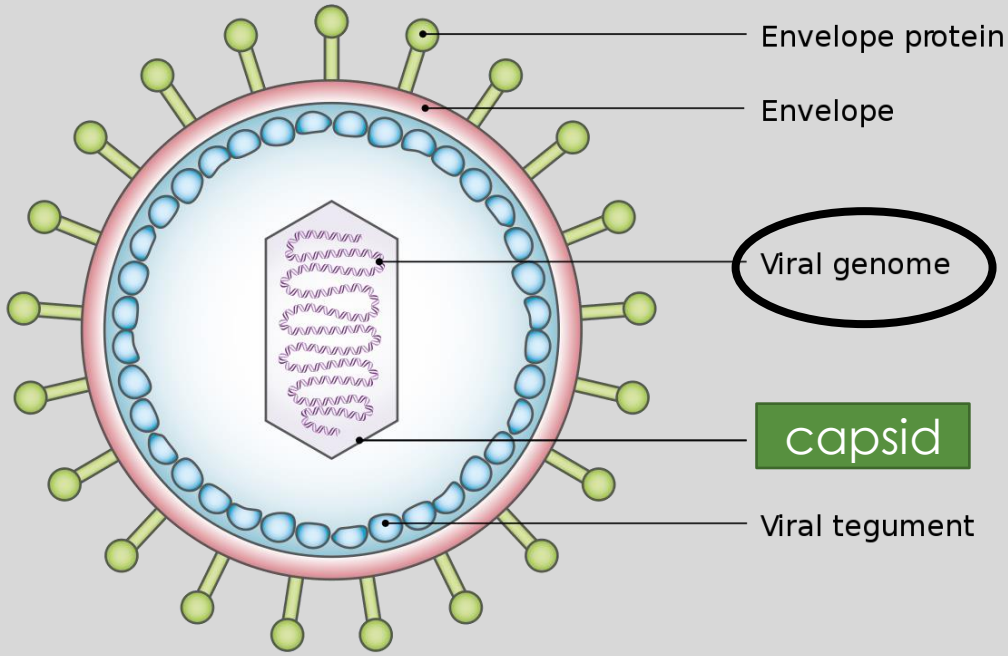
1) Oropharyngeal infection
2) Keratoconjunctivitis
3) Genital disease
4) herpetic whitlow, herpes gladiatorum & Eczema herpeticum
5) Encephalitis
6) Neonatal infections
7) Immune compromised infections

1- Structure and composition

Biologic Properties				Examples	
Subfamily ("-herpesvirinae")	Growth Cycle and Cytopathology	Latent Infections	Genus ("-*virus*")	Official Name ("Human Herpesvirus")	Common Name
Alpha	Short, cytolytic	Neurons	*Simplex*	1	Herpes simplex virus type 1
				2	Herpes simplex virus type 2
			Varicello	3	Varicella-zoster virus
Beta	Long, cytomegalic	Glands, kidneys	*Cytomegalo*	5	Cytomegalovirus
	Long, lymphoproliferative	Lymphoid tissue	*Roseolo*	6	Human herpesvirus 6
				7	Human herpesvirus 7
Gamma	Variable, lymphoproliferative	Lymphoid tissue	*Lymphocrypto*	4	Epstein-Barr virus
			Rhadino	8	Kaposi sarcoma-associated herpesvirus

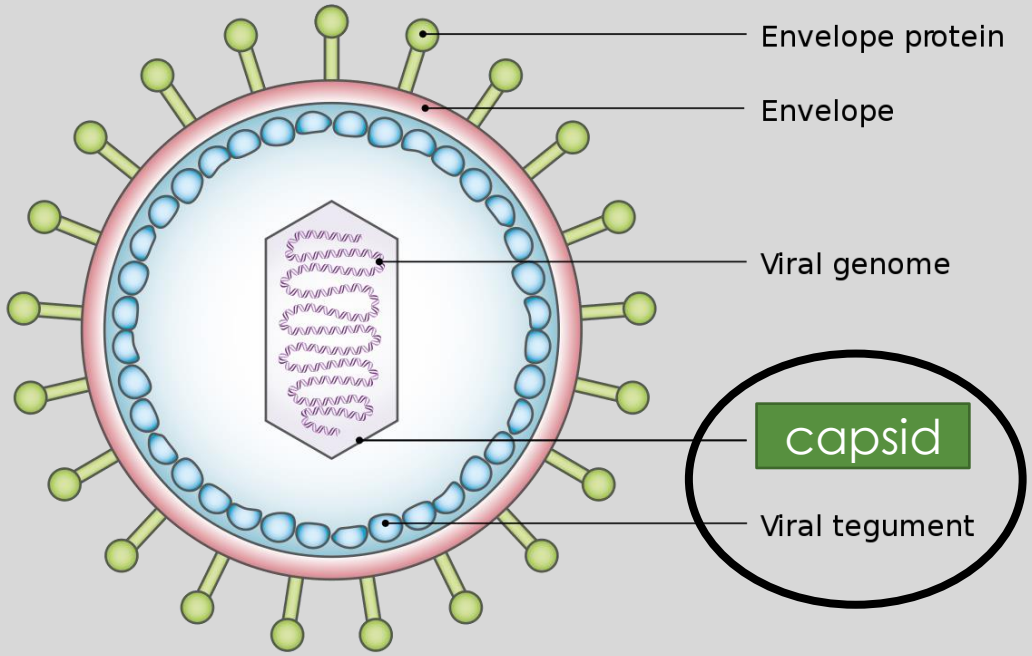
1- Structure and composition

- Genome: Double-stranded DNA, linear, 125-240 kbp (different among types), reiterated sequences
  There is little DNA homology among different herpesviruses except for HSV-1 and HSV-2, which show 50% sequence homology, and human herpesviruses 6 and 7 (HHV-6 and HHV-7), which display limited (30–50%) sequence homology.
  Treatment with restriction endonucleases yields characteristically different cleavage patterns for herpesviruses and even for different strains of each type. This "fingerprinting" of strains allows epidemiologic tracing of a given strain.



