Virology
Herpesviruses

Asst. Prof. Dr. Dalya Basil

In This Lecture:

- Enveloped DNA Viruses
  - Herpesviruses

Introduction

- The herpesvirus family contains several of the most important human viral pathogens.
- Clinically, the herpesviruses exhibit a spectrum of diseases.
- Some have a wide host-cell range, whereas others have a narrow host-cell range.
- Ability to establish lifelong persistent infections in their hosts and to undergo periodic reactivation. Their frequent reactivation in immunosuppressed patients causes serious health complications.
- Herpesviruses possess a large number of genes, some of which have proved to be susceptible to antiviral chemotherapy.

Properties of Herpesviruses

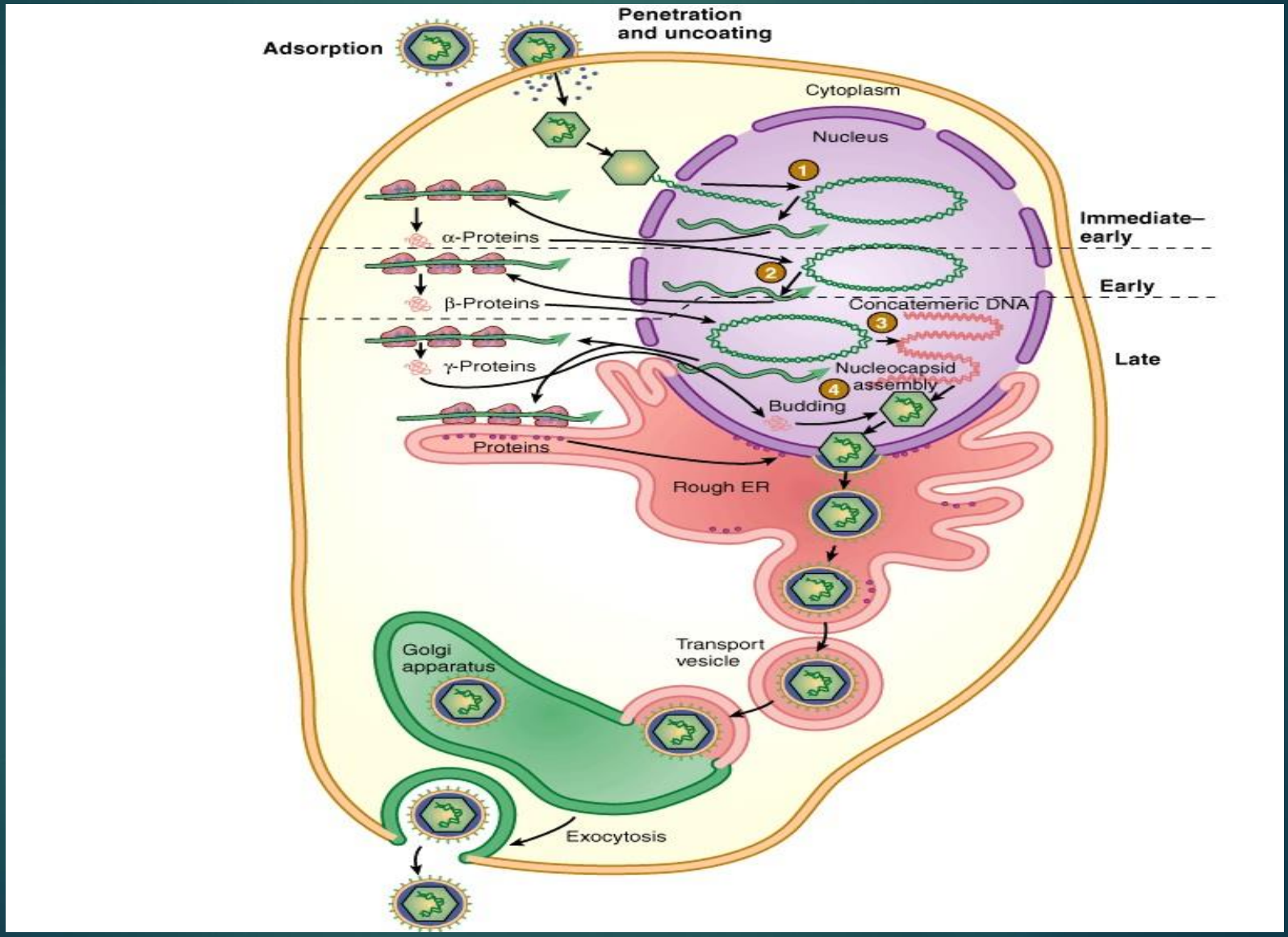
Important properties of herpesviruses are summarized in Table 33

