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Human herpesvirus 6

Abbreviations: HHV-6; Previous name: human B lymphotropic virus, HBLV

Stephen Dewhurst, David Skrincosky and Nanette van Loon

Human herpesvirus 6 (HHV-6) is a T-lymphotropic herpesvirus, which infects almost all children by the age of two years and persists lifelong. Two distinct variants of HHV-6, HHV-6A and HHV-6B, have been described, and the latter has been shown to be a common cause of acute febrile illnesses in young children, including exanthem subitum (roseola). HHV-6 has also been associated with a number of neurological disorders, including encephalitis and seizures, and the virus has been postulated to play a role in acquired immunodeficiency syndrome (AIDS), multiple sclerosis (MS) and chronic fatigue immunodeficiency syndrome (CFIDS). This review provides a critical summary of research conducted on HHV-6.

In 1986, a new herpesvirus was isolated from the peripheral blood mononuclear cells of six adults with lymphoproliferative disorders, some of whom were infected with human immunodeficiency virus type 1 (HIV-1) (Ref. 1). This virus, which was initially named human B-lymphotropic virus, or HBLV, was the first new human herpesvirus to be identified since the discovery of Epstein-Barr virus over 20 years earlier. The isolation of HHV-6 opened the doorway to an exciting period in herpes virology, and has been followed by the identification of two additional herpesviruses that infect humans, human herpesvirus 7 (HHV-7) and the Kaposi's sarcoma-associated herpesvirus (KSHV), which is also known as human herpesvirus 8 (HHV-8). Genetic analysis has revealed that KSHV has little similarity to HHV-6; in contrast, HHV-7 and HHV-6 represent closely related siblings with significant biological and genetic similarities.

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Classification and Subtypes

Classification

Among all the known herpesviruses, HHV-6 is most closely related to HHV-7 at the genetic level; its next closest sibling is human cytomegalovirus (HCMV). This genetic similarity, combined with commonalities in the biological properties of HHV-6 and HCMV (such as lymphotropism and a slow replicative cycle), has prompted the International Committee on Viral Taxonomy (http://www.ncbi.nlm.nih.gov/ICTV/) to classify HHV-6 in the beta herpesvirus subfamily (genus *Roseolovirus*).

Subtypes

HHV-6A and HHV-6B represent distinct variants of HHV-6 and the two variants can be distinguished by differences in their antigenicity and biologic properties (Ref. 2). In addition, the viral genomes differ by approximately 4–6% at the nucleotide level (Refs 3, 4, 5); this compares with a much lower level of nucleotide divergence (approximately 1%) between different strains of the same virus variant.

Despite the high overall level of sequence identity between HHV-6A and HHV-6B, several loci exhibit more extensive sequence divergence. This is illustrated by the presence of numerous open reading frames (ORFs) in which there is at least 10% difference in predicted amino acid content between the two variants (Refs 3, 4, 5). The significance of these localised differences remains uncertain.

The two variants of HHV-6 can also differ in other respects. First, their geographic distribution might be distinct. In North America, HHV-6A was detected in the peripheral blood mononuclear cells (PBMC) of less than 3% of children who had acute febrile illness resulting from HHV-6 (Ref. 6); whereas in Central Africa, this same variant was present in 44% of PBMC samples collected from infants with a first febrile episode resulting from HHV-6 (Ref. 7). Second, the two variants might infect distinct tissue compartments, consistent with differences in their *in vitro* host cell range (Ref. 2). For example, in North America, HHV-6A has been commonly identified in lung tissues of both healthy and diseased adults, even though it is rare in the PBMC of this population (Ref. 8). Third, the variants might differ in their relative potential for pathogenicity or their reactivation properties. For example, the frequency of detection of HHV-6A DNA in PBMC from adults with chronic fatigue immunodeficiency syndrome was found to be significantly higher than in PBMC from healthy adults (Ref. 9). Likewise, HHV-6A was found to be the predominant HHV-6 variant in lymph nodes from HIV-1 infected adults (Ref. 10). Clearly, additional studies will be needed to adequately determine the prevalence, anatomic and geographic distribution, and pathogenicity of HHV-6A.

Lifecycle

The biological properties and genetics of HHV-6 are discussed below, and are summarised in Table 1 (tab001sdr).

Host cell tropism

Isolates of HHV-6 have been shown to replicate with varying efficiency in a wide array of host cell types, including primary T cells, monocyte/macrophages, natural killer (NK) cells and astrocytes, as well as various continuous cell lines of T cell, B cell, megakaryocyte and glial cell lineages (reviewed in Ref. 2). In general, the host cell range of laboratory-adapted isolates of HHV-6A appears to be somewhat broader than that of HHV-6B.