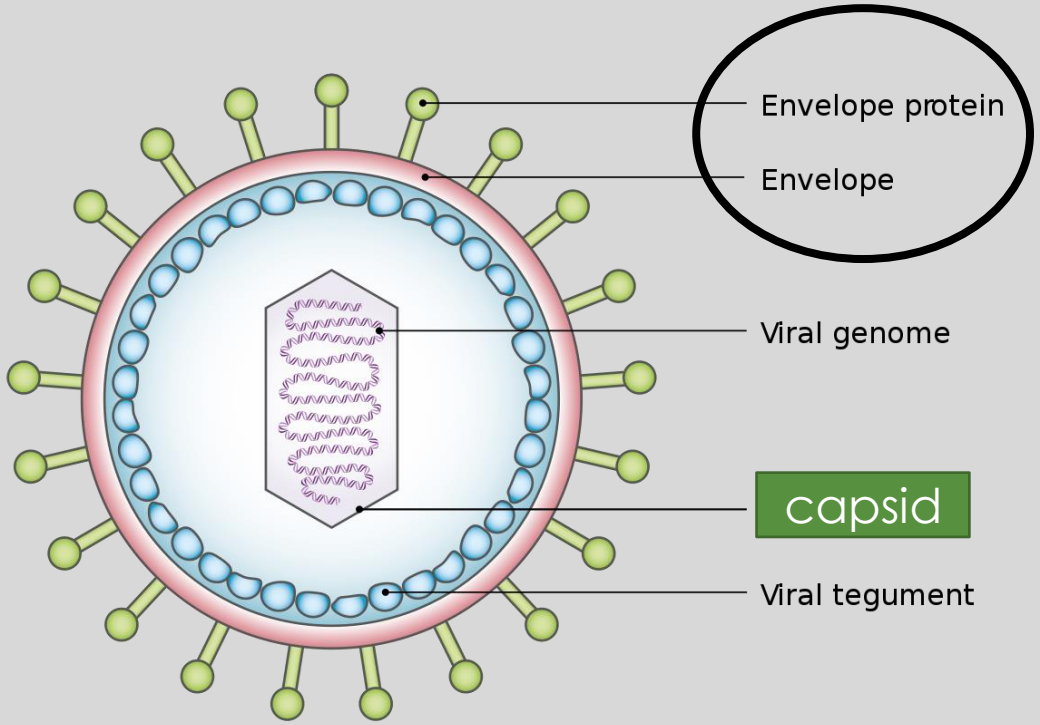
1- Structure and composition

- Capsid: Icosahedral capsid, has 162 capsomeres, and it's about 125nm
- Tegument: An amorphous, sometimes asymmetric structure between the capsid and envelope, it's important in the initiation of the viral replication
- Proteins of the capsid & tegument are about 25 types.



1- Structure and composition

- Envelope: spherical, about 150- 200 nm in diameter, have about 10 types of proteins
- Very important: The envelope is formed from the nucleus
- Proteins help in penetration of the cell during infection, and they are important for the host in immune response

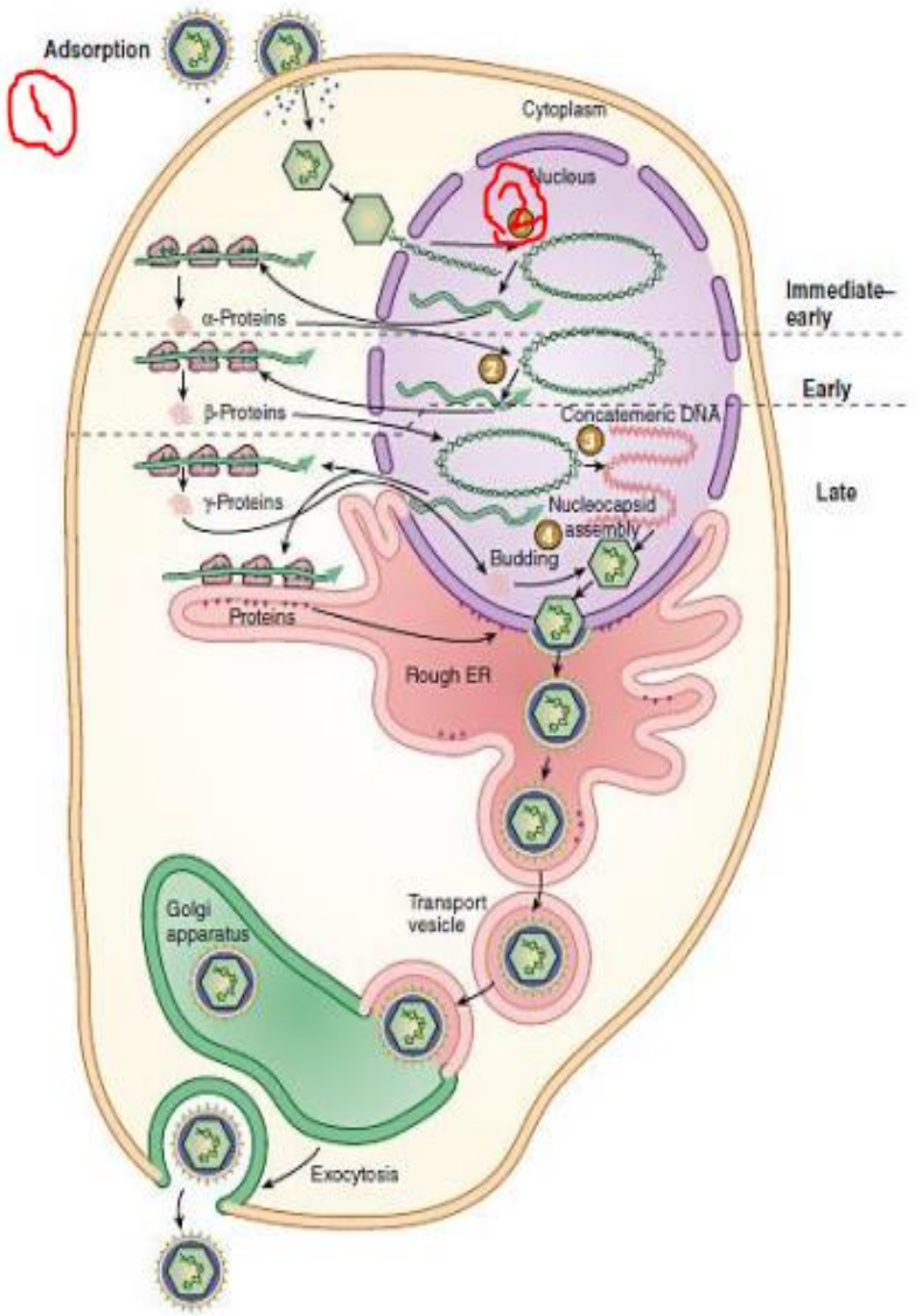


2- General characteristics

- Different members of the group share architectural details and are indistinguishable by electron microscopy
- There is little antigenic relatedness among members of the herpesvirus group. Only HSV-1 and HSV-2 share a significant number of common antigens. HHV-6 and HHV-7 exhibit a few cross-reacting epitopes.
- The herpesvirus genome is large and encodes at least 100 different proteins. Of these, more than 35 polypeptides are involved in the structure of the virus particle; at least 10 are part of the viral envelope, and many of the proteins are enzymes
- Herpesviridae causes latent infection, and frequently reactive in immunosuppressant hosts
- Some Herpesviridae are considered as oncoviruses (can cause cancer)

