Herpesviruses

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Glossary
antiviral drugs A class of medication used specifically for treating viral infections. As with antibiotics for bacterial infections, specific antivirals are used for specific viruses.
immunocompetent An individual with a normal immune system; the individual is capable of developing an immune response to an infection.
immunocompromised An individual whose immune system is compromised in some way, the individual lacks the ability to mount a normal immune response to an infection and is often unable to resist or fight off infection.
latency A quiescent period of infection when most or all of the viral lytic genes are silenced, and the virus is not making progeny virus.
lytic A type of infection in which viral lytic genes are switched on and the virus is actively undergoing replication and making progeny virions. This is also referred to as a productive infection.
seropositive A situation where an individual has antibodies against a certain pathogen in their blood, being seropositive indicates that the individual was previously exposed to that pathogen.
vaccine A preparation that contains an antigen, consisting of an organism or a part of an organism, that is used to confer immunity against the disease that the organism causes. Vaccines can be natural, synthetic or derived from recombinant DNA technology.

Abbreviations
ACV acyclovir
BL Burkitt’s lymphoma
CD8+ cluster of differentiation 8
CD21 complement receptor 2
E genes Early genes
EBNA EBV-coded nuclear antigens
EBV Epstein-Barr virus
CAEBV chronic active EMV
ES exanthem subitum
NHANES National Health and Nutrition Examination Survey
HPC hematopoietic progenitor cells
HSE herpes simplex encephalitis
HSV herpes simplex virus
HSK herpetic stromal keratitis
HCF host cell factor
HCMV human cytomegalovirus
HHV4 human herpesvirus 4
HHV-6 Human herpesvirus 6
HHV8 human herpesvirus 8
HHV Human herpesvirus
IE genes immediate early genes
IM infectious mononucleosis
IFN-γ interferon-γ
KS Kaposi’s sarcoma
KSHV Kaposi’s sarcoma-associated herpesvirus
L genes Late genes
LATs latency-associated transcripts
LMPs latent membrane proteins
LCV Lymphocryptovirus
MHC major histocompatibility complex
MCMV models with murine CMV
NK cells Natural killer cells
NPC nuclear pore complexes
Oct-1 octamer binding protein 1
PHN post-herpetic neuralgia
PTLD posttransplant lymphoproliferative disease
PEL primary effusion lymphoma
RDV Rhadinovirus
Defining Statement

The family *Herpesviridae* includes over 100 different species of DNA viruses, eight of which are currently known to infect humans. These viruses are discussed with relation to the diseases they cause, their ability to establish latent infections, their biology, replication and pathogenesis, and the treatment options available for each.

**Family Herpesviridae**

The family *Herpesviridae* is a family of large DNA viruses containing over 100 different virus species that infect hosts ranging from humans to birds to reptiles. Classification of a virus as a member of the family *Herpesviridae* is based on a shared virion structure: a linear, double-stranded DNA genome is contained within a central core, surrounded by an icosahedral capsid. This capsid is in turn surrounded first by an amorphous protein layer, known as the tegument, and then by an envelope containing viral glycoprotein spikes (Figure 1). Herpesviruses also share four significant biological properties:

1. They encode a large number of enzymes involved in nucleic acid metabolism, DNA synthesis, and processing of proteins.
2. The synthesis of viral DNAs and capsid assembly occurs in the nucleus of the infected cell. During infection, virus-specific compartments are assembled within the nucleus of the infected cell, commonly referred to as replication compartments (Figure 2). It is within these compartments that viral DNA replication, late viral gene expression, and encapsidation of progeny viral genomes occur. These compartments lead to the formation of basophilic nuclear inclusion bodies, which are diagnostic of herpes virus infection.
3. Production of infectious progeny virus is generally accompanied by the destruction of the infected cell.
4. The viruses are able to establish a latent infection in their natural hosts.

There are currently eight herpesviruses that are known to infect humans: herpes simplex virus (HSV)-1 and HSV-2, human cytomegalovirus (HCMV), varicella zoster virus (VZV), Epstein–Barr virus (EBV), Kaposi’s sarcoma-associated herpesvirus (KSHV) and human herpesvirus (HHV)-6 and HHV-7. These viruses, along with the majority of herpesviruses that infect other mammals and birds, have been divided into three subfamilies, alpha, beta, and gamma, based on the biological properties of the viruses. HSV-1, HSV-2, and VZV are members of the *Alphaherpesvirinae* subfamily, EBV and KSHV are both members of the *Gammaherpesvirinae* subfamily, while the remaining viruses, HCMV and HHV-6A, HHV-6B, and HHV-7 are all members of
the Betaherpesvirinae subfamily. Despite the many similarities in structure and biological properties shared by herpesviruses, it is not surprising that in a group of this size there are also many differences. Host range, length of replicative cycle, cell type in which latency is established, and clinical manifestations of disease all vary among the different members of the family.

The Alphaherpesvirinae Subfamily

Members of the Alphaherpesvirinae subfamily are characterized by a variable host range, short reproductive cycles, the ability to spread rapidly in culture and efficiently destroy infected cells, and the capacity to establish latent infections primarily, although not solely, in sensory ganglia. The members of the Alphaherpesvirinae subfamily that infect humans are HSV-1 and HSV-2, and VZV.

HSV

Disease

The two HSV species, HSV-1 and HSV-2, are capable of causing a variety of diseases within an infected host. The most common of which are orolabial lesions, commonly referred to as cold sores or fever blisters and most often caused by HSV-1, and genital herpes which is most often caused by HSV-2. The viruses are extremely widespread throughout the world's population. The US National Health and Nutrition Examination Survey (NHANES) conducted between 1999 and 2004 has put seroprevalence rates in the United States at 58% for HSV-1 and 17% for HSV-2. Seroprevalence rates in Europe tend to be slightly higher for HSV-1 and slightly lower for HSV-2 when compared to the United States, although there are large intercountry differences. In developing Asian countries, the seroprevalence of HSV-1 and HSV-2 appear to match those seen in Europe and the United States. However, in Africa and Central and Southern America, the picture is quite different. In these regions, HSV-1 is becoming an almost ubiquitous pathogen with greater than 90% of the population seropositive by their fourth decade of life. HSV-2 seroprevalence rates range from 30 to 80% in women and 10 to 50% in men in sub-Saharan Africa, and between 20 and 40% in women in Central and South America. Universally, HSV-2 seropositivity is higher in women than in men. Changes in sexual practices also mean that HSV-1 is becoming a more common cause of genital infection than it once was.

In an immunocompetent host, primary infections with HSV can be asymptomatic, with an individual only realizing that they have been infected when a recurrent infection occurs at a later point. However in some cases, primary infections can be symptomatic, and in these instances disease is usually more severe than that seen with recurrent infection. During symptomatic primary HSV infection, individuals can present with fever, malaise, and large quantities of painful vesicular lesions at and around the site of infection, lasting for a period of up to 3 weeks. Recurrent infections, at either the orofacial or genital site, generally involve a much smaller number of vesicular lesions that persist for 7–10 days.

