INTRODUCTION

Herpesviruses are a family of DNA viruses found commonly in humans and animals. Nearly 100 herpesviruses have been at least partially characterized, and most animal species have been shown to be infected by at least one member of the family. The name, derived from the Greek *herpein*, to creep, refers to the characteristic lesions caused by two common human herpesviruses: fever blisters caused by herpes simplex and varicella and shingles induced by herpes zoster. The known herpesviruses have a common virion architecture and four significant biological properties:

(i) They encode a large variety of enzymes involved in nucleic acid metabolism, DNA synthesis and protein processing.

(ii) Synthesis of viral DNA and assembly of the capsid occur in the nucleus of infected cells.

(iii) The production of infectious viral progeny is usually accompanied by destruction of the infected cell.

(iv) Herpesviruses can remain latent and persist for life in their natural hosts. Latent infection occurs in specific sets of cells that differ from one virus to another. The latent viral genomes usually take the form of circular episomes, and only a small subset of viral genes is expressed.

According to the official nomenclature endorsed by the International Committee on the Taxonomy of Viruses, herpesviruses are designated by serial Arabic numbers and the family or subfamily of the natural host; e.g. human herpesviruses (HHV) 1, 2, 3 and equine herpesviruses 1, 2, 3. This nomenclature is used in the following text with the common names of the most relevant viruses.

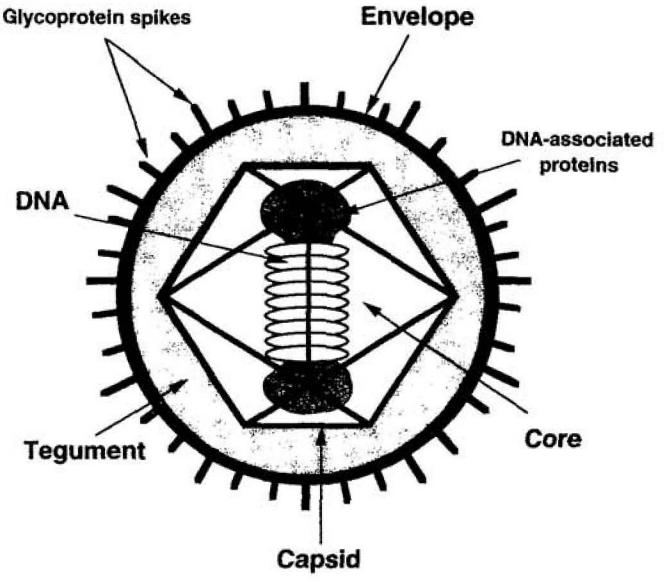
1. Structure of herpesviruses

The structure of herpesviruses has been reviewed by Roizman (1996).

1.1 *The virion*

A typical herpesvirion consists of a core containing linear double-stranded DNA, an icosahedral capsid, an amorphous tegument and a lipid envelope with viral glycoprotein spikes on its surface (Figure 1). Herpesvirus particles have a diameter of about 120 to more than 200 nm and contain, in addition to viral DNA, 25–35 virus-encoded proteins and host-specific phospholipids derived from the nuclear membrane. Many of the particles within a population of virions do not possess envelopes, and some are empty capsids.