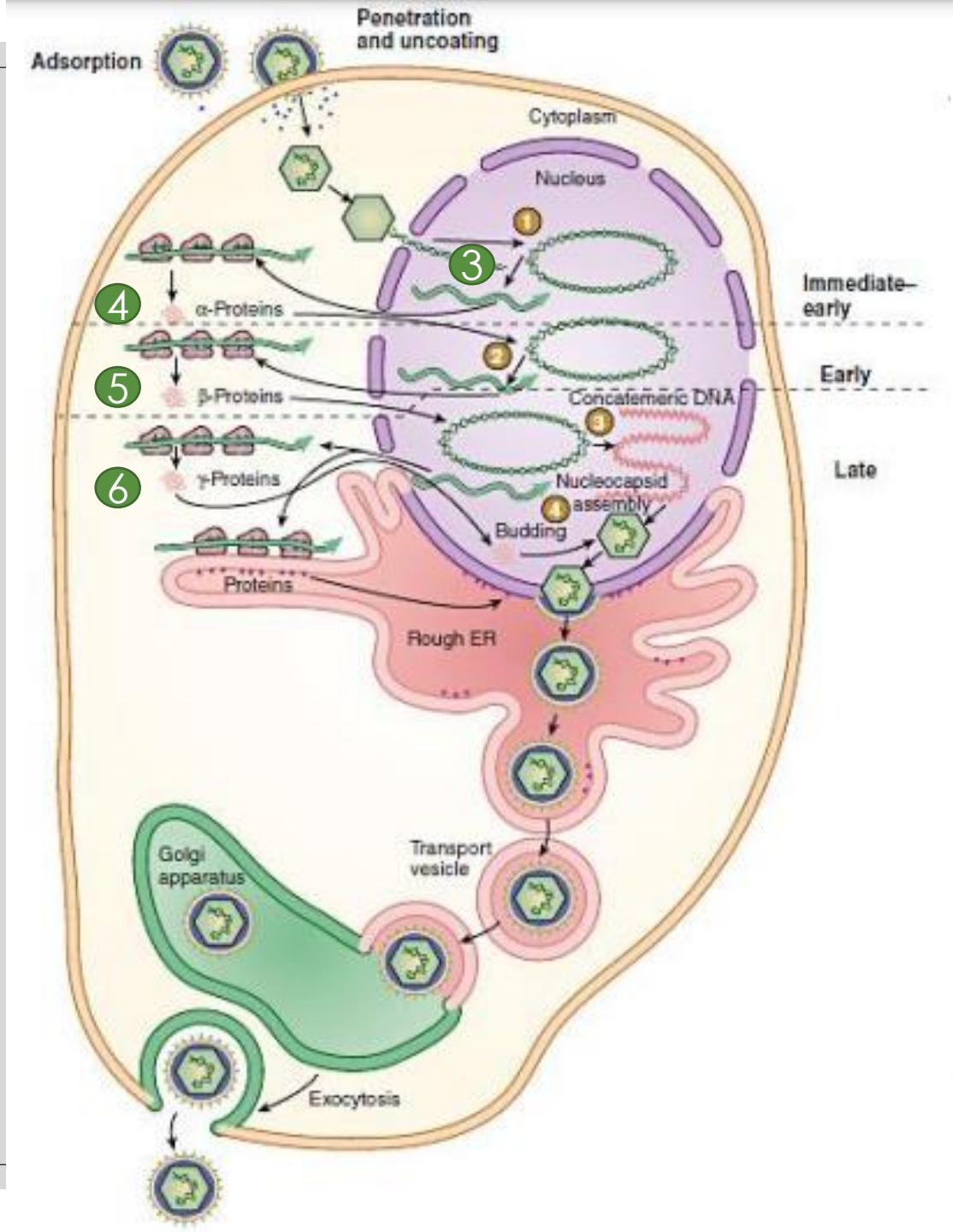
3- Replication

- 1) The virus enters the cell by fusion with the cell membrane after binding to specific cellular receptors via envelope glycoproteins.
- Several herpesviruses bind to cell surface glycosaminoglycans, principally heparan sulfate. Virus attachment also involves binding to one of several coreceptors (e.g., members of IgSF).
- 2) After fusion, the capsid is transported through the cytoplasm to a nuclear pore, uncoating occurs, and the DNA becomes associated with the nucleus.
- The viral DNA forms a circle immediately upon release from the capsid. Expression of the viral genome is tightly regulated and sequentially ordered in a cascade fashion.



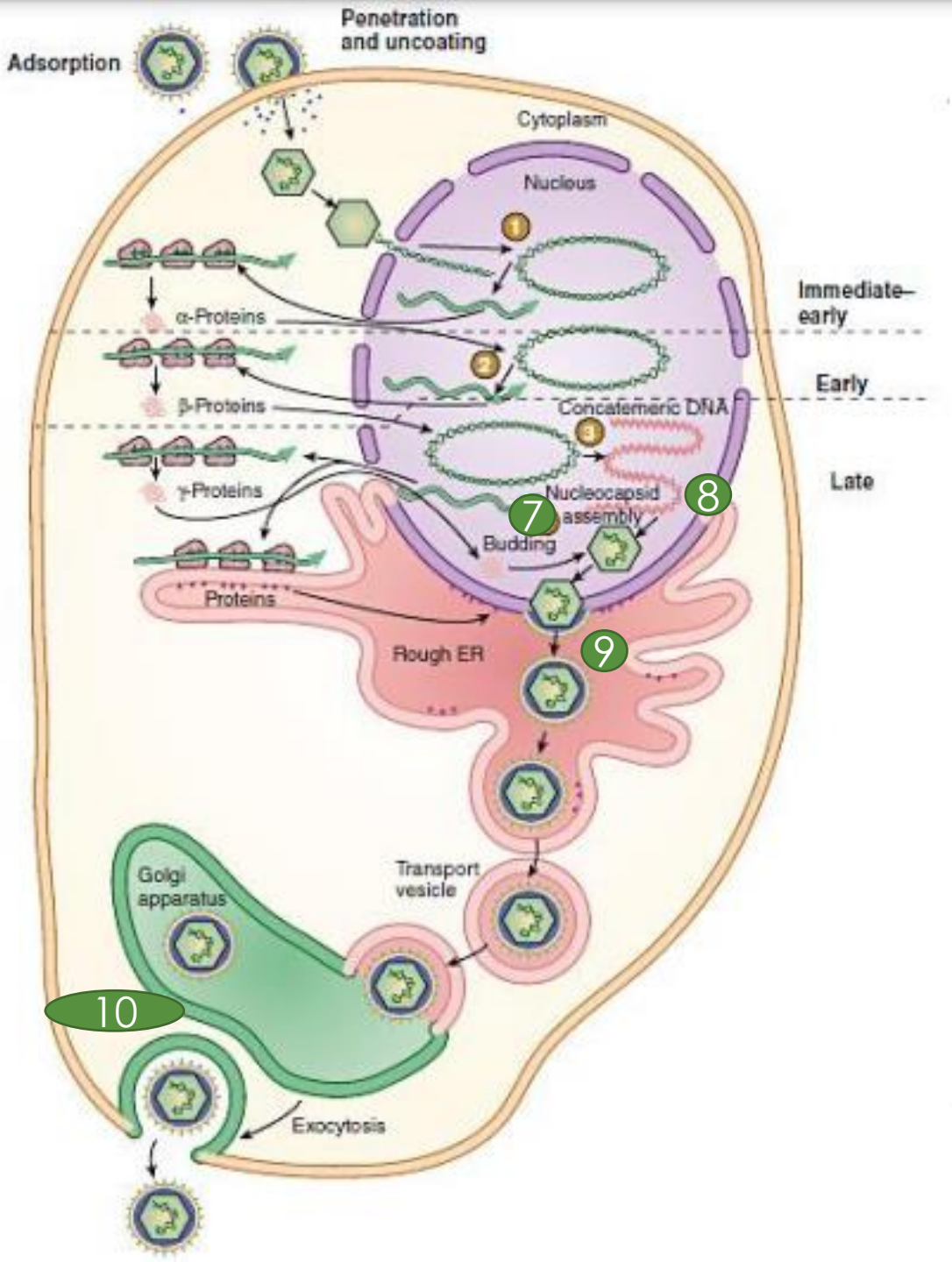
3- Replication

- 3) The tegument protein VP16, complexes with several cellular proteins and activates initial viral gene expression.
- 4) Immediate-early genes are expressed, yielding "α" proteins.
- 5) These proteins permit expression of the early set of genes, which are translated into "β" proteins.
- 6) Viral DNA replication begins, and late transcripts are produced that give rise to "γ" proteins
- Notes: More than 50 different proteins are synthesized in herpesvirus-infected cells. Many α and β proteins are enzymes or DNA-binding proteins; most of the γ proteins are structural components.