Along with the common mucosal herpetic lesions associated with orofacial and genital infections, HSV is also associated with a number of more severe complications. In immunocompetent individuals, the most serious complications are herpetic stromal keratitis (HSK) and herpes simplex encephalitis (HSE). Ocular infection with HSV can lead to HSK, the leading cause of infectious corneal blindness. Initially, recurrent infections within the cornea can produce ulcers that result in pain, light sensitivity, and blurred vision. Repeated episodes of recurrent disease can lead to involvement of the underlying stroma, resulting in HSK, which can eventually lead to blindness due to corneal scarring and vascularization. HSE, while extremely rare, has a high risk of mortality if left untreated (>70%). It is usually caused by HSV-1 and results in inflammation and swelling of the brain tissue, with patients presenting with weakness, visual disturbances, and seizures. Although antiviral drugs can be used to decrease mortality, almost 50% of patients fail to regain complete normal function.

As is common with herpes viruses, individuals with compromised or absent immune responses are at high risk of HSV complications. Patients with atopic dermatitis, where the immune response in the skin is skewed toward a Th2 response, can develop a disseminated HSV infection throughout the skin known as eczema herpeticum. Evidence from HIV-positive patients and people undergoing immunosuppressive therapy has demonstrated the increased severity of HSV infection in such populations, with these patients also more prone to chronic or atypical infections. Finally, HSV infection in neonates is associated with increased mortality and morbidity. Infection in this setting usually results from transmission from mother to child during delivery and is estimated to occur at a rate of one in every 3–5000 deliveries. Localized infections of the skin, eyes, and mouth are rarely fatal. However, children with disseminated infections or those involving the central nervous system are at high risk of mortality or ongoing neurological impairment. Prompt antiviral treatment has been able to reduce mortality rates; however, neurological sequelae remain high in children who recover from either disseminated HSV or HSV encephalitis.

Virus and biology

The genome of HSV-1 is 152 kbp in length, while that of HSV-2 is 154 kbp. The two viruses have approximately 50% nucleotide sequence identity and encode protein
products with high levels of amino acid sequence identity. Both viruses have the same genome structure of a unique long and unique short region flanked by inverted repeats and share the common herpesvirus virion structure described previously. The high level of shared protein sequence results in antigenic cross-reactivity between the two viruses but despite this they have different neutralization patterns and tend to produce different clinical symptoms.

One biological property, common to both HSV-1 and HSV-2, that influences the ability of these viruses to cause disease in humans is neurovirulence. The ability of the virus to invade and replicate within the host nervous system primarily enables the virus to establish a latent reservoir of virus within this site, from which reactivation and subsequent transmission can occur. However, it also provides a situation whereby the virus can produce severe disease within the host, such as is seen in cases of HSV encephalitis.

**Replication**

In permissive cells, the process of HSV viral replication takes 18–20 h (Figure 3). The initial step in this process is the attachment to and entry of the virus into the target cell, a process that involves five viral glycoproteins – gB, gC, gD, gH, and gL. The initial attachment is mediated by contact between glycoprotein C (gC) and/or gB with heparan sulfate on the surface of the cell. Viral attachment is closely followed by interaction between gD and one of the several cell surface receptors that facilitate entry into the cell; three different classes of receptors have been identified for gD. Viral entry can occur via two pathways, the well-characterized method of direct penetration of the cellular membrane via fusion with the viral envelope and the less well-characterized method of endocytosis. This second method of entry has to date only been demonstrated using in vitro systems with several different cell lines. Hence, the importance of endocytosis in a natural infection remains to be determined. The kinetics of both modes of viral entry appears to be similar, with the transition from attachment to penetration occurring within minutes.

Following entry into the cell, the de-enveloped viral capsid is transported through the cytosol to the nuclear pore complexes (NPC) where the viral DNA is released into the nucleus and takes on a circularized form. Movement of the capsid through the cytosol is rapid, reaching the nucleus within approximately 1 h. This transport is most likely mediated by microtubules. Once the viral DNA has entered the nucleus, the host RNA polymerase II is then used to transcribe the viral genome in a sequential fashion, resulting in the expression of over 80 viral proteins. The viral proteins are preferentially translated within the infected cell, in part due to the action of the viral protein VHS (virion host shutoff).
This tegument protein remains in the cytoplasm as the viral capsid is transported to the nucleus. It induces destabilization of host mRNA and causes a rapid cessation of host protein synthesis, resulting in the loss of the cellular mRNA pool and thus, the preferential translation of viral proteins. The sequential pattern of viral gene expression results in the HSV genes being divided into three categories, loosely based on the timing of their expression in infected cells. The categories are the immediate early (IE) or α genes, the early or β genes, and the late (L) or γ genes.

**IE genes**

The IE genes are expressed within 2–4 h of infection and include six different viral proteins. These genes can be expressed in the absence of de novo viral protein synthesis, using the viral tegument protein VP16 (viral protein number 16) as a transactivator. VP16 is transported to the nucleus with the cellular host cell factor (HCF) protein. Once within the nucleus, the VP16–HCF complex binds to a second cellular factor, Oct-1 (octamer binding protein 1) and forms a stable transcription regulatory complex called the VP16-induced complex. This complex is able to stimulate expression of the IE genes.

The IE genes ensure the orderly expression of subsequent viral genes and the evasion of the cellular responses to the infection. To do this, many of the IE genes perform multiple functions, and a variety of posttranslational processing is employed to enable these proteins to fulfil the roles required. In brief, ICP4 is required for the expression of all early (E) and L genes; ICP0 acts as a nonspecific or ‘promiscuous’ transactivator, capable of stimulating the transcription of α, β and, γ genes; ICP27 is required for the transcription of the L viral genes and some E genes; ICP47 is involved in immune evasion; and ICP22 and U_{5.1.5} are thought to be involved in promoting the expression of some L genes.

**E genes**

The E genes are maximally expressed between approximately 5–7 h after infection. The E proteins include those that make up the viral DNA replication machinery. Thus, the expression of the E genes signals the initiation of viral DNA replication. However, the expression of certain E genes is also involved in downregulating IE gene expression, in particular, ICP8 has been shown to downregulate expression of the IE gene ICP4.

**L genes**

The L genes are the final group of viral genes to be expressed within the infected cell. Some L genes, such as gB and gD, are actually expressed early in the infected cell, and their expression simply increases with the onset of viral DNA replication. Alternatively, other L genes, including gC and U_{5.11}, are only expressed following viral DNA replication. Many of the L genes encode viral structural proteins, and their expression enables the production of progeny virion particles.

**Viral egress from infected cells**

Following the expression of the L genes, viral capsids are assembled within the nucleus. These capsids, predominantly made up of four viral proteins, are then filled with viral DNA, a process that utilizes viral proteins. It is generally accepted that the nucleocapsids then bud through the inner nuclear membrane and upon doing so acquire an envelope. However, the subsequent events that lead to the egress of the newly formed virus particle from the infected cell are not yet fully understood. Three competing theories exist, each with varying amounts of supporting evidence. The first theory argues that the enveloped nucleocapsid buds through the inner nuclear membrane and is transported to the surface by vesicular movement through the Golgi apparatus; thus, in this model, the tegument would be acquired in the nucleus. The second theory argues that the enveloped virus fuses with the outer nuclear membrane, leaving the de-enveloped nucleocapsid to bud into the Golgi apparatus, regaining an envelope, and then to travel to the surface via vesicular movement. In this model, the tegument could be acquired in the nucleus or the cytoplasm, with work supporting this model demonstrating that the majority of virions gain their tegument and envelope in the cytoplasm. The third model involves capsids exiting the nucleus via nuclear pores and then budding through Golgi membranes.