Figure 1. Schematic structure of a herpesvirus

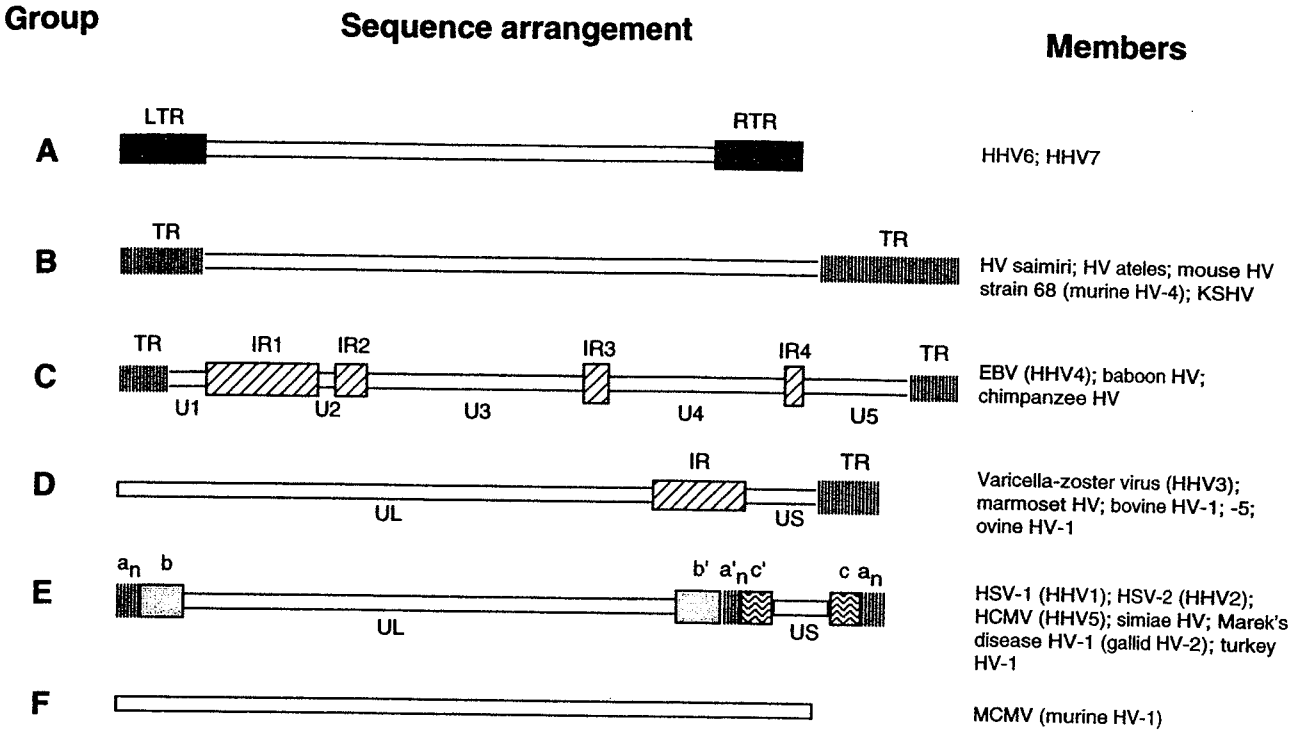


The core of the mature virion contains the double-stranded viral DNA arranged in a torus of about 75 nm in diameter. In some virions, the DNA appears to be wrapped around a DNA-associated spindle-shaped protein consisting of fibrils attached to the inside of the capsid. The icosahedral capsid is approximately 100–110 nm in diameter and contains 162 capsomers. The hexameric capsomers are 9.5 × 12.5 nm in longitudinal sections with a channel of 4 nm in diameter running along the long axis. The pentameric capsomers located at the vertices of the capsid have not been characterized. The capsid is surrounded by an amorphous material, the tegument, composed of globular proteins. The tegument is frequently distributed asymmetrically, and its thickness may vary depending on the location of the virion within the infected cells. The envelope of herpesviruses has a typical trilamellar structure and is derived from patches of altered cellular membranes. Its high lipid content results in relative instability of the virions at room temperature and their rapid inactivation by lipid solvents such as diethyl ether and chloroform and by detergents. The envelope bears numerous projections or spikes, approximately 8 nm long and consisting of glycoproteins, the composition of which varies widely among the different members of the family.

1.2 *Genomic organization*

Herpesvirus DNA can be distinguished on the basis of size, base composition and structural arrangement in unique and repeated sequences. The length of herpesvirus DNA varies from approximately 120 to more than 230 kilobases (kb) and is characteristic for each genus (e.g. simplex virus and cytomegalovirus). Minor variations in the size of individual isolates of the same virus are due mainly to variations in the number of internal and terminal repeat regions. Herpesviruses can be divided into six structurally distinct groups on the basis of the presence and location of repeated sequences greater than 100 base pairs (Figure 2). In group A viruses, exemplified by the human herpes-

Figure 2. Architecture of herpesvirus genomes



LTR, left terminal repeat; RTR, right terminal repeat; TR, terminal repeat; IR, internal repeat; U, unique sequence; UL, long unique sequence; US, short unique sequence; HV, herpesvirus

For symbols used in Group E, see text.