3- Replication

- 7) "γ" proteins will form empty capsids
- 8) Newly synthesized viral DNA is packaged into preformed empty nucleocapsids in the cell nucleus.
- 9)Maturation occurs by budding of nucleocapsids through the altered inner nuclear membrane.
- 10) Enveloped virus particles are then transported by vesicular movement to the surface of the cell.
- Notes:
  - Viral DNA is transcribed throughout the replicative cycle by cellular RNA polymerase II but with the participation of viral factors.
  - Viral DNA is synthesized by a rolling-circle mechanism.
  - Herpesviruses differ from other nuclear DNA viruses in that they encode a large number of enzymes involved in DNA synthesis.

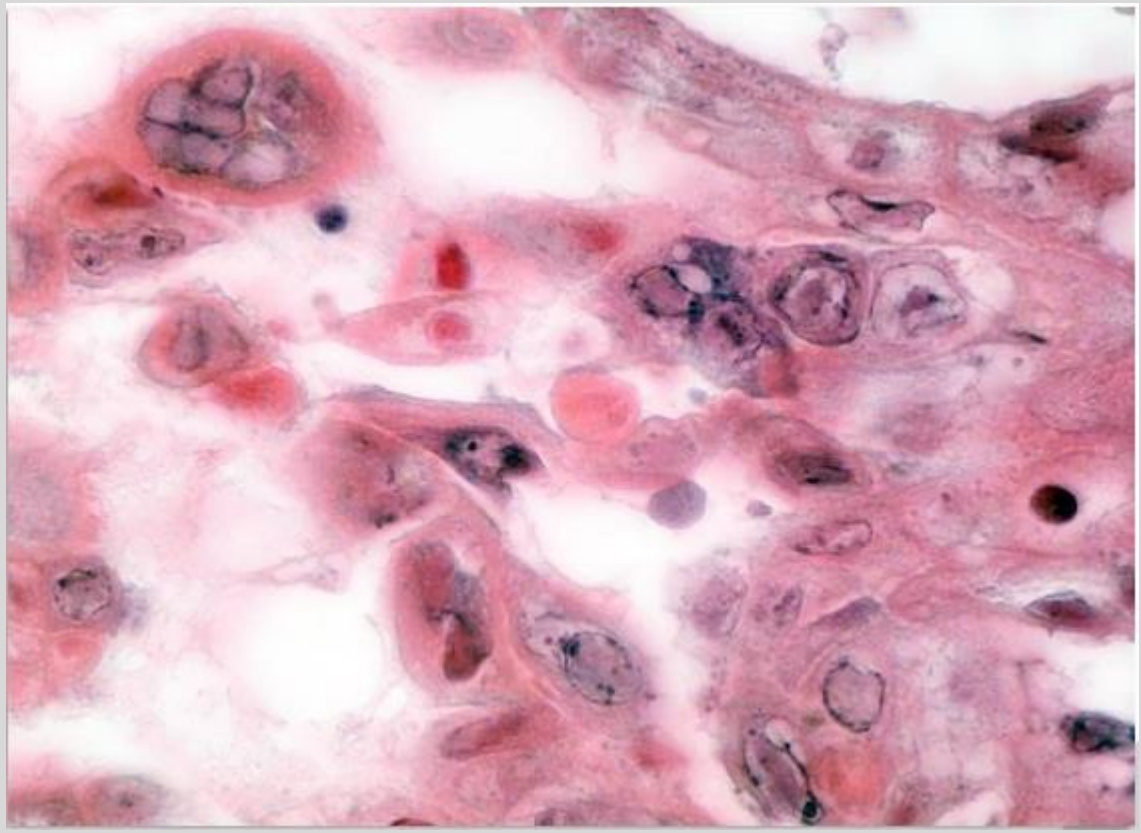


3- Replication

- The length of the replication cycle varies from about 18 hours for HSV to more than 70 hours for CMV.
- Cells productively infected with herpesviruses are invariably killed.
- Host macromolecular synthesis is shut off early in infection; normal cellular DNA and protein synthesis virtually stop as viral replication begins.
- Cytopathic effects induced by human herpesviruses are quite distinct (swelling rounding, multinucleated giant cell containing acidophilic intranuclear inclusions.
- The number of potential protein-coding open-reading frames in herpesvirus genomes ranges from about 70 to more than 200.

3- Replication

- Cytopathic effects induced by human herpesviruses are quite distinct (swelling rounding, multinucleated giant cell containing acidophilic intranuclear inclusions.
  Note: Cell fusion provides an efficient method for cell-to-cell spread of HSV, even in the presence of neutralizing antibody.
- Herpesviruses have recently been found to express multiple microRNAs, small (~22 nucleotides) single-stranded RNAs that function post-transcriptionally to regulate gene expression.
- It is predicted that these viral microRNAs are important in regulating entry into or exit from (or both) the latent phase of the virus life cycle and may be attractive targets for antiviral therapy.



4- Herpesvirus Simplex Viruses - Overview

- HSV are extremely widespread humans.
- They exhibit a broad host range, being able to replicate in many types of cells and to infect many different animals.
- They grow rapidly and are highly cytolytic.
- The HSVs establish latent infections in nerve cells; recurrences are common.

4- Herpesvirus Simplex Viruses - Overview

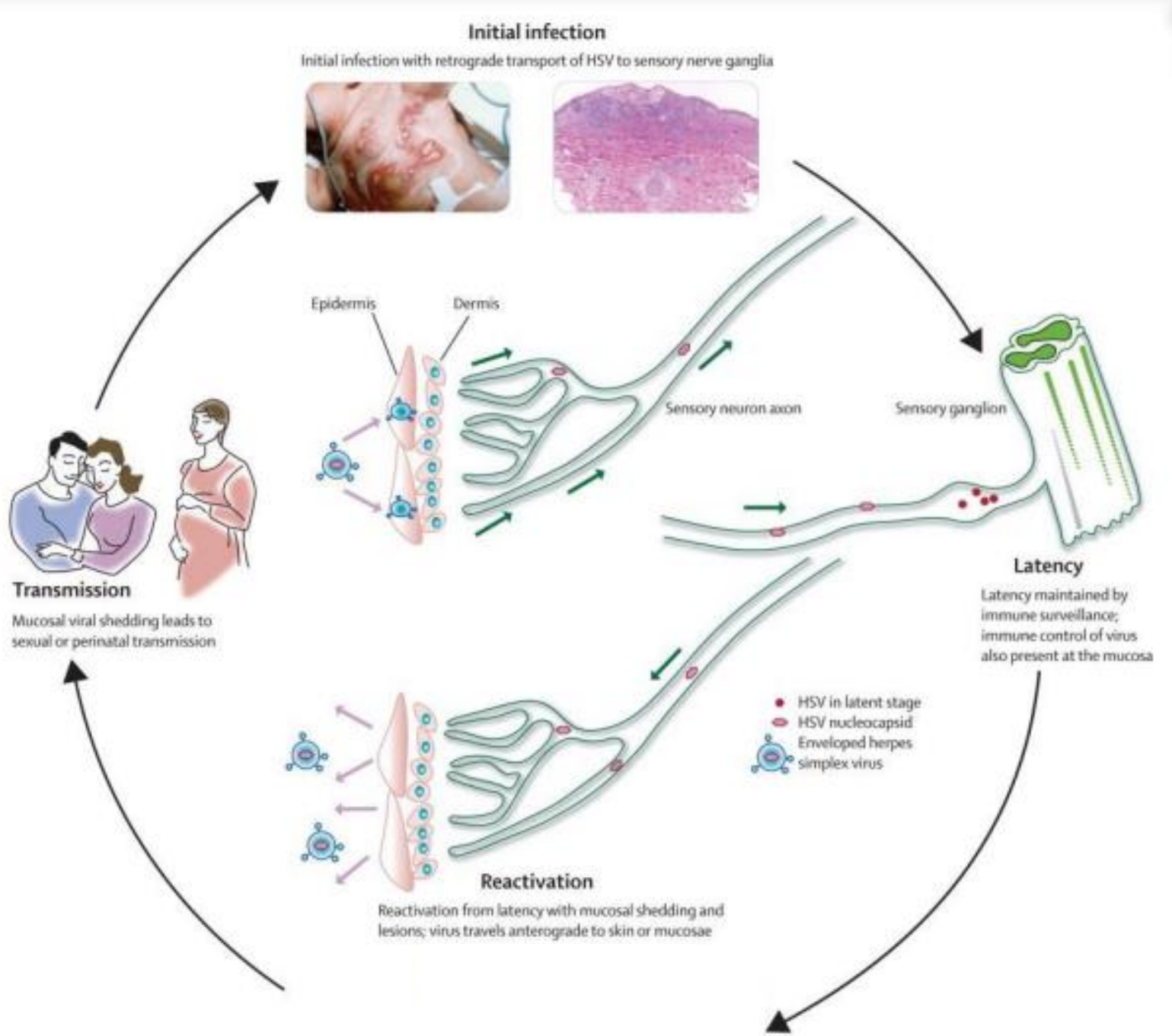
Characteristics	HSV-1	HSV-2
Biochemical		
Viral DNA base composition (G + C) (%)	67	69
Buoyant density of DNA (g/cm^3)	1.726	1.728
Buoyant density of virions (g/cm^3)	1.271	1.267
Homology between viral DNAs (%)	~50	~50
Biologic		
Animal vectors or reservoirs	None	None
Site of latency	Trigeminal ganglia	Sacral ganglia
Epidemiologic		
Age of primary infection	Young children	Young adults
Transmission	Contact (often saliva)	Sexual