Release of virus from an infected cell results in the shedding of newly formed virions, enabling the virus to spread to susceptible individuals. However, within the body, the virus can also spread directly from cell to cell. This process involves the viral glycoproteins gE and gI, which form a heterodimer, and is facilitated by cell contact. In general, cells infected with replicating HSV do not survive the infection, due to the cytopathic effects of viral infection.

**Latent infection**

HSV persists for the life of the host by establishing a latent infection in sensory neurons. During a primary infection, virus enters the sensory nerve endings in the epithelium and travels to the neuronal cell body. Animal models have suggested that within the neuronal cell body viral replication can occur initially. However, within several days, no replicating virus can be detected. Concurrent with the short-lived lytic infection within the ganglia, the virus also establishes latency and, following clearance of the replicating virus, latent virus persists. Evidence from animal models and human studies has indicated that the latent HSV genome most likely exists...
as an extrachromosomal circular episome, with human studies suggesting a latent viral burden of between 1 and 10 viral copies per neuron, remembering that not all neurons within a ganglion will harbor latent virus. Viral replication within the nerves or even at the primary site of infection is not required for the establishment of latency. However, lack of viral replication appears to reduce the quantity of latent virus within a latently infected ganglion through a reduction in the number of latently infected cells. The traditional view of latency is that lytic viral gene expression is shut down and only the latency-associated transcripts (LATs) are produced. The primary LAT is an 8.5 kb transcript that is cleaved to produce the 2.0 kb and 1.5 kb major LATs, referred to as such based on their abundance. LATs may play a role in silencing lytic genes, preventing cell death, or exerting other effects during latent infection.

As mentioned previously, latent virus can reactivate periodically. It is thought that only a small percentage of latently infected neurons will reactivate at any given time. Following reactivation within the ganglion, viral components such as the nucleocapsid and the glycoproteins travel down the neuronal axon individually via anterograde axonal flow and are assembled into virus particles prior to virus emergence into the periphery. Within the periphery, reactivated virus can result in either asymptomatic shedding or a clinical recurrent lesion. Although the mechanisms are not fully understood, a number of stimuli are known to induce reactivation including nerve damage, stress, ultraviolet (UV) light, menstruation, and hormonal imbalances. The fate of virus-infected neurons continues to be contentious, with some believing that neurons can survive a lytic HSV-1 infection and others arguing that they cannot.

**Pathogenesis**

Transmission of HSV requires close, personal contact between the susceptible individual and an individual secreting the virus, enabling the virus to come into contact with either mucosal surfaces or abraded skin. As previously mentioned, HSV-1 is generally the cause of orofacial infections while HSV-2 is usually transmitted via genital contact, and thus causes genital infections, although it should be noted that both viruses are capable of infecting either sites. At each site, the virus replicates in the epithelium and infects the innervating sensory nerve endings. Virus travels along the neuronal axon to the innervating sensory ganglion, the trigeminal ganglion in orofacial infections, and the sacral ganglia in genital infections. Within the sensory ganglion, HSV establishes a lifelong latent infection in which viral gene expression is silent except for transcription of the LAT.

A major factor in the pathogenesis of HSV is the ability of the virus to reactivate from latency. Although we are yet to fully understand the mechanisms through which this occurs, it has been demonstrated that the frequency of reactivation correlates with the severity of the primary infection. When reactivation occurs, progeny virions are produced within the ganglion and travel back down the neuronal axon to be released into the epithelium at or near the site of initial infection. Such reactivation events, which can be either symptomatic or asymptomatic, provide the virus with the opportunity to spread to other susceptible individuals. Interestingly, HSV-1 is more likely to reactivate within a trigeminal ganglion than a sacral ganglion, while the opposite is true for HSV-2. In this way, the tissue tropism of each virus appears to be coupled with a site-specific frequency of reactivation.

**Drugs and vaccines**

A number of nucleoside analogues have been used effectively to treat herpes infections, including acyclovir (ACV), famciclovir, and valacyclovir. These drugs exploit the fact that viral enzymes recognize certain molecules that the endogenous cellular enzymes do not, enabling the drugs to target only virus-infected cells. One of the most successful antiviral drugs, ACV, a guanine base attached to an acyclic sugar-like molecule, is used to block HSV lytic replication (Figure 4). ACV is highly specific because it targets two viral enzymes, virus-encoded thymidine kinase (TK) and DNA polymerase. The viral TK phosphorylates ACV to the monophosphate form while the cellular enzymes phosphorylate it to the di- and triphosphate forms. The HSV DNA polymerase then incorporates the monophosphate form of ACV into the growing DNA chain, but the nascent DNA chain cannot be extended because ACV lacks a 3’-hydroxyl group. Viral DNA synthesis is thereby inhibited. Minimal toxicity is observed because uninfected host cells lack the two enzymes needed for ACV incorporation into DNA.

ACV effectively blocks productive infection but does not affect latent infection. Resistance to ACV is uncommon except in individuals who are immunocompromised, such as AIDS patients, and those undergoing immunosuppression. In such cases, viral replication occurs at a high level and mutant viruses resistant to ACV can arise.

Drugs such as ACV, when given promptly, have proved effective in reducing the mortality and morbidity associated with HSV encephalitis and ocular and neonatal infections. The chemical structure of acyclovir is shown below (Figure 4).

![Figure 4](image)

**Figure 4** The chemical structure of acyclovir.
infections. However, given the emerging link between HSV-2 and the acquisition and progression of HIV, a method of preventing HSV infection is needed. To this end, a number of different vaccine approaches have been investigated, including killed virus vaccines, subunit vaccines, and genetically engineered live virus vaccines. On the whole, killed virus vaccines have proven ineffective at preventing acquisition of HSV, and of two subunit vaccines that have been through human trials, only one showed some efficacy in a subgroup of patients. At this point, the use of replication-defective mutant viruses as vaccines appears to be the most promising approach. A current candidate, dl-529, has been rendered replication-defective through deletions in both U_29 and U_11 and has been shown to induce both high titers of neutralizing antibodies and strong cell-mediated responses.

**VZV**

**Disease**

VZV is the causative agent of varicella or ‘chickenpox’, a common childhood disease with the highest prevalence occurring in the 4–10 years age group, and herpes zoster or shingles, a disease most often seen in older individuals. The virus is highly communicable, though it is not considered contagious. It is thought to enter susceptible individuals via the respiratory tract. From here, it spreads to the lymphoid system before producing the characteristic vesicular rash in the skin 10–21 days later. A fever and general feeling of malaise accompany the appearance of the rash. Most individuals become infected with VZV as children. However, approximately 10% of young adults remain susceptible. It should be noted that the incidence of varicella in the United States, particularly in children aged 1–4 years, has declined by approximately 85% since the introduction of a vaccine into the United States pediatric immunization schedule in 1995.