viruses 6 and 7 (HHV6 and HHV7), a large sequence from one terminus is directly repeated at the other terminus (left terminal repeat and right terminal repeat). In group B viruses, exemplified by Kaposi's sarcoma herpesvirus (HHV8; see the monograph in this volume), the primate herpesviruses saimiri (HVS or SHV-2) and ateles (HVA-2) and the mouse herpesvirus strain 68 (MHV-4), the terminal sequence is directly repeated numerous times at both termini. In group C viruses, exemplified by Epstein-Barr virus (EBV, HHV4; see the monograph in this volume), both terminal and internal repeat sequences are present throughout the viral genome, which subdivide it into well-defined unique sequences. In group D viruses, exemplified by varicella–zoster virus (VZV, HHV3) and by numerous viruses isolated from mammals and birds, the terminal region is repeated in an inverted orientation internally. The short unique region contained between the terminal repeat and this inverted form can assume two possible orientations relative to the long unique sequence, such that virions isolated from infected cells consist of two equimolar populations. A more complex architecture is observed in group E viruses, exemplified by herpes simplex viruses types 1 (HSV-1, HHV1) and 2 (HSV-2, HHV2), human cytomegalovirus (CMV, HHV5) and Marek's disease virus (MDV or GHV-2). Sequences from both termini (a_nb and a_nc) are repeated in inverse orientation and juxtaposed internally (a'_nb' and a'_nc'), dividing the genome into two components consisting of long and short unique sequences separated by inverted repeats. Both

components can occur in two orientations relative to each other, resulting in four equimolar populations of virions. There are no repeat regions in the genome of the group F viruses, exemplified by murine herpesvirus 1.

The base composition varies significantly among the herpesviruses, the guanine-cytosine (GC) content ranging from 46 mol % in VZV to 69 mol % in HSV (Roizman, 1996). An under-representation of the CpG dinucleotide pair and a relative excess of CpA and TpG dinucleotides has been observed in the lymphotropic herpesviruses, possibly due to methylation-dependent CpG suppression in rapidly dividing cells (Honess *et al.*, 1989). Despite these major differences, comparison of herpesvirus DNA sequences shows large regions of distant collinear homology at the predicted protein level. Relatively well-conserved genes code for *trans*-activating factors, enzymes involved in viral replication, such as DNA polymerase, ribonucleotide reductase and thymidine kinase, and some structural glycoproteins, including the major spike components (Stewart *et al.*, 1996). The similarities are largely restricted to the early and late genes expressed during the productive cycle, while genes expressed in latently infected cells are usually unique, suggesting a possible origin from cellular DNA.

2. Taxonomy of herpesviruses

Herpesviruses are classified into three subfamilies — alpha, beta and gamma — with different biological properties and tissue tropism. Further subdivision into genera is based on DNA sequence homology, similarities in genomic sequence arrangement and relatedness of viral proteins demonstrable by immunological methods (Roizman *et al.*, 1981; Roizman, 1982) (Table 1). A compilation of the major herpesviruses in animals is given in Table 2, which also includes a comparable list of human herpesviruses.

Table 1. Biological characteristics of herpesvirus subfamilies

Characteristic	Alpha	Beta	Gamma
Genus	Simplexvirus Varicellovirus	Cytomegalovirus Muromegalovirus	Lymphocryptovirus Rhadinovirus
Host range	Broad	Restricted	Restricted
Prevalent genomic organization	D, E	Variable	B, C
Productive cycle	Short	Long	Long
Spread in culture	Efficient	Moderate	Poor
Site of latency	Sensory ganglia	Lymphoreticular tissues	Lymphocytes
Proliferation of latently infected cells	No	No	Yes

Adapted from Roizman (1996)

2.1 *Alphaherpesviruses*

The subfamily Alphaherpesvirinae includes the genera *Simplexvirus* and *Varicellovirus*, of which the human HSV-1, HSV-2 and VZV (HHV1, 2 and 3, respectively) are the best-known examples. Members of the alpha subfamily have a relatively broad host range and may infect other, related species, in addition to their natural host species. These viruses have a relatively short productive cycle in epithelial cells and spread very efficiently in tissue cultures. A hallmark of the family is the capacity to establish latent infection primarily, but not exclusively, in sensory ganglia.