4- Herpesvirus Simplex Viruses - Overview

- There are two distinct HSVs: types 1 and 2 (HSV-1 and HSV-2)
- Their genomes are similar in organization and exhibit substantial sequence homology. However, they can be distinguished by sequence analysis or by restriction enzyme analysis of viral DNA.
- The two viruses cross-react serologically, but some unique proteins exist for each type.
- They differ in their mode of transmission. Whereas HSV-1 is spread by contact, usually involving infected saliva, HSV-2 is transmitted sexually or from a maternal genital infection to a newborn. This results in different clinical features of human infections.

4- Herpesvirus Simplex Viruses - Overview

- The HSV growth cycle proceeds rapidly, requiring 8–16 hours for completion.
- The HSV genome is large (~150 kbp) and can encode at least 70 polypeptides; the functions of many of the proteins in replication or latency are not known.
- At least eight viral glycoproteins are among the viral late gene products.
- One (gD) is the most potent inducer of neutralizing antibodies:
  - Glycoprotein C is a complement (C3b)-binding protein, and gE is an Fc receptor, binding to the Fc portion of immunoglobulin G (IgG).
  - Glycoprotein G is type specific and allows for antigenic discrimination between HSV-1 (gG-1) and HSV-2 (gG-2).


Initial infection
Initial infection with retrograde transport of HSV to sensory nerve ganglia
Epidermis
Dermis
Sensory neuron axon
Sensory ganglion
Latency
Latency maintained by immune surveillance; immune control of virus also present at the mucosa
HSV in latent stage
HSV nucleocapsid
Enveloped herpes simplex virus
Reactivation
Reactivation from latency with mucosal shedding and lesions; virus travels anterograde to skin or mucosae
Transmission
Mucosal viral shedding leads to sexual or perinatal transmission

5- Pathogenesis

- In primary infection, the virus must encounter mucosal surfaces or broken skin for an infection to be initiated (unbroken skin is resistant)
- Viral replication occurs first at the site of infection. Virus then invades local nerve endings and is transported by retrograde axonal flow to dorsal root ganglia, where, after further replication, latency is established
- Whereas oropharyngeal HSV-1 infections result in latent infections in the trigeminal ganglia, genital HSV-2 infections lead to latently infected sacral ganglia
- Viremia is more common during primary HSV-2 infections than during HSV-1 infections.
- Primary HSV infections are usually mild; (mostly asymptomatic). Only rarely does systemic disease develop.

5- Pathogenesis

- Cytopathic effects induced by human herpesviruses are quite distinct (swelling rounding, multinucleated giant cell containing acidophilic intranuclear inclusions.
- Lesions induced in the skin and mucous membranes by HSV-1 and HSV-2 are the same and resemble those of VZV.
- Changes induced by HSV are similar for primary and recurrent infections but vary in degree, reflecting the extent of viral cytopathology.
- Cell fusion provides an efficient method for cell-to-cell spread of HSV, even in the presence of neutralizing antibody.
- Because HSV causes cytolytic infections, pathologic changes are due to necrosis of infected cells together with the inflammatory response.

5- Pathogenesis

- In latent infection, the virus resides in latently infected ganglia in a nonreplicating state; only a very few viral genes are expressed.
- Viral persistence in latently infected ganglia lasts for the lifetime of the host.
- No virus can be recovered between recurrences at or near the usual site of recurrent lesions.
- Provocative stimuli can reactivate virus from the latent state, including axonal injury, fever, physical or emotional stress, and exposure to ultraviolet light.
- The virus follows axons back to the peripheral site, and replication proceeds at the skin or mucous membranes.

5- Pathogenesis

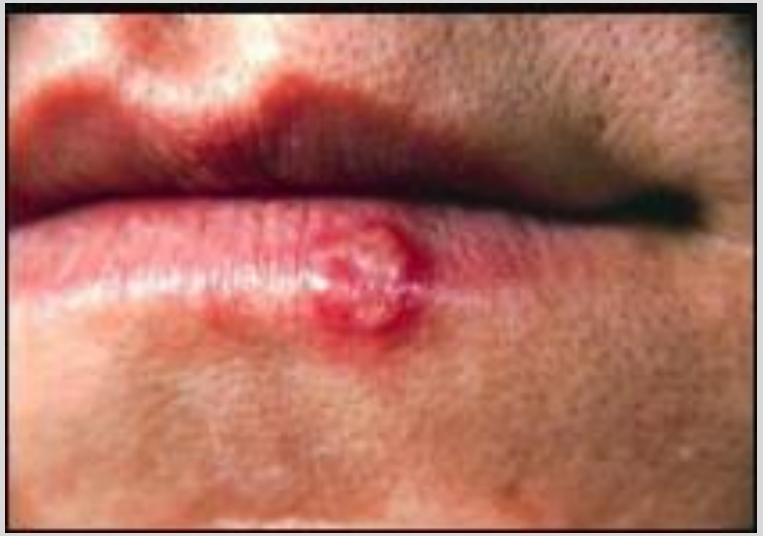
- Spontaneous reactivations occur despite HSV-specific humoral and cellular immunity in the host. However, this immunity limits local viral replication, so that recurrent infections are less extensive and less severe.
- Many recurrences are asymptomatic, reflected only by viral shedding in secretions.
- When symptomatic, episodes of recurrent HSV-1 infection are usually manifested as cold sores (fever blisters) near the lip.
- More than 80% of the human population harbor HSV-1 in a latent form, but only a small portion experience recurrences.
- It is not known why some individuals have reactivations and others do not.