Following a primary infection, VZV establishes a latent infection in the sensory ganglia, with 10–20% of people experiencing a recurrent infection after several decades. Recurrent VZV infection manifests as a vesicular rash in the dermal nerve innervated by the latently infected ganglion and is referred to as herpes zoster or ‘shingles’. It first presents with a prodrome, a painful burning sensation throughout the soon-to-be-affected dermatome. Several days later, the characteristic vesicular rash appears in the skin, which is generally accompanied by flu-like symptoms and can last up to 7–10 days. It is common for the burning, piercing pain to continue after the resolution of lesions in the skin, and in cases where pain persists for longer than 30 days after such resolution the patient is deemed to have post-herpetic neuralgia (PHN). PHN is generally self-limiting and most patients are pain-free by 6 months post-zoster, although pain can be significant until resolution.

The fact that herpes zoster is more common among the elderly and immunocompromised individuals supports the idea that the immune response plays an important role in determining whether VZV is able to reactivate from latency or not and whether symptomatic disease ensues. For those aged 20–50 years, the incidence of herpes zoster is around 0.25%, this rises to 0.8% in people aged over 60 and can reach as high as 50% in people who reach 85 years of age. Individuals with compromised immune systems are also at an increased risk of herpes zoster. People with HIV, leukemia, Hodgkin’s and non-Hodgkin’s lymphoma, and those who have undergone either bone marrow or renal transplants are at risk. It should also be noted that in immunocompromised individuals, the cutaneous rash is usually more extensive and widespread viremia is also common.

**Virus and biology**

VZV shares the common herpesvirus virion structure of a core, containing a single copy of the 125 kbp linear, double-stranded DNA genome, surrounded by a nucleocapsid, a proteinaceous tegument layer, and an outer envelope. It also shares the ability to establish lifelong latent infections in the sensory ganglia with the other human alphaherpesviruses HSV-1 and HSV-2. However, unlike the HSVs that are able to replicate in cells from a wide range of hosts, VZV has a very narrow host range, restricted to selected cell types of human and simian origin. Another difference between VZV and HSV relates to the spread of the virus through the host. HSV is generally confined to the epithelium infected during lytic infection and the neuronal cells within the sensory ganglia, where latency is established. VZV on the contrary has the ability to disseminate widely through the bloodstream of the infected host, infecting skin, mucous membranes, and visceral and nervous system tissues.

**Replication**

The infectious cycle of VZV is similar to that seen with HSV-1 and HSV-2. The virus uses surface glycoproteins, definitely gB and possibly gC, to attach to cellular surface glycosaminoglycans, such as heparan sulfate. Several other viral glycoproteins, gH, gE, and gI are also involved in the attachment and penetration process, following which the viral nucleocapsid, along with several tegument proteins, is transported to the nuclear surface and the viral genome is inserted into the nucleus. It is thought that, like VP16 during HSV infection, the VZV tegument proteins may be involved in initiating transcription of viral genes. The transcription of viral genes occurs in a sequential pattern with IE, E, and L genes, designated as such by the timing of their transcription. Each class of genes is transcribed in the nucleus, the mRNAs are then transported into the cytoplasm where they are translated, and the resulting proteins are then transported back into the
nucleus. The IE genes are involved in the regulation of transcription of IE, E, and L genes and each VZV IE protein has homology to one of the HSV IE proteins, although the exact roles played by these proteins are not always homologous. The E proteins are involved in viral DNA replication, and the L proteins are generally structural, used to produce the capsids for progeny virions. The newly formed capsids travel out of the nucleus, becoming enveloped in the process, and are then transported to the cytoplasmic membrane where they are released from the infected cell. In cell culture systems, the entire process can occur in as little time as 8–16 h.

Pathogenesis
VZV is transmitted via inhalation of infectious respiratory secretions or skin-to-skin contact with infectious vesicular fluid and manifests as a vesicular rash throughout the skin 10–21 days later. Due to a lack of animal models for VZV, the pathogenesis of this virus was originally modeled on that of mousepox. Based on this model, it is thought that the inhalation of the virus enables infection of regional lymph nodes, resulting in a primary viremia that enables the virus to disseminate throughout the body, spreading to reticuloendothelial organs such as the liver. Within these organs, it is hypothesized that a phase of viral amplification occurs followed by a second round of viremia during which the virus is transported to the skin.

During primary infection, VZV is able to establish latency within sensory ganglia; VZV DNA is widely detected in the trigeminal ganglia and in many dorsal root ganglia of infected individuals. It is widely accepted that neuronal cells are the primary reservoir of latent virus, infected either hematogenously or by virus transported along neuronal axons from the skin via anterograde axonal transport. VZV latency differs from the situation during HSV infection in two main ways; first, unlike HSV infection, a number of VZV genes are believed to be transcribed and translated while the virus is in a latent state, and second, VZV latency lacks the frequent episodes of asymptomatic reactivation seen with HSV infection. This later observation is thought to be due to the ability of the host immune response to quickly control reactivation events and maintain the virus in a latent state.

Many aspects of the host immune response come into play when dealing with a VZV infection. The innate response in epidermal cells plays an important role in slowing the spread of virus through the skin. NK cells and interferon (IFN-γ) also play a role in the innate defense against VZV infection, helping to contain the virus prior to the development of the adaptive response. In terms of adaptive immunity, VZV induces both cell-mediated and humoral immunity, with T cells thought to be particularly important in clearing infectious virus and helping to maintain VZV in a latent state.

Drugs and vaccines
As with HSV, nucleoside analogues such as ACV and related drugs have been useful in treating VZV infections. In cases of varicella, oral ACV can be given to healthy individuals to reduce the severity of symptoms, while intravenous ACV is given to immunocompromised individuals to reduce the risk of disseminated infections. In cases of herpes zoster, ACV can be given to immunocompetent individuals to shorten the period of lesion outbreaks, the healing period, and the severity of acute neuropathic pain. Similarly for immunocompetent individuals, intravenous ACV can be used to shorten the period of disease and prevent disseminated infection.

VZV is the first HHV for which there is a licensed vaccine, a live attenuated virus vaccine derived from a clinical viral isolate known as the Oka strain. The Oka strain was attenuated by passage into guinea pig fibroblasts, producing a virus with reduced efficiency for replication in human skin. In clinical trials, a single dose of the vaccine was sufficient to induce seroconversion rates of 90% or greater in children 12 years and under and provided complete protection from disease in approximately 85% of exposures. The vaccine induces strong T cell responses with a single dose and also achieves high antibody titers when a second dose is administered and is now recommended for routine vaccination of infants and susceptible older children and adults in the United States. A recent study has also demonstrated that vaccination of healthy adults aged 60 years and older can significantly reduce the frequency and morbidity of herpes zoster, suggesting that a vaccination regimen in this population may also be useful.

The Gammaherpesvirinae Subfamily
Gammaherpesviruses are classified as such based on their ability to replicate in epithelial cells, establish latency in lymphocytes, and their oncogenic effects. Within the gammaherpesvirus subfamily, there are two genera: the Lymphocryptovirus (LCV) genus, which includes the human pathogen EBV, and the Rhadinovirus (RDV) genus, which includes KSHV. It is thought that the viruses within the LCV genus likely evolved from those in the RDV genus.