Important Properties of Herpesviruses
Virion: Spherical, 150â€“200 nm in diameter (icosahedral)
Genome: Double-stranded DNA, linear
Proteins: More than 35 proteins in virion
Envelope: Contains viral glycoproteins, Fc receptors
Replication: Nucleus, bud from nuclear membrane
Outstanding characteristics:
Encode many enzymes
Establish latent infections
Persist indefinitely in infected hosts
Frequently reactivated in immunosuppressed hosts
Some are cancer-causing

Classification

Classification of Human Herpesviruses					
	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

Life cycle


Adsorption
Penetration and uncoating
Cytoplasm
Nucleus
1
α-Proteins
Immediate–early
2
Early
β-Proteins
Concatemeric DNA
3
γ-Proteins
Late
Nucleocapsid assembly
4
Budding
Proteins
Rough ER
Golgi apparatus
Transport vesicle
Exocytosis

Herpesvirus Diseases

- HSV-1 and HSV-2 infect epithelial cells and establish latent infections in neurons. Type 1 is classically associated with oropharyngeal lesions and causes recurrent attacks of "fever blisters." Type 2 primarily infects the genital mucosa. Both viruses also cause neurologic disease. Both type 1 and type 2 can cause neonatal infections which are often severe.
- Varicella-zoster virus causes chickenpox (varicella) on primary infection and establishes latent infection in neurons. Upon reactivation, the virus causes zoster (shingles). Adults who are infected for the first time with varicella-zoster virus are apparent to develop serious viral pneumonia.
- Cytomegalovirus replicates in epithelial cells of the respiratory tract, salivary glands, and kidneys and persists in glands and kidnies. It causes an infectious mononucleosis. It is an important cause of congenital defects and mental retardation.

Herpesvirus Diseases

- EBV replicates in epithelial cells of the oropharynx and parotid gland and establishes latent infections in lymphocytes. It causes infectious mononucleosis and is the cause of human lymphoproliferative disorders, especially in immunocompromised patients.
- Human herpesvirus 6 infects T lymphocytes. It is typically acquired in early infancy and causes exanthem subitum (roseola infantum).
- Human herpesvirus 7, also a T-lymphotropic virus, has not yet been linked to any specific disease.
- Human herpesvirus 8 appears to be associated with the development of Kaposi sarcoma, a vascular tumor that is common in patients with AIDS.

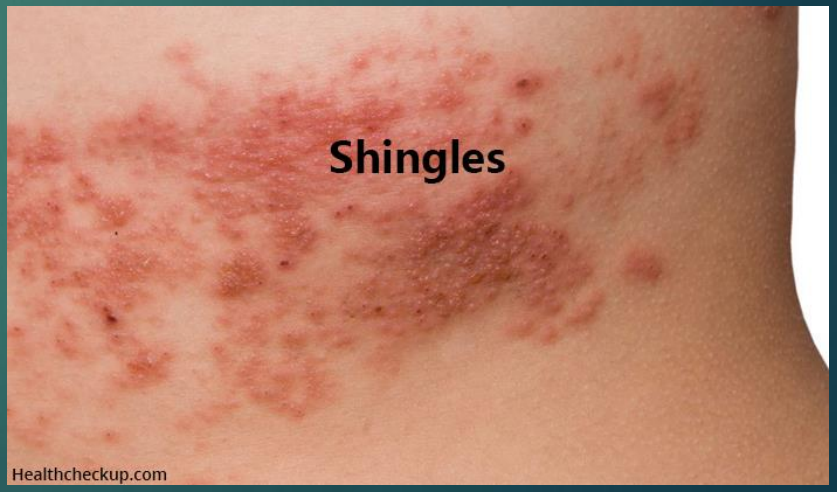
Varicella-Zoster Virus

- Varicella (chickenpox) is a mild, highly contagious disease, chiefly of children, characterized clinically by a generalized vesicular eruption of the skin and mucous membranes. The disease may be severe in adults and in immunocompromised children.