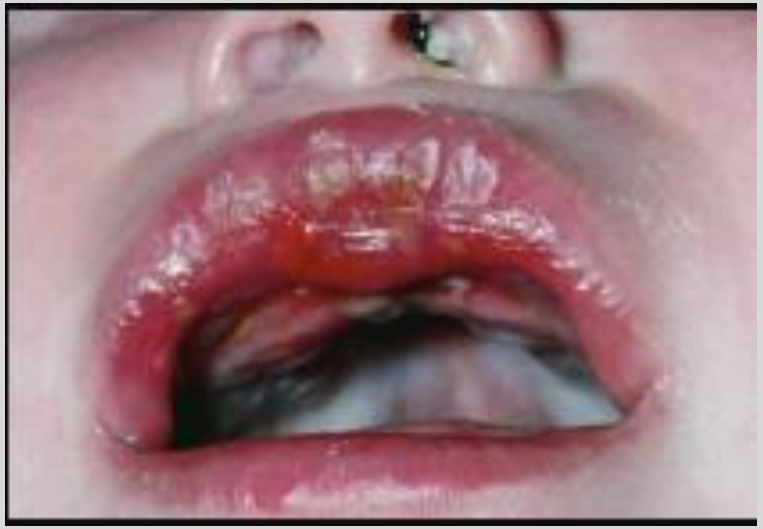
6- Clinical manifestations

- The HSVs are responsible for a spectrum of diseases, ranging from oral infections to genital disease, keratoconjunctivitis, encephalitis, and infections of newborns.

6- Clinical manifestations

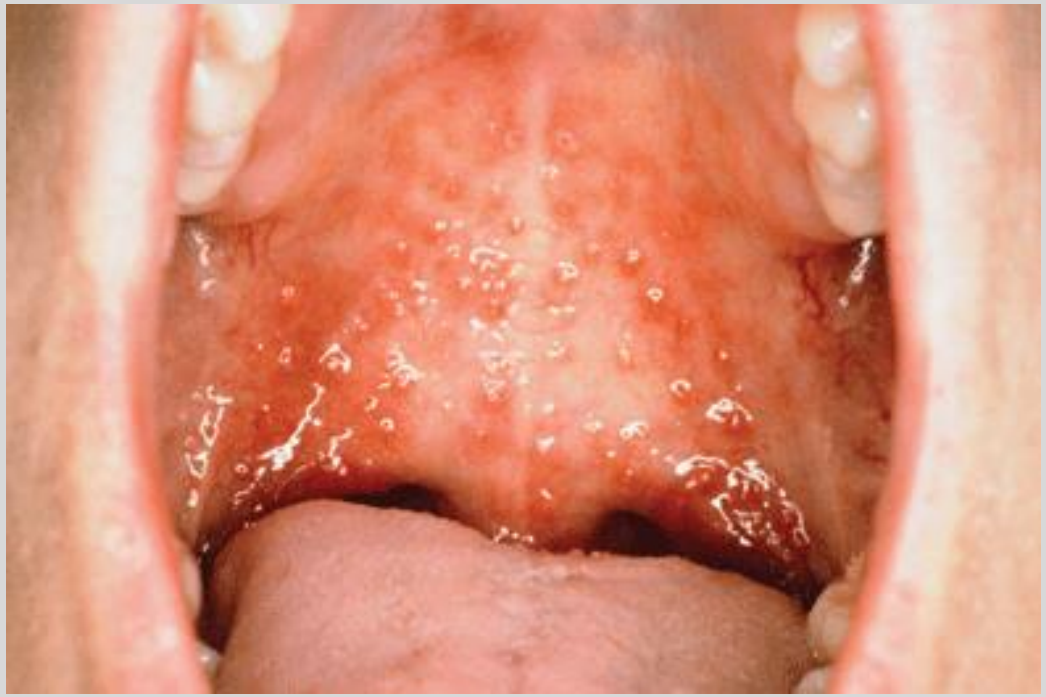
- 1) Oropharyngeal infection (usually by HSV-1)
- Primary HSV-1 infections are mostly asymptomatic.
- The incubation period is short (~3–5 days, with a range of 2–12 days), and clinical illness lasts 2–3 weeks.
- Symptoms include fever, sore throat, vesicular and ulcerative lesions, gingivostomatitis.
- Primary infections in adults commonly cause pharyngitis and tonsillitis. Localized lymphadenopathy may occur.
- Recurrent disease is characterized by a cluster of vesicles most commonly localized at the border of the lip.





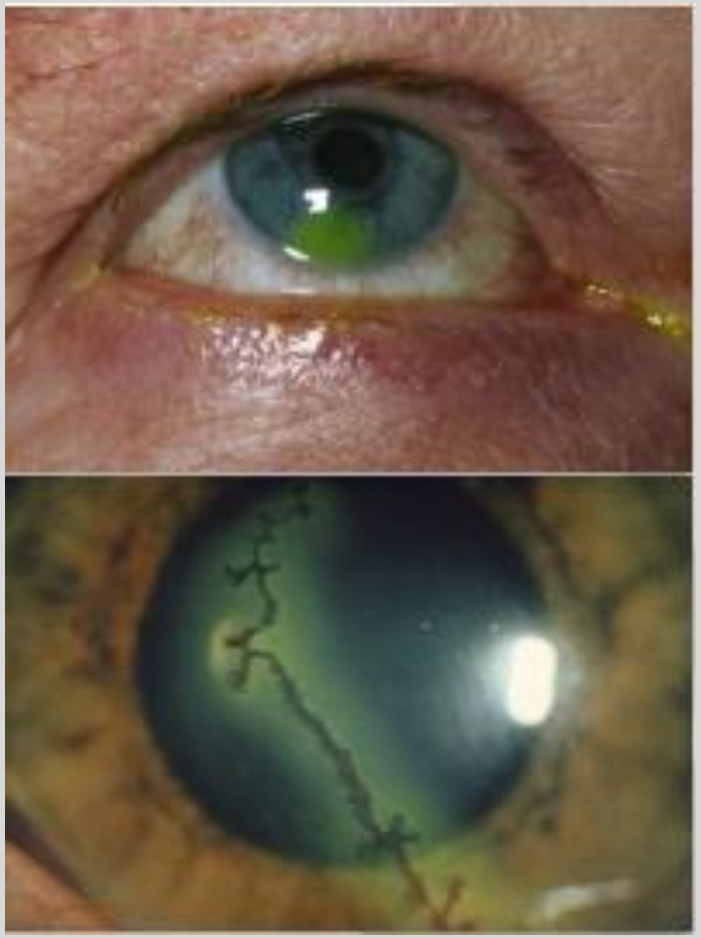
6- Clinical manifestations

- Intense pain occurs at the outset but fades over 4–5 days.
- Lesions progress through the pustular and crusting stages, and healing without scarring is usually complete in 8–10 days.
- The lesions may recur in the same location.
- Many recurrences of oral shedding are asymptomatic and of short duration (12 – 24 hours).