EBV
Disease
EBV, also known as HHV-4, is a widespread human pathogen with 90% of adults testing seropositive. In developing countries, most children are infected within the first three years of life, while in developed countries around 50% of individuals remain seronegative through
childhood. It is estimated that 25% of people who then acquire EBV during adolescence or young adulthood will present with acute disease called infectious mononucleosis (IM), although it should be noted that childhood cases of IM are common in Asian populations and are possibly underdiagnosed in other parts of the world. Patients with IM can present with symptoms ranging from a mild and transient fever to a period of malaise and pharyngitis lasting several weeks. This period of EBV disease is closely linked to the emergence of the cytotoxic T cell response to infection, and it is widely accepted that IM is mostly an immunopathologic disease, with the proinflammatory cytokines secreted by active T cells thought to be responsible for many of the IM symptoms. In a small subset of patients, IM is poorly controlled and can lead to more severe, possibly fatal, outcomes. Males with X-linked lymphoproliferative (XLP) syndrome are highly sensitive to EBV infection. In these patients, primary EBV infection results in severe IM-like symptoms and can rapidly result in mortality, thought to be due to an uncontrolled T cell response to infection. Virus-associated hemophagocytic syndrome (VAHS) and chronic active EBV infection (CAEBV) are two other serious outcomes of EBV primary infection. Both involve EBV infection of T cells, resulting in virus-driven proliferation of these cells (much like the proliferation of B cells during a classical primary infection). The infected T cells release huge amounts of proinflammatory cytokines, which results in hemophagocytosis, where macrophage begin phagocytosing red blood cells, platelets, leukocytes, and other cells. The risk of mortality with either syndrome is high.

Following primary infection, EBV establishes a latent infection in B cells, which is generally maintained as such for the life of the host with no clinical manifestations. However, this is not always the case, and EBV is associated with a number of different human malignancies. In immunocompetent individuals, usually following several decades of EBV latency, EBV is associated with the development of certain types of Hodgkin’s lymphoma, several B-lymphoproliferative lesions, T cell and NK cell nasal lymphomas, and gastric and nasopharyngeal carcinomas. In immunocompromised individuals, the virus is capable of rapid tumor development, with some cases of tumorigenesis evident within months of EBV infection. In transplant settings, a link has been demonstrated between EBV and posttransplant lymphoproliferative disease (PTLD), with EBV association as high as 100% in early onset cases and 80% with late onset cases. AIDS patients show a heightened risk of B cell lymphoma with approximately 50% linked to EBV, and most settings involving immunosuppression have demonstrated a link between EBV and smooth muscle cell tumors. EBV is also associated with endemic Burkitt’s lymphoma (BL), the most common childhood cancer in equatorial Africa which is geographically linked to areas of holoendemic malarial infection, although the mechanisms through which EBV contributes to BL are not fully understood.

**Virus and biology**

EBV shares the common herpesvirus virion structure and has a 184 kbp genome. There are two strains of the virus, types 1 and 2 or types A and B, which circulate in most populations. Individuals can be infected with both types and this is a common occurrence in immunocompromised individuals. Type 1 is generally more prevalent in developed countries while type 2 is dominant in equatorial Africa and New Guinea. The main differences between the two strains are seen in the nuclear protein genes that encode EBV-coded nuclear antigen (EBNA)-LP, EBNA-2, EBNA-3A, EBNA-3B, and EBNA-3C.

**Replication**

EBV is known to infect both B cells and epithelial cells during primary infection, with infection of epithelial cells thought to result in a lytic infection and infection of B cells thought to generally result in a latent infection. In B cells, the virus binds to CD21 and MHC class II on the surface of target cells using glycoproteins in the virus envelope. A cell surface receptor for epithelial cell infection has yet to be found, and it is hypothesized that virus may be transferred to epithelial cells directly from lytically infected B cells. The entry of virus into each cell type differs in that virus enters B cells via the endocytic pathway while virus entering epithelial cells does so at the cell surface, in both cases viral glycoproteins are involved in facilitating fusion and entry of the virus into the target cell. Following entry of the virus into the target cell, the nucleocapsid is transported to the nucleus into which the viral genome is inserted.

If a lytic infection ensues, as is thought to occur in epithelial cells in *vivo*, the sequential expression of IE, E, and L genes, common to herpesviruses, is seen. The IE proteins are primarily involved in activation of E gene expression, the E proteins are primarily involved in viral DNA replication, while the L proteins are involved in the production of progeny virions. At this time, it is thought that newly formed nucleocapsids initially acquire an envelope at the inner nuclear membrane, are de-enveloped as they are released into the cytoplasm, and then reacquire an envelope as they bud through the plasma membrane.

It is widely accepted that initial infection of B cells results in a latent or persistent infection. In fact, *in vitro* studies demonstrated that infection of B cells with EBV resulted in a latent infection that was capable of causing perpetual B cell proliferation, helping to confirm the oncogenic properties of EBV. During latency, the viral genome is maintained in the nucleus of the infected cell in
an episomal form with variable levels of gene expression possible. There are four different forms of EBV latency: latency 0, I, II, and III. These stages are classified as such based on the level of expression of the EBNA proteins and latent membrane proteins (LMPs), with latency 0 having no viral antigens expressed and latency III having all latency proteins expressed.

These different forms of latency are used by the virus to ensure the maintenance of the viral genome within progeny B cells, and as such the virus uses cellular differentiation controls to determine which level of latency is required at any given time. For example, during a primary infection, EBV is present in infected B cells in latency III form, and the expression of viral genes at this stage is used to drive the proliferation and differentiation of these cells into a latent infected memory pool. Once the memory pool is established, and in order to prevent further detection by virus-specific cytotoxic T cells, EBV switches off all gene expression, thus entering latency 0. At times when memory B cells are induced to divide by homeostatic signals, the virus reactivates to latency I to ensure the viral genome is not lost during such cell division. In this way, the virus is able to establish a balance between avoiding immune detection and maintaining the viral genome. At times of cell proliferation, the virus uses cellular differentiation to ensure maintenance of the viral genome within daughter cells.

**Pathogenesis**

EBV infection is transmitted via the oral route and is generally asymptomatic. As such, knowledge of the primary infection is not commonly studied. These individuals shed virus in saliva and throat washings. However, the source of this virus remains contested. It is generally assumed that because B cell-deficient individuals show no sign of EBV infection in the throat, initial infection of a naïve host is B cell-dependent. However, it is becoming more widely accepted that epithelial cells may also be sites of viral replication, with studies suggesting that virus bound to the surface of a B cell is highly efficient at infecting epithelial cells. Interestingly, recent evidence further suggests that virus released from B cells is defective for B cell infectivity but shows enhanced infection of epithelial cells, while virus released from epithelial cells has the opposite phenotype.