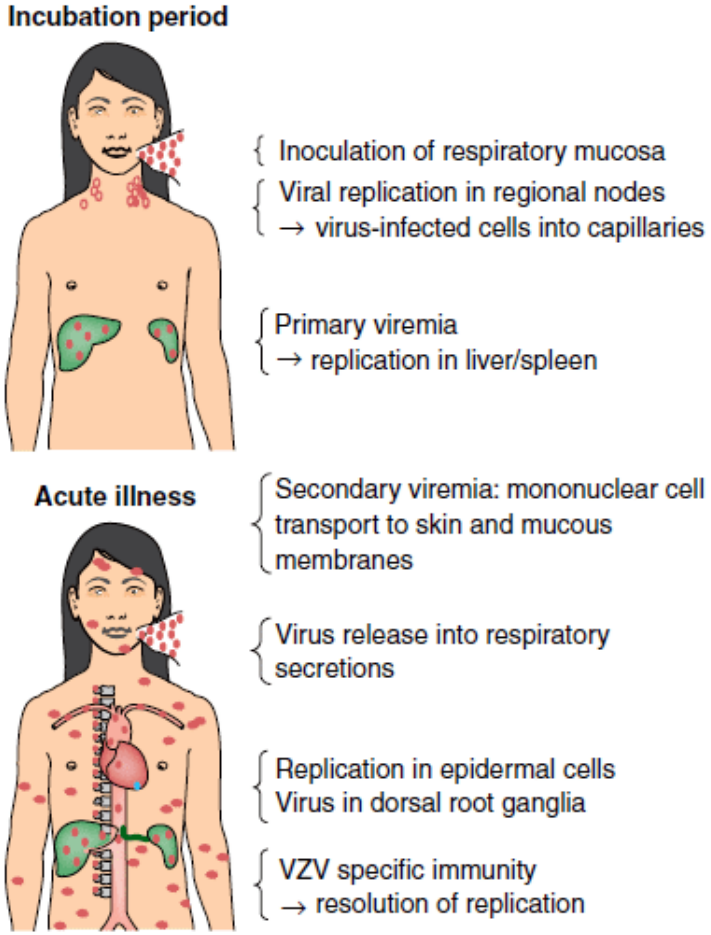
- Zoster (shingles) is a sporadic disease of adults or immunocompromised individuals that is characterized by a rash limited in distribution to the skin innervated by a single sensory ganglion. The lesions are similar to those of varicella.

- the Varicella Zoster Virus may live in a dormant state in the nerve cell system of the spine. Anyone with a history of chicken pox can be infected by Shingles. Shingle usually appears on a small portion of a face or body in a strip or a band.

Both diseases are caused by the same virus. Varicella is the acute disease that follows primary contact with the virus, whereas zoster is the response of the partially immune host to reactivation of varicella virus present in latent form in neurons in sensory ganglia.



Varicella-Zoster Virus



Source: Brooks GF, Carroll KC, Butel JS, Morse SA, Mietzner TA: *Jawetz, Melnick, & Adelberg's Medical Microbiology, 25th Edition*: http://www.accessmedicine.com

The pathogenesis of primary infection with varicella-zoster virus (VZV). The incubation period with primary viremia lasts from 10 to 21 days. A secondary viremic phase results in the transport of virus to skin and respiratory mucosal sites. Replication in epidermal cells causes the characteristic rash of varicella, referred to as chickenpox. The induction of varicella-zoster virus-specific immunity is required to terminate viral replication. The virus gains access to cells of the trigeminal and dorsal root ganglia during primary infection and establishes latency. (Reproduced with permission from Arvin AM: Varicella-zoster virus. In: *Fields Virology*, 3rd ed. Fields BN et al [editors]. Lippincott-Raven, 1996.)