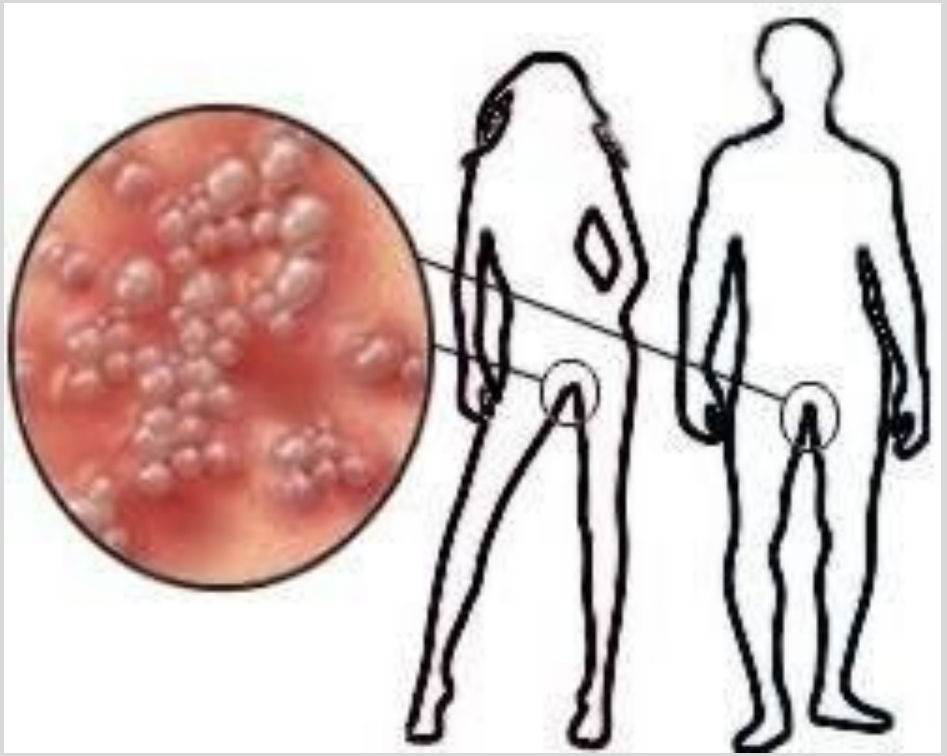
6- Clinical manifestations

- 2) Keratoconjunctivitis (caused by HSV-1)
- Recurrent lesions of the eye are common and appear as dendritic keratitis or corneal ulcers or as vesicles on the eyelids.
- With recurrent keratitis, there may be progressive involvement of the corneal stroma, with permanent opacification and blindness.
- HSV-1 infections are second only to trauma as a cause of corneal blindness in the US



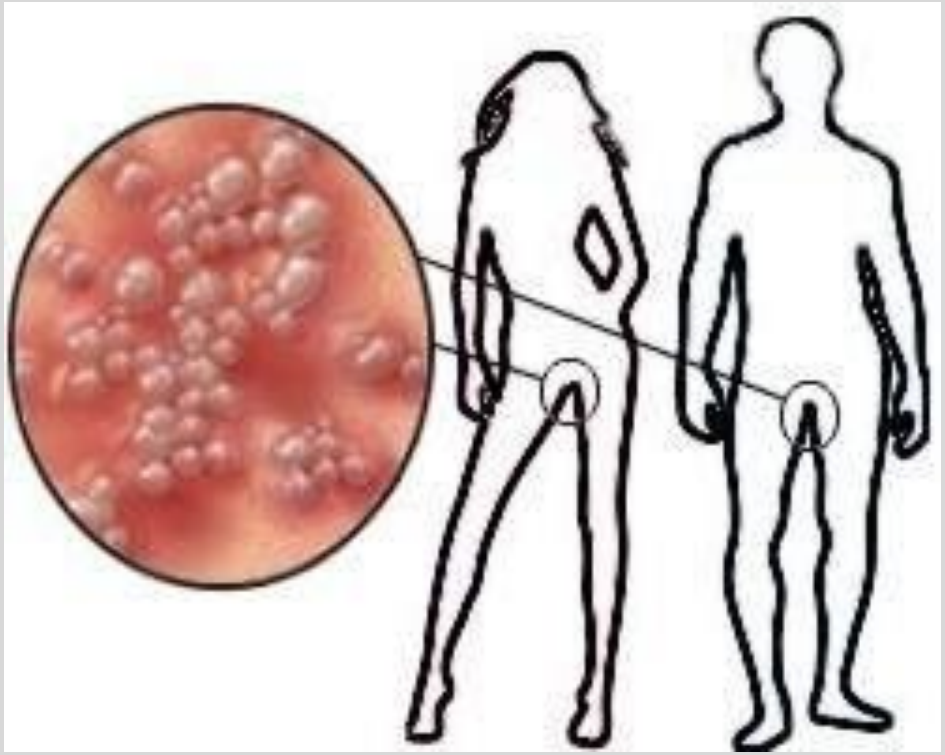
6- Clinical manifestations

- 3) Genital disease
- usually caused by HSV-2, although HSV-1 can also cause clinical episodes of genital herpes.
- Primary genital herpes infections can be severe, with illness lasting about 3 weeks.
- Genital herpes is characterized by vesiclo-ulcerative lesions of the penis of the male or of the cervix, vulva, vagina, and perineum of the female.
- The lesions are very painful and may be associated with fever, malaise, dysuria, and inguinal lymphadenopathy.
- Complications include extragenital lesions (~20% of cases) and aseptic meningitis (~10% of cases).