EBV establishes a latent infection in B cells at the site of primary infection, the tonsillar tissue. Studies suggest that latently infected B cells express a memory phenotype, and it has been proposed that infection of naïve B cells with EBV mimics the process of B cell differentiation, resulting in activation and proliferation of the infected cell population, and thus the production of an expanded pool of latently infected memory cells. It is generally accepted that the cell-mediated immune response brings the proliferating B cells under control. The memory pool of latently infected B cells, which circulates through the body, is able to disperse the latently infected cells throughout the lymphoid system. Individuals latently infected with EBV will have peripheral blood B cells that harbor virus and, following clearance of the primary infection, these individuals will continue to shed low levels of infectious virus via the oral cavity. This virus comes from the latent B cell reservoir. It is thought that memory B cells containing latent virus may undergo reactivation when they receive an activation signal, and that such cells, which localize near mucosal surfaces, would be capable of transmitting lytic virus to epithelial cells where viral replication and subsequent shedding can occur.

In a healthy individual with an intact immune system, EBV persists in this form for the life of the host with no clinical manifestations. The latent pool is constantly maintained by the virus moving forward and backward through the various forms of latency as required, and infectious virus is sporadically shed from the oral cavity with the potential of infecting other susceptible hosts. However, when immune suppression occurs, either through disease or drug intervention, this balance is destroyed and the individual is put at risk of EBV-associated disease.

**Drugs and vaccines**

To date, attempts to develop preventative vaccines against EBV have been largely unsuccessful. The finding that the major viral envelope protein gp350 was the dominant target of the neutralizing antibody response led to attempts to develop a gp350 subunit vaccine. However, some evidence suggests that neutralizing antibodies alone are not sufficient to protect against EBV, with clinical trials showing that the gp350 subunit vaccine failed to prevent primary infection, although it was able to reduce the incidence of IM symptoms. It is now widely believed that an integrative approach is required, where a vaccine to prime the antibody response (such as the gp350 subunit vaccine) would be given in combination with a vaccine aimed at priming the CD8+ T cell response. However, it should be noted that even this integrative approach would probably be most successful at limiting rather than preventing infection.

In parallel with efforts to design a preventative vaccine, efforts are also being aimed at developing immunotherapeutics for EBV-associated malignancies. Current strategies being developed include adoptive transfer of activated T cells specific for viral antigens expressed on EBV-associated tumors and the development of vaccines that can boost the host T cell response to these same antigens. Both strategies are aimed at increasing T cell recognition and subsequent destruction of EBV-associated tumors.
**KSHV**

**Disease**
KSHV, also known as HHV-8, is the most recently identified HHV. The virus was originally identified because of its association with Kaposi's sarcoma (KS), an endothelial neoplasms. It was later recognized as a member of the gammaherpesvirus subfamily of herpesviruses.

Infection rates with KSHV in the United States and in Europe are relatively low with approximately 3% of the population infected. In Africa, a different picture emerges, with KSHV reaching endemic rates of infection of between 40 and 60%. The various strains of KSHV can be divided into four major groups or clades: A, B, C, and D, with each virus within a given clade sharing a single common ancestor. A and C tend to cluster together and are more prevalent in Europe and in the United States, B is the most commonly isolated in infected individuals in sub-Saharan Africa, and D is the dominant clade seen in South Asia and Australia. The pattern of distribution and the evolutionary relationship between viruses in the different clades suggest that KSHV entered the human population at about the time when modern man emerged in Africa, with the different clades being produced as different groups moved out of Africa to Europe and Asia, respectively. The fact that the distribution of these clades seems to have been maintained over millions of years also suggests that, particularly in areas of high seroprevalence, transmission of KSHV is primarily familial, moving vertically from parent to child and horizontally between different members in a family unit possibly via salivary exchange. It should be noted that in areas of low seroprevalence, such as Europe and the United States, the pattern of infection appears to follow that of a sexually transmitted disease, and virus has been successfully isolated from both saliva and genital secretions.

The most common malignancy associated with KSHV is KS. KS is a complex, angioproliferative, and inflammatory lesion. It was historically a disease of elderly Mediterranean men until it emerged as the most common neoplasm seen as a complication of HIV/AIDS. In both settings, the disease is a slow progressing malignancy, although it can result in death in AIDS patients if organ involvement is present. Unlike a classical tumor, KS lesions contain many different cell types with the driving cell being a KSHV-infected spindle cell (an elongated endothelial cell). The spindle cells produce proinflammatory and angiogenic products and may actually require factors released from proinflammatory cells for survival and growth. It is possible for KS lesions to be locally or systemically invasive, requiring chemotherapy or radiotherapy.

While strong evidence suggests that KSHV is necessary for KS development, it is certainly not sufficient. Within the general population, only 1 in 10 000 infected individuals will develop KS annually. Therefore, it is assumed that there are other cofactors involved in the development of KS. In AIDS-related KS, the assumption is that HIV infection is the cofactor. It has been proposed that an HIV protein may act as a growth factor for KSHV or that the immunodeficiency seen during HIV infection may enable KSHV to disseminate more widely through the host, increasing the chances of endothelial cell infection. The cofactor in non-AIDS-related KS remains unknown.

Along with KS, KSHV has been implicated in two B cell diseases, primary effusion lymphoma (PEL) and Castleman's disease. PEL is a rare disease seen in end-stage AIDS patients and is characterized by proliferation of B cells primarily in body cavities such as the pleura, pericardium, and peritoneum. Unlike KS, PEL is a classical malignancy with every cell in the tumor harboring KSHV DNA. Castleman's disease is a rare, lymphoproliferative lesion that is seen in both HIV-positive and HIV-negative individuals. In HIV-negative individuals, Castleman's disease generally presents as a benign tumor localized to a single lymph node. This form of Castleman's disease does not involve KSHV and is usually treated by excision of the involved tissue. Multicentric Castleman's disease is a more aggressive, systemic illness characterized by sustained fever, sweats, and weight loss. This form of Castleman's disease is seen with increased frequency in patients with AIDS and, in this setting, is almost always linked to KSHV infection.

**Virus and biology**
KSHV shares the standard herpesvirus virion structure described above. The virion contains a double-stranded linear DNA genome of between 165 and 170 kbp in length that contains four blocks of highly conserved genes, many of which encode replication proteins common to alphaherpesviruses, the genome also encodes several small noncoding mRNAs, the function of which remains unknown.

**Replication**
The replication cycle of KSHV follows a pattern similar to that seen with the other herpesviruses and thus will not be discussed in detail here. Virus attachment and entry are facilitated by several viral glycoproteins, following which the viral genome and several tegument proteins are delivered into the nucleus of the infected cell. If, at this point, the virus enters the lytic cycle, the sequential expression of over 90 viral genes is initiated. These genes
are divided into IE, delayed early (DE), and L genes. The mechanism of KSHV egress has yet to be fully elucidated.

Despite the obvious ability of the virus to induce a lytic infection, as demonstrated by the intermittent shedding of virus from infected individuals, studies in cell culture systems suggest that the default pathway in KSHV infection is latency. From in vitro work, it appears that only a small number of cells (1–3%) will enter the true lytic pathway and that this will subside following several days of infection. In the majority of cells, a defective version of lytic infection arises, which is quickly terminated and latency established. In these cells, a range of lytic cycle genes are expressed during the first 12 h of infection. However, the expression of these genes ceases by 24 h postinfection and the genes are not expressed in their correct sequential order, thus providing evidence of the defective nature of this ‘lytic’ infection. Latency is then quickly established in these cells. The role that the faulty lytic infection plays in the overall virus infection remains unknown, although it has been proposed that the transient expression of some of the viral immune evasion mediators may be beneficial during the early stages of infection.