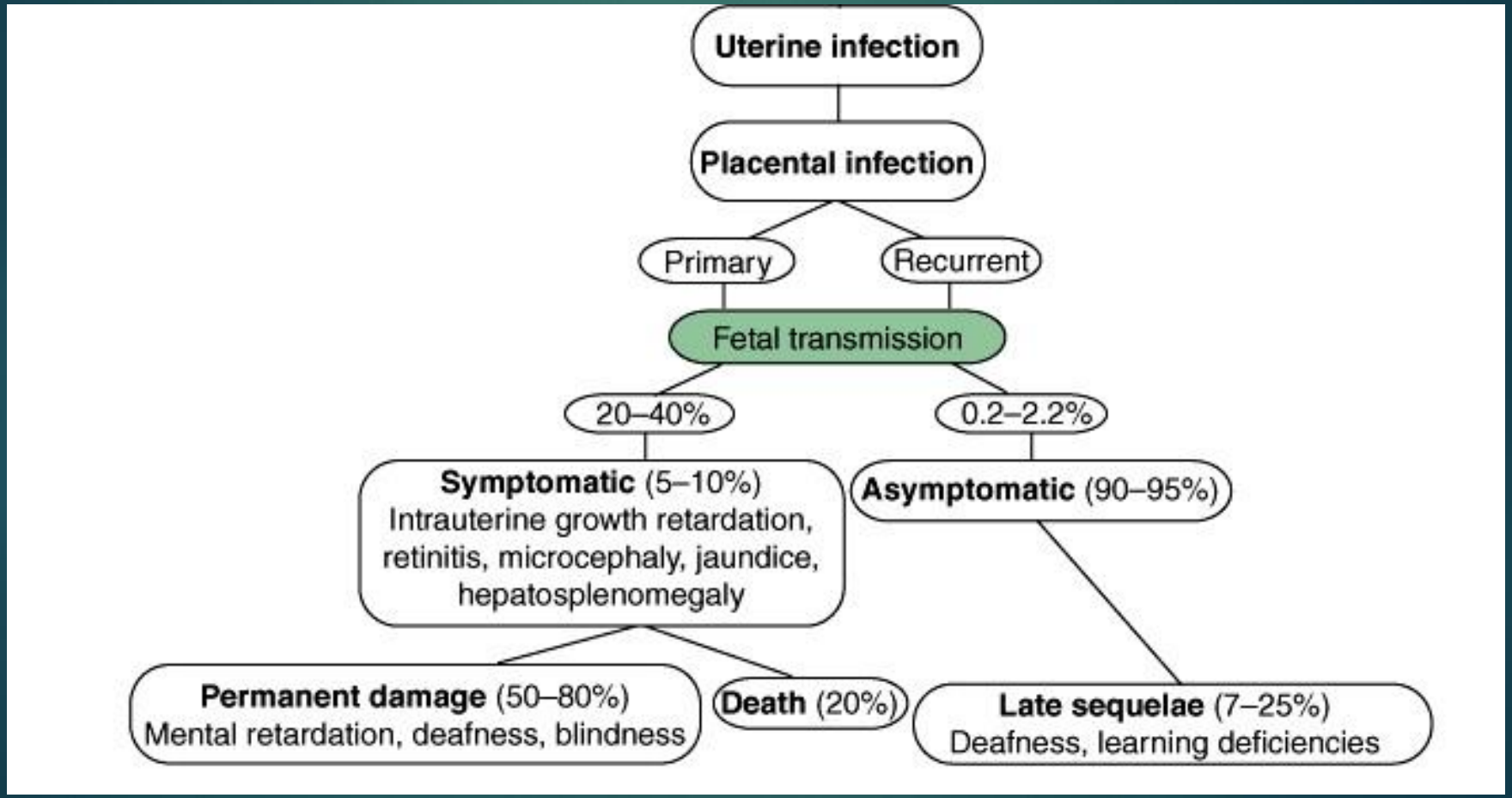
Cytomegalovirus

- Cytomegaloviruses are the agents of the most common congenital infection .
- Cytomegalic inclusion disease is a generalized infection of infants caused by intrauterine or early postnatal infection with the cytomegaloviruses.
- The name for the classic cytomegalic inclusion disease derives from the massive enlargement of cytomegalovirus-infected cells. Cytomegalovirus poses an important public health problem because of its high frequency of congenital infections, which may lead to severe congenital anomalies.
- Inapparent infection is common during childhood and adolescence. Severe cytomegalovirus infections are frequently found in adults who are immunosuppressed.

Pathogenesis & Pathology

- Cytomegalovirus may be transmitted person-to-person in several different ways, all requiring close contact with virus-bearing material.
- There is a 4 to 8 weeks incubation period in normal older children and adults after viral exposure.
- The virus causes a systemic infection; it has been isolated from lung, liver, esophagus, colon, kidneys, monocytes, and T and B lymphocytes.
- The disease is an infectious mononucleosis-like syndrome, although most cytomegalovirus infections are subclinical.
- Like all herpesviruses, cytomegalovirus establishes lifelong latent infections. Virus can be shed intermittently from the pharynx and in the urine for months to years after primary infection.

Congenital & Perinatal Infections



Treatment & Control

- Drug treatments of cytomegalovirus infections have shown some encouraging results. Ganciclovir, a nucleoside structurally related to acyclovir, has been used successfully to treat life-threatening cytomegalovirus infections in immunosuppressed patients .
- Both live and recombinant cytomegalovirus vaccines are under development.