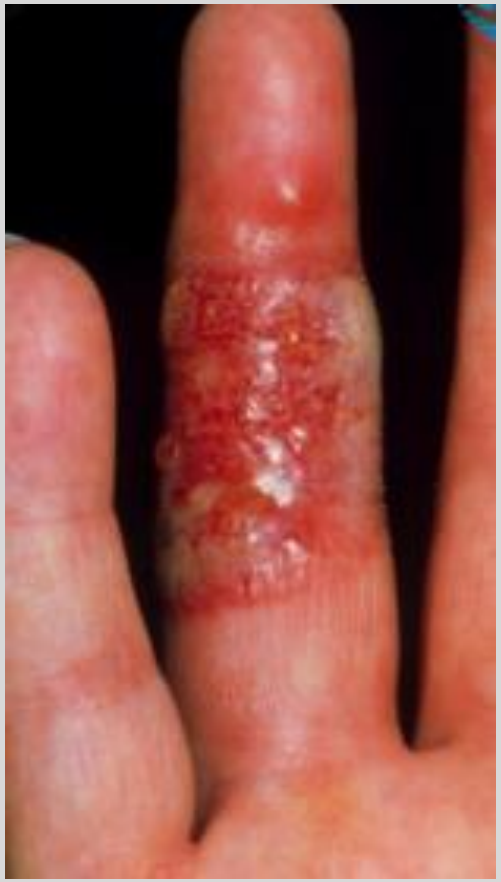
6- Clinical manifestations

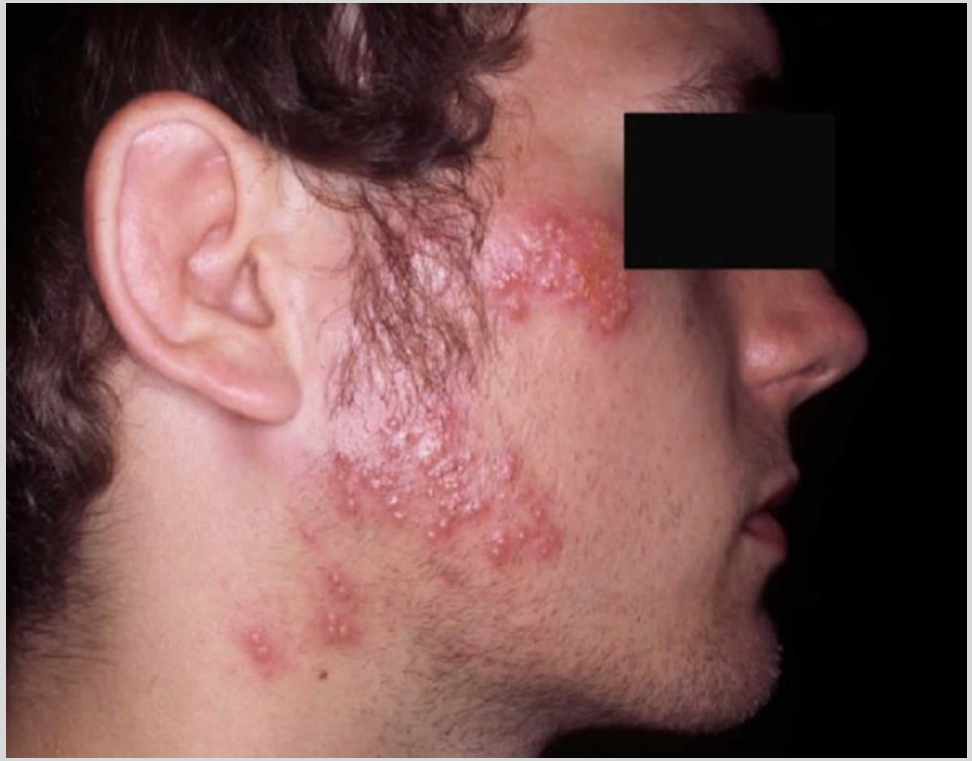
- Because of the antigenic cross-reactivity between HSV-1 and HSV-2, pre-existing immunity provides some protection against heterotypic infection.
- An initial HSV-2 infection in a person already immune to HSV-1 tends to be less severe.
- Recurrences of genital herpetic infections are common and tend to be mild. A limited number of vesicles appear and heal in about 10 days.
- Some recurrences are asymptomatic with anogenital shedding lasting less than 24 hours.
- Whether a recurrence is symptomatic or asymptomatic, a person shedding virus can transmit the infection to sexual partners.

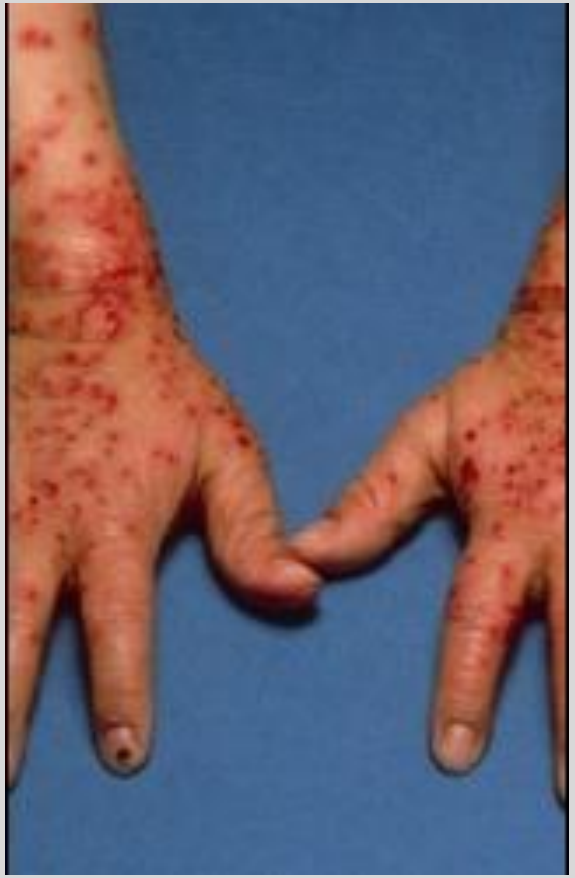


6- Clinical manifestations

- 4) herpetic whitlow, herpes gladiatorum & Eczema herpeticum
- Intact skin is resistant to HSV.
- Localized lesions caused by HSV-1 or HSV2 may occur in abrasions that become contaminated with the virus (traumatic herpes); on the fingers of dentists and hospital personnel (herpetic whitlow) and on the bodies of wrestlers (herpes gladiatorum or mat herpes).
- Cutaneous infections are often severe and life threatening when they occur in individuals with disorders of the skin, such as eczema or burns.
- Eczema herpeticum is a primary infection, usually with HSV-1, in a person with chronic eczema. In rare instances, the illness may be fatal.







6- Clinical manifestations

- 5) Encephalitis:
- A severe form of encephalitis may be produced by herpesvirus
- HSV-1 infections are considered the most common cause of sporadic, fatal encephalitis in the US.
- The disease carries a high mortality rate, and those who survive often have residual neurologic defects.
- About half of patients with HSV encephalitis appear to have primary infections, and the rest appear to have recurrent infection

6- Clinical manifestations

- 6) Neonatal infections:
- HSV infection of the newborn may be acquired in utero, during birth, or after birth. The mother is the most common source of infection in all cases.
- Neonatal herpes is estimated to occur in about 1 in 5000 deliveries per year. The newborn infant seems to be unable to limit the replication and spread of HSV and has a propensity to develop severe disease.
- The most common route of infection (~75% of cases) is for HSV to be transmitted to a newborn during birth by contact with herpetic lesions in the birth canal. To avoid infection, delivery by C/S has been used in pregnant women with genital herpes lesions.
- However, many fewer cases of neonatal HSV infection occur than cases of recurrent genital herpes, even when the virus is present at term

6- Clinical manifestations

- 6) Neonatal infections:
- Neonatal herpes can be acquired postnatally by exposure to either HSV-1 or HSV-2.
- Sources of infection include family members and hospital personnel who are shedding virus.
- About 75% of neonatal herpes infections are caused by HSV-2.
- There do not appear to be any differences between the nature and severity of neonatal herpes in premature or full-term infants, in infections caused by HSV-1 or HSV-2, or in disease when virus is acquired during delivery or postpartum.

6- Clinical manifestations

- 6) Neonatal infections:
- Neonatal herpes infections are almost always symptomatic.
- The overall mortality rate of untreated disease is 50%. Babies with neonatal herpes exhibit three categories of disease: (1) lesions localized to the skin, eye, and mouth; (2) encephalitis with or without localized skin involvement; (3) disseminated disease involving multiple organs, including the central nervous system.
- The worst prognosis (~80% mortality rate) applies to infants with disseminated infection, many of whom develop encephalitis. The cause of death of babies with disseminated disease is usually viral pneumonitis or intravascular coagulopathy. Many survivors of severe infections are left with permanent neurologic impairment.

6- Clinical manifestations

- 7) Immuno-compromised infections:
- Immunocompromised patients are at increased risk of developing severe HSV infections. These include patients immunosuppressed by disease or therapy (especially those with deficient cellular immunity) and individuals with malnutrition.
- Renal, cardiac, and bone marrow transplant recipients are at particular risk for severe herpes infections. Patients with hematologic malignancies and patients with AIDS have more frequent and more severe HSV infections.
- Herpes lesions may spread and involve the respiratory tract, esophagus, and intestinal mucosa.
- Malnourished children are prone to fatal disseminated HSV infections. In most cases, the disease reflects reactivation of latent HSV infection.

Title Lorem Ipsum

LOREM IPSUM DOLOR SIT AMET, CONSECTETUER ADIPISCING ELIT.

NUNC VIVERRA IMPERDIET ENIM. FUSCE EST. VIVAMUS A TELLUS.

PELLENTESQUE HABITANT MORBI TRISTIQUE SENECTUS ET NETUS.