Once latency is established, the viral genome is replicated as an episome. The viral LANA protein tethers the viral episome to the cellular chromosome so that the viral genome is distributed to progeny cells during cell division. At this time, only a few of the 90-plus viral genes are expressed. However, the exact roles that these proteins play during the latent infection still require much investigation. Work to date would suggest that they may be involved in maintenance of the viral genome in dividing cells, prevention of apoptosis and, surprisingly, upregulation of proinflammatory responses. The switch from the latent to the lytic phase of infection is thought to be facilitated by the so-called lytic switch protein, known as RTA. This protein is a viral transcriptional activator that is capable of inducing lytic gene expression on its own, but becomes even more efficient when bound to one of several different HCFs. In experimental systems, deletion of RTA prevents both spontaneous and chemically triggered induction of the lytic cycle.

Pathogenesis

Primary infection of a susceptible host is followed quickly by the establishment of latency, primarily in B cells. In most individuals, the latent infection is asymptomatic and is accompanied by intermittent, clinically silent viral reactivation that enables shedding of virus in the saliva. Given the apparent absence of an extended primary lytic infection, asymptomatic reactivation during latency would appear to play a major role in virus transmission.

The exact role of KSHV in the pathogenesis of KS is currently unknown. It appears that both latent and lytic stages of infection are important, with KSHV latency much less potent than EBV latency at inducing cell immortalization. Most KS spindle cells are latently infected but a small percentage demonstrates lytic infection. It would appear that this low level of lytic replication is important in the development of KS, possibly enabling the reactivation of spindle cells that have lost the KSHV genome, providing a reservoir of newly infected cells to replace cells within the tumor mass that have died, or even providing some of the inflammatory and angiogenic signals that play a role in KS pathogenesis.

**Drugs and vaccines**

There are currently no drugs or vaccines available for the prevention or treatment of KSHV. In most individuals, the immune response is adequate to control the virus and prevent virus-associated disease. With this in mind, in immunocompromised individuals, it is common to treat the underlying cause of immunosuppression or to attempt to treat the malignancy itself rather than the viral infection.

**The Betaherpesvirinae Subfamily**

The betaherpesviruses are characterized by a restricted host range, a long productive cycle, and the ability to establish latent infections in secretory glands, lymphoreticular cells, and kidneys. The betaherpesviruses have the highest level of evolutionary and genetic diversity of the three herpesvirus subfamilies, which can make the use of animal models to study human pathogens within this subfamily difficult. There are four genera within the betaherpesvirus subfamily: the cytomegaloviruses, the muromegaloviruses, the roseoloviruses, and the proboscivirus (which has only a single member).

**HCMV**

**Disease**

HCMV is a ubiquitous human pathogen, infecting those in developing countries in their youth and those in developed countries across a slightly wider timeframe. In most individuals, HCMV causes an asymptomatic infection, with disease generally only seen in those unable to mount a cellular response to infection, such as neonates or individuals with some form of immunosuppression. As is characteristic of herpesviruses, HCMV establishes a latent infection within the host, although interestingly this is also accompanied by what can be called a chronic infection, with infected individuals shedding virus sporadically from their bodily fluids for life.

HCMV can be classified as an opportunistic pathogen, only causing disease in situations where the immune response is severely compromised (such as HIV) or absent (such as congenital infection). In most healthy individuals,
infection with HCMV is clinically silent, although it should be noted that in a small number of cases a short bout of fever and malaise can occur, similar to the mononucleosis caused by EBV.

**Congenital infection**

Transmission of HCMV from mother to fetus or newborn is a very common occurrence and can occur via three routes: transplacental, intrapartum, and via human milk. HCMV is the only herpesvirus known to exhibit natural transplacental transmission, and it is this congenital route of transmission that causes serious morbidity. That said, intrapartum and transmission via breast milk, while not associated with the morbidity of congenital infections, both play an important role in viral epidemiology. These newborn children infected with HCMV will continue to shed virus capable of infecting susceptible hosts for many years after the primary infection.

Congenital infection can occur when the mother has either a primary or reactivated infection during pregnancy, with evidence from those undergoing a primary infection suggesting that transmission to the fetus can occur in 20–40% of cases. Although less than 1% of live births involve a child with congenital HCMV, the long-term sequelae for these children make it a serious disease, with HCMV estimated to be the leading cause of infectious brain damage in the United States. Approximately 5–10% of those born with a congenital HCMV infection will be symptomatic, showing clinical manifestations such as hearing loss, seizures, jaundice and brain abnormalities, with long-term sequelae such as mental retardation, cerebral palsy, and impaired vision. In 10% of cases, symptomatic congenital HCMV infection will be fatal. Even the 90% of congenitally infected children born without symptoms remain at risk of long-term CNS sequelae such as hearing loss.

**Infection in an immunocompromised host**

Patients with compromised or suppressed immune systems are at greater risk of CMV-associated disease than healthy individuals, with the severity of disease often matching the level of immunosuppression. In patients with HIV or those undergoing solid organ or hematopoietic stem cell transplants, HCMV can disseminate into a number of different organs, causing clinical manifestations such as pneumonitis, retinitis, and hepatitis. In organ transplant patients, HCMV has also been shown to cause dysfunction of the transplanted organ and put the patient at greater risk of fungal and bacterial infections. The thorough screening of transplant patients and the use of antivirals in this setting and HAART in the HIV setting is helping to reduce the morbidity and mortality associated with HCMV infection in immunocompromised individuals.

**Virus and biology**

Compared to the other HHVs, HCMV is a very large virus. With a genome between 196 and 241 kbp, the virus encodes in excess of 166 gene products (less than half of which are conserved in all betaherpesviruses), and while HCMV shares the common herpesvirus virion structure, the actual size of the virions is larger than that of the other HHVs.

**Replication**

The replication cycle of HCMV follows a similar pattern to that described for the other herpesviruses. The virus uses heparan sulfate as an initial binding receptor on target cells and then enters the cell via either fusion of the viral envelope with the cellular membrane or the endocytic pathway. The viral genome is released into the nucleus and the lytic viral genes are expressed in a sequential manner: IE, DE, and L. Unlike the alphaherpesviruses, evidence suggests that HCMV most likely undergoes a two-stage envelopment/de-envelopment/re-envelopment process in order to exit an infected cell. Newly synthesized nucleocapsids are enveloped as they pass through the inner nuclear membrane and then deenveloped as they pass through the outer nuclear membrane. The envelope-free nucleocapsid is thus released into the cytoplasm where it reacquires an envelope at the ERGIC membranes before being transported out of the infected cell via the cellular exocytic pathway.

In terms of replication, the main difference between HCMV and other HHVs is the length of the replication cycle. DE gene expression begins at 6 h postinfection and continues through 18–24 h when viral DNA synthesis is initiated. From initial attachment to the initiation of progeny virion release, the complete infectious cycle takes between 42 and 78 h. During this time, the virus has a profound effect on the infected cell, blocking IRF-3 activation, IFN signaling, and apoptosis responses and interrupting the cell cycle in such a way that infected cells are able to survive for several days of productive infection.