Table 2. International nomenclature of herpesviruses (shortened list)

Designation	Common name and synonyms	Sub-family	G+C (mol %)	Group	Size (kb)
Human viruses					
Human herpesvirus 1	Herpes simplex virus 1	α	68.3	E	152
Human herpesvirus 2	Herpes simplex virus 2	α	69	E	152
Human herpesvirus 3	Varicella-zoster virus	α	46	D	125
Human herpesvirus 4	Epstein-Barr virus	γ_1	60	C	172
Human herpesvirus 5	Cytomegalovirus	β	57	E	229
Human herpesvirus 6		β	42	A	162
Human herpesvirus 7		β		A	
Human herpesvirus 8		γ_2			230
Viruses of non-human primates					
Aotine herpesvirus 1	*Herpesvirus aotus* type 1	β	55	E	220
Aotine herpesvirus 3	*Herpesvirus aotus* type 3	β	56	D	219
Cercopithecine herpesvirus 1	B virus, *Herpesvirus simiae*	α	75	E	160
Cercopithecine herpesvirus 2	Herpesvirus simian agent 8 (SA-8)	α	67	E	150
Cercopithecine herpesvirus 3	Herpesvirus simian agent 6 (SA-6)	β	51		
Cercopithecine herpesvirus 4	Herpesvirus simian agent 15 (SA-15)	β			
Cercopithecine herpesvirus 5	African green monkey cytomegalovirus	β			
Cercopithecine herpesvirus 6	Liverpool vervet monkey virus	α	52		
Cercopithecine herpesvirus 7	Patas monkey herpesvirus; MMV or PHV delta herpesvirus	α			
Cercopithecine herpesvirus 8	Rhesus monkey cytomegalovirus	β	52		
Cercopithecine herpesvirus 9	Medical Lake macaque herpesvirus; simian varicella herpesvirus	α			
Cercopithecine herpesvirus 10	Rhesus leukocyte-associated herpesvirus strain I				
Cercopithecine herpesvirus 12	*Herpesvirus papio*, baboon herpesvirus	γ_1		C	170

Table 2 (contd)

Designation	Common name and synonyms	Sub-family	G+C (mol %)	Group	Size (kb)
Viruses of non-human primates (contd)					
Cercopithecine herpesvirus 13	*Herpesvirus cyclopis*				
Cercopithecine herpesvirus 14	African green monkey EBV-like virus	γ_1			
Cercopithecine herpesvirus 15	Rhesus EBV-like herpesvirus	γ_1			
Ateline herpesvirus 1	Spider monkey herpesvirus	α	72		
Ateline herpesvirus 2	*Herpesvirus ateles*	γ_2	48	B	135
Callitrichine herpesvirus 1	*Herpesvirus saguinus*				
Callitrichine herpesvirus 2	SSG, marmoset cytomegalo-virus	β			
Cebine herpesvirus 1	Capuchin herpesvirus (AL-5)	β			
Cebine herpesvirus 2	Capuchin herpesvirus (AP-18)	β			
Pongine herpesvirus 1	Chimpanzee herpesvirus; pan herpesvirus	γ_1		C	170
Pongine herpesvirus 2	Orangutan herpesvirus	γ_1			
Pongine herpesvirus 3	Gorilla herpesvirus	γ_1			
Saimiriine herpesvirus 1	Marmoset herpesvirus; herpes T, *Herpesvirus tamarinus*, *Herpesvirus platyrrhinae*	α	67	D	152
Saimiriine herpesvirus 2	Squirrel monkey herpesvirus, *Herpesvirus saimiri*	γ_2	46	B	155
Bovine viruses					
Bovine herpesvirus 1	Infectious bovine rhinotracheitis herpesvirus	α	72	D	140
Bovine herpesvirus 2	Bovine mammillitis virus, Allerton virus, pseudolumpy skin disease herpesvirus	α	64	E	133
Bovine herpesvirus 4	Movar herpesvirus	γ_2	50	B	145
Bovine herpesvirus 5	Bovine encephalitis herpesvirus	α	72	D	140
Ovine herpesvirus 1	Sheep pulmonary adenomatosis-associated herpesvirus			D	137
Ovine herpesvirus 2	Sheep-associated malignant catarrhal fever	γ		B	
Caprine herpesvirus 1	Goat herpesvirus	α			
Alcelaphine herpesvirus 1	Wildebeest herpesvirus, malignant catarrhal fever herpesvirus	γ	61	B	160
Alcelaphine herpesvirus 2	Hartebeest herpesvirus	γ		B	
Cervid herpesvirus 1	Red deer herpesvirus	α		D	
Cervid herpesvirus 2	Reindeer (*Rangifer tarandus*) herpesvirus	α		D	
Murid viruses					
Murid herpesvirus 1	Mouse cytomegalovirus	β	59	F	235
Murid herpesvirus 2	Rat cytomegalovirus		47		