Epstein-Barr Virus

- EBV is the causative agent of
  - acute infectious mononucleosis
  - and is associated with nasopharyngeal carcinoma.
  - Burkitt lymphoma.
  - Hodgkin and non-Hodgkin lymphomas.
  - other lymphoproliferative disorders in immunodeficient individuals.
  - and gastric carcinoma.

Biology of Epstein-Barr Virus

- The major target cell for EBV is the B lymphocyte. When human B lymphocytes are infected with EBV, continuous cell lines can be established, indicating that cells have been immortalized by the virus. Very few of the immortalized cells produce infectious virus.

- EBV initiates infection of B cells by binding to the viral receptor, which is the receptor for the C3d component of complement. EBV directly enters a latent state in the lymphocyte without undergoing a period of complete viral replication.

Pathogenesis & Pathology

- **Primary Infection**

  EBV is commonly transmitted by infected saliva and initiates infection in the oropharynx. Viral replication occurs in epithelial cells (or surface B lymphocytes) of the pharynx and salivary glands. Many people shed low levels of virus for weeks to months after infection. Infected B cells spread the infection from the oropharynx throughout the body. In normal individuals, most virus-infected cells are eliminated, but small numbers of latently infected lymphocytes persist for the lifetime of the host

  Primary infections in children are usually subclinical, but if they occur in young adults acute infectious mononucleosis often develops.

Pathogenesis & Pathology

- **Reactivation from Latency**

  Reactivations of EBV latent infections can occur, as evidenced by increased levels of virus in saliva and of DNA in blood cells. These are usually clinically silent. Immunosuppression is known to reactivate infection, sometimes with serious consequences.

Clinical Findings

- **Infectious Mononucleosis**

  The typical illness is self-limited and lasts 2-4 weeks. During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes. Many of these are large, atypical T lymphocytes. Low-grade fever and malaise may persist for weeks to months after acute illness.

Human Herpesvirus 6

- The T-lymphotropic human herpesvirus 6 was first recognized in 1986 .
- Isolates of human herpesvirus 6 segregate into two closely related but distinct antigenic groups (designated A and B).
- The virus grows well in CD4 T lymphocytes. Other cell types also support viral replication, including B cells and cells of glial, fibroblastoid. Cells in the oropharynx must become infected, since virus is present in saliva.

Epidemiology & Clinical Findings

- It is estimated that over 90% of children over age 1 and adults are virus positive.
- Infections with human herpesvirus 6 typically occur in early childhood. This primary infection causes exanthem subitum (roseola infantum, or "sixth disease"), the mild common childhood disease characterized by high fever and skin rash. The virus is associated with febrile seizures in children.

Human Herpesvirus 7

- A T-lymphotropic human herpesvirus, designated human herpesvirus 7, was first isolated in 1990 from activated T cells recovered from peripheral blood lymphocytes of a healthy individual.
- Human herpesvirus 7 is immunologically distinct from human herpesvirus 6, though they share about 50% homology at the DNA level.
- Human herpesvirus 7 appears to be a ubiquitous agent, with most infections occurring in childhood.

Human Herpesvirus 7

- Persistent infections are established in salivary glands, and the virus can be isolated from saliva of most individuals.
- Similar to human herpesvirus 6, primary infection with human herpesvirus 7 has been linked with roseola infantum in infants and young children.
- Any other disease associations of human herpesvirus 7 remain to be established.

Human Herpesvirus 8

- A new herpesvirus, human herpesvirus 8 and also called KSHV, was first detected in 1994 in Kaposi sarcoma specimens. KSHV is lymphotropic and is more closely related to EBV than to other known herpesviruses.
- The KSHV genome contains numerous genes related to cellular regulatory genes involved in cell proliferation, apoptosis, and host responses (cyclin D, cytokines, chemokine receptor) that presumably contribute to viral pathogenesis. KSHV is the cause of Kaposi sarcomas, vascular tumors of mixed cellular composition, and is involved in the pathogenesis of body cavity-based lymphomas occurring in AIDS patients.

Human Herpesvirus 8

- Contact with oral secretions is likely the most common route of transmission. The virus can also be transmitted sexually, vertically, by blood, and through organ transplants. Viral DNA has also been detected in breast-milk samples in Africa. Infections are common in Africa (>50%) and are acquired early in life.
- Viral DNA can be detected in patient specimens using PCR assays. Direct virus culture is difficult and impractical. Serologic assays are available to measure persistent antibody to KSHV, using ELISA.
- Foscarnet, ganciclovir, and cidofovir have activity against KSHV replication.


thank
you