**Pathogenesis**

In an immunocompetent host, HCMV infection is generally asymptomatic. Primary infection is usually initiated in the mucosal epithelium following direct contact with infectious secretions from another individual, aerosol transmission does not occur. A systemic phase of infection then follows with a leukocyte-associated viremia. Animal models with murine CMV (MCMV) suggest that the virus uses immature leukocytes from the bone marrow to facilitate dissemination to the salivary glands, kidneys, and other tissues. This systemic phase of infection is associated with high levels of persistent viral shedding in the saliva, urine, breast milk, and genital secretions and continues for a long time after the onset of the adaptive
immune response. It can last for months in adults and for years in young children, supposedly due to a less effective cellular immune response in younger patients. The ability of the virus to persist in the face of the cellular immune response is thought to be due, in part, to the fact that more than 25 viral genes have been found to play a role in modulating the host response to infection.

When virus is cleared following primary infection, HCMV is maintained in a latent state in hematopoietic progenitor cells (HPC). However, unlike the human alphaherpesviruses, this latent infection is accompanied by what can be called a chronic infection in epithelial cells of the salivary glands and kidneys, which results in sporadic shedding of virus in the bodily fluids for the life of the host. Reactivation of virus from latency, as opposed to the sporadic viral shedding achieved by the persistent infection in the salivary glands and kidneys, seems to be an issue only in situations of immunosuppression.

Immune responses to HCMV are well maintained for years beyond the primary infection, at levels not seen with other herpesviruses or persistent infections. Innate immune responses such as IFN and NK cells are important during the early stages on infection and may play a role in containing the infection until the adaptive immune response develops. T cell responses appear to be of greater importance than antibody responses, although in certain settings antibodies play a crucial protective role. Despite the persistence of the primary viremia in the face of an active cellular immune response, the fact that viral reactivation is only seen in cases of immunosuppression suggests that the immune response plays an important role in helping to maintain the virus in a latent state and preventing CMV-associated disease.

**Drugs and vaccines**

There are currently four drugs approved for the treatment of HCMV infection in immunocompromised individuals: Ganciclovir, Valganciclovir, Foscarnet, and Cidofovir. All four have been shown to reduce or eliminate viremia, reduce viral shedding, and prevent or control CMV disease. However, due to risks of severe toxicity, the drugs are only used when a patient is at risk of serious disease. At this time, no drugs are approved for the treatment of congenital CMV, although a small Ganciclovir trial did produce some positive results.

Given the seriousness of congenital CMV infection and the difficulty in preventing maternal infections, a preventative vaccine would have a large public health benefit. Several different vaccine approaches have been tested to date. However, a CMV vaccine is yet to reach the market. Strategies that have reached clinical trials have included a live attenuated vaccine, a gB subunit vaccine, a canary pox vector expressing CMV gB and pp65, and a DNA vaccine with antibody and CTL epitopes. Several of these vaccines have shown promising results in inducing strong immune responses.

**HHV-6 and HHV-7**

**Disease**

HHV-6 was first isolated in 1986 and is classified into two variants, A and B. HHV-6B is the major causative agent of exanthem subitum (ES), while HHV-6A has not been clearly linked with any disease. HHV 7 was first isolated in 1990 and is also a causative agent of ES as well as being associated with febrile convulsions in young children. Both HHV-6 and HHV-7 are ubiquitous pathogens, with greater than 90% of adults seropositive for both.

ES or roseola is a classical childhood disease (sixth disease). It initially presents as a fever lasting for 3–4 days. As the fever clears, a rash appears, first on the trunk and hands and then on the lower limbs, lasting several days. HHV-6B is the major cause of ES, with the magnitude of viral replication correlating with the severity of disease. HHV-7, while also a cause of ES, has a lower frequency of disease as compared to HHV-6B. It is possible for children to have successive bouts of ES caused by one virus and then the other. Most cases of ES are benign and are associated with other symptoms such as diarrhea, cough, and febrile convulsions. However, it is possible for HHV-6 infection to result in encephalitis, meningitis, and hepatitis, which can be fatal.

Following primary infection, both HHV-6 and HHV-7 persist in a latent state. As with other herpesviruses, reactivation is generally only a problem in situations where the immune system is compromised. In bone marrow transplant recipients, asymptomatic HHV-6 reactivation is common. However, reactivation has also been linked to bone marrow suppression, encephalitis, colitis, pneumonitis, and graft-versus-host disease. In solid organ transplant recipients, HHV-6 reactivation has been associated with kidney rejection.

**Virus and biology**

HHV-6A, HHV-6B, and HHV-7 are members of the roseovirus genus of the betaherpesvirus family, sharing the common characteristics of growth in T cells, high prevalence, and association with febrile rash illness. HHV-6A and HHV-6B are closely related but actually meet the requirements for recognition as two separate viruses—they differ in cell tropism, interactions with cells and the immune system, DNA sequences, and epidemiology. As with the other human betaherpesvirus, HCMV, both HHV-6 and HHV-7 have protracted replication cycles and share some betaherpesvirus-specific genes.

The virion structure of HHV-6 and HHV-7 follows the common herpesvirus structure of a dsDNA genome within an icosahedral capsid that is surrounded by a tegument layer and finally a lipid bilayer envelope.
HHV-6 has a genome of up to 170 kbp, while the HHV-7 genome is 145 kbp in length.

**Replication**
HHV-6 and HHV-7 have a similar replication cycle to that of the other HHV. Following virus attachment and entry, the viral genome is delivered to the nucleus where viral gene transcription is initiated in a sequential manner: IE, E, and L. Egress of newly formed virions from the infected cell follows the same path as that used by HCMV: envelopment/de-envelopment/re-envelopment.

**Pathogenesis**
Transmission of HHV-6 and HHV-7 is not fully understood. It is thought that transmission during infancy occurs horizontally, possibly via saliva during close personal contact. However, it is also thought that the viruses can be transmitted across the placenta, during delivery, or even intrauterine. The exact site of primary infection is also yet to be determined. It is currently thought that infection is initiated through respiratory pathways, however the exact cells that are infected are not known.

Both HHV-6 and HHV-7 establish latent infections within their hosts. It is thought that HHV-6 establishes latency in monocyte or macrophage cells and certain stem cells. HHV-6 DNA and antigens can also be detected in a range of other sites including the saliva, brain, and lung, suggesting a concurrent persistent infection. HHV-7 establishes a latent infection in CD4\(^+\) T cells while maintaining a persistent infection in the salivary glands and a variety of other tissues.

**Drugs and vaccines**
Several drugs approved for use against CMV have been shown to be effective against HHV-6 and HHV-7 *in vitro*, these include Ganciclovir, Foscarnet, and Cidofovir. IFN-\(\alpha\) and IFN-\(\beta\) have also been shown to inhibit HHV-6 replication *in vitro*. However, no drugs are currently approved for use in the treatment of HHV-6 or HHV-7 infection.

**See also:** Antiviral Agents; HIV/AIDS

**Further Reading**