Table 2 (contd)

Designation	Common name and synonyms	Sub-family	G+C (mol %)	Group	Size (kb)
Murid viruses (contd)					
Murid herpesvirus 3	Mouse thymic herpesvirus				
Murid herpesvirus 4	Mouse herpesvirus strain 68	γ_2		B	135
Murid herpesvirus 5	Field mouse herpesvirus; *Microtus pennsylvanicus* herpesvirus				
Murid herpesvirus 6	Sand rat nuclear inclusion agents				
Murid herpesvirus 7	Murine herpesvirus				
Gallid viruses					
Gallid herpesvirus 1	Infectious laryngotracheitis virus	α	46	D	165
Gallid herpesvirus 2	Marek's disease herpesvirus 1	α	47	E	180
Gallid herpesvirus 3	Marek's disease herpesvirus 2	α			
Gruid viruses					
Gruid herpesvirus 1	Crane herpesvirus				
Meleagrid herpesvirus 1	Turkey herpesvirus	α	48	E	150
Ranid viruses					
Ranid herpesvirus 1	Lucke frog herpesvirus		46		
Ranid herpesvirus 2	Frog herpesvirus		56		

Modified from Roizman (1996) and the International Committe on the Taxonomy of Viruses (Murphy *et al.*, 1995)

Lymphoma-associated herpesvirus, a lymphocryptovirus isolated from cynomolgus monkeys (*Macaca fascicularis*), is not yet included on this list since it has not yet been given an official name by the International Committee on the Taxonomy of Viruses.

2.2 *Betaherpesviruses*

The subfamily Betaherpesvirinae includes the genera *Cytomegalovirus* and *Muromegalovirus*, of which human CMV (HHV5) and murine CMV (MHV-1) are the prototypes, respectively. The recently discovered human lymphotropic herpesviruses HHV6 and HHV7 have been classified in this subfamily on the basis of their genetic homology with human CMV, although these viruses share several biological properties with the gammaherpesviruses. The betaherpesviruses have a restricted host range, and many animal species are infected with their own CMV. These viruses appear to replicate in a variety of cell types *in vivo*, including epithelial cells, while the host cell range is more restricted *in vitro*. The infection progresses slowly and is accompanied by cell enlargement (cytomegaly) and by the appearance of characteristic nuclear eosinophilic inclusion bodies, formed by the accumulation of defective particles containing enveloped viral proteins without DNA or assembled capsids. The viruses can be maintained in a latent

form in lymphoreticular cells, secretory glands, kidneys and other tissues. Human CMV is often isolated from explants of apparently normal human adenoids and salivary glands, as have CMVs from mice, rats, hamsters and guinea-pigs.

2.3 *Gammaherpesviruses*

The subfamily Gammaherpesvirinae includes the genera *Lymphocryptovirus* and *Rhadinovirus*. Viruses of this subfamily are characterized by their tropism for lymphoid cells and their capacity to induce cell proliferation *in vivo*, resulting in transient or chronic lymphoproliferative disorders, and *in vitro*, where many can immortalize the infected cells. Gammaherpesviruses have a narrow natural host range which is restricted to the family or order to which the natural host belongs. Most gammaherpesviruses replicate inefficiently in haematopoietic cells, but some have efficient productive cycles in epithelial cells and fibroblasts. Latent virus is usually detected in lymphoid organs. The lymphocryptoviruses (or gamma-1 herpesviruses) include EBV (HHV4) and related viruses of Old World primates such as chimpanzees (*Herpesvirus pan*), orangutans (*Herpesvirus orangutan*) and gorillas (*Herpesvirus gorilla*). These viruses share tropism for B lymphocytes, a genomic architecture of group B or C and similar gene organization. Furthermore, several of their structural and nonstructural proteins are antigenically related, especially among the primate viruses, resulting in the presence of cross-reactive antibodies (Gerber & Birch, 1967; Chu *et al.*, 1971; Landon & Malan, 1971). In contrast, there is little nucleotide sequence homology or antigenic cross-reactivity between the lymphocryptoviruses and the rhadinoviruses (or gamma-2 herpesviruses). The genus is exemplified by the herpesviruses of primates, such as the ateles virus of spider monkeys and the saimiri virus of squirrel monkeys and some viruses of horses (equid herpesvirus 2; Telford *et al.*, 1993) and mice (mouse herpesvirus strain 68; Sunil-Chandra *et al.*, 1992, 1994). The recently described human Kaposi's sarcoma-associated herpesvirus (KSHV or HHV8) has been classified in this genus owing to its close similarity to the saimiri virus. The rhadinoviruses have a group B genome.

2.4 *Current classification*

The current classification of herpesviruses, which is based mainly on biological properties, does not help in defining evolutionary relatedness. The distinction between the alpha, beta and gamma subfamilies has been somewhat blurred by more detailed molecular studies and by the discovery of new viruses that co-express the structural features of one subfamily and at least some biological properties of another. Good examples are HHV6 and HHV7, which are classified as betaherpesviruses on the basis of their genetic homology to human CMV although their primary T-cell tropism is a typical feature of gammaherpesviruses (Berneman *et al.*, 1992; Lusso, 1996), and Marek's disease virus, which is included in the alpha subfamily in spite of its lymphotropism and its capacity to induce proliferation of latently infected cells (Buckmaster *et al.*, 1988).

The rapid accumulation of DNA sequences provides increased opportunities to study molecular evolution and phylogenetic relationships. Several methods have been used for constructing phylogenetic trees for groups of organisms. These are usually based on the

alignment of homologous DNA or protein sequences, followed by tree construction based on various statistical criteria such as parsimony, distance matrices, maximum likelihood, invariants and paralinear distances. Alternatively, evolutionary distances have been assessed on the basis of the relative abundance of di-, tri- and tetranucleotides in representative DNA sequences. These studies have shown a relatively good consistency with the alpha, beta and gamma classification but have generally failed to clarify finer details of branching between subfamilies (Karlin *et al.*, 1994; McGeoch *et al.*, 1995). It was estimated that the three subfamilies arose between 180 and 200 million years ago, i.e. 100–160 million years before the emergence of mammals. The speciation within sublineages took place within the last 80 million years, probably including a major component of co-speciation with the host lineages (McGeoch *et al.*, 1995). Distance assessment based on dinucleotide-relative abundance placed the HHV6 genome in the most central position, i.e. nearest to the consensus herpesvirus genome, suggesting that it may be closest to the progenitor virus. According to this criterion, herpesvirus sequences are closer to the chicken than the human DNA sequence collection, indicating that the ancient host of the viruses was avian species (Karlin *et al.*, 1994).

3. Herpesviruses and human disease

An overview of the pathogenic properties of the known human herpesviruses is shown in Table 3.

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Table 3. Pathogenic properties of human herpesviruses

Herpesvirus	Prevalence in adults[a]	Transmission	Diseases associated with primary infection	Diseases associated with reactivation	Suspected tumour association
Herpes simplex type 1 (HHV1)	High	Direct contact	Oral and ocular herpes	Oral and ocular herpes	None
Herpes simplex type 2 (HHV2)	Low–intermediate	Sexual	Genital herpes	Genital herpes	None
Varicella-zoster virus (HHV3)	Intermediate–high	Inhalation, direct contact	Varicella (chickenpox)	Zoster (shingles)	None
Epstein-Barr virus (HHV4)	High	Saliva, blood	Infectious mononucleosis	Oral hairy leukoplakia (associated with severe immunodepression)	Multiple types, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease
Cytomegalovirus (HHV5)	Intermediate	Transplacental, saliva, blood?, urine?, semen?	Congenital infection, mononucleosis	e.g. Pneumonia, hepatitis (associated with severe immunodepression)	None
HHV6	High	Saliva	Exanthem subitum (mainly variant B), heterophil myeloma, infectious mononucleosis	Pneumonia, encephalitis, retinitis	None
HHV7	High	Saliva	Exanthem subitum, iosidu excitem	Unknown	None
Kaposi's sarcoma-associated herpesvirus (HHV8)	?	Unknown (semen?)	Unknown	Unknown	Multiple types, including Kaposi's sarcoma, primary effusion lymphoma, Castleman's disease

[a]May vary significantly among different populations

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