Receptor interactions

The binding events involved in herpesvirus infection are understood best for the prototypic human herpesvirus, herpes simplex virus type 1 (HSV-1). In this case, infection is believed to proceed via an initial interaction with cell surface heparan sulphate proteoglycans (HSPGs), which is then followed by binding to a specific cellular receptor. For many strains of HSV-1, this receptor is a membrane protein known as the herpesvirus entry mediator (HVEM) (Ref. 11), which is a member of the tumour necrosis factor receptor superfamily.

In the case of HHV-6, little is known about the events that are involved in virus attachment to host cells. It is probable that HHV-6 also binds to cell surface HSPG because the virus encodes a homologue of HSV-1 gB, a protein that is known to bind to proteoglycans (see below). However, the specific receptor(s) for HHV-6 remain unknown.

Permissive and latent infections by HHV-6

Despite the fact that HHV-6 does not bind directly to the cellular CD4 molecule, $CD4^+$ T cells

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Table 1. Genetics and cell infection of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) (tab001sdr)

	HHV-6	HHV-7
Tropism	T-lymphotropic. A broad host-cell range can be infected *in vitro* (particularly for HHV-6A), which includes primary T cells, NK cells and astrocytes, as well as continuous cell lines of T cells, B cells, megakaryocyte and glial lineages.	T-lymphotropic. Tropism is restricted to: $CD4^+$ T cells and the SupT1 cell line
Variants	HHV-6A, HHV-6B. HHV-6A might have a different host-cell range/pathogenesis and is ~5% divergent at the nucleotide level from HHV-6B.	None known.
Receptor (for binding to cells and entry)	Unknown. The broad host-cell tropism of HHV-6 suggests that either (1) the receptor is ubiquitous or (2) more than one molecule can be used for virus entry.	CD4 is a necessary receptor component, but is not 'sufficient' for virus entry.
Cell markers	HHV-6 can induce expression of CD4 on some $CD4^-$ cells.	HHV-7 induces loss of cell-surface CD4.
Monocyte infection	HHV-6 can persist in monocytes.	HHV-7 does not infect monocytes.
Genome size	U1102 strain of HHV-6A is 159 kb with DRs of 8 kb.	JI strain of HHV-7 is 145 kb with DRs of 6 kb.
AAV-2 rep gene homologue	ORF U94 is a homologue of AAV-2 *rep*.	No homologue of AAV-2 *rep*.
Unique virion glycoprotein	Encodes gp105, a viral glycoprotein that derives from a highly spliced mRNA spanning multiple ORFs at the right end of the unique segment of the HHV-6 genome (U96-100). gp105 is a major virion component and contains a major neutralising antibody epitope.	Predicted to encode a homologue of gp105.
	Shared properties of HHV-6 and HHV-7	
Replication	In PBMCs, replication is slow and lytic; syncytia are induced.	
Genetics and viral genome	HHV-6 and HHV-7 are closely related and co-linear. Telomeric DNA is present near (not at) the genomic termini. They share a common *ori*Lyt organisation, similar to HSV-1 *ori*S. They encode: (1) U73: a homologue of the HSV-1 origin-binding protein; (2) U12 and U51: two homologues of cellular G-protein-coupled receptors; (3) U20 and U85: two genes with homology to genes of the immunoglobulin family (U85 is homologous to OX-2, a molecule that mediates a recently described T-cell co-stimulatory pathway); (4) gB, gH and gL: homologues of three of the four essential virion glycoproteins in HSV-1. They do not encode: (1) a homologue of gD, the receptor-binding HSV-1 glycoprotein.	

Abbreviations used: AAV = adeno-associated virus; DR = direct repeat; HHV = human herpesvirus; HSV-1 = herpes simplex virus type 1; kb = kilobase; NK = natural killer; ORF = open reading frame; PBMC = peripheral blood mononuclear cells. Other details, including citations, are described in the main text .

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constitute the major population of cells within tissue cultured PBMC that are permissive for replication of both HHV-6A and HHV-6B. In addition, cellular activation (i.e. mitogenic stimulation of resting T cells) appears important for efficient virus production.

Once HHV-6 enters a permissive host cell, virus replication occurs relatively slowly and cells undergo cytopathic effects (CPE) within 3–5 days after infection; changes include membrane blebbing, swelling and induction of multinucleated cells (syncytia). Ultimately, productive infection of cultured PBMC with HHV-6 results in apoptosis of $CD4^+$ T cells, with cell death occurring predominantly in virus-negative bystander cells, as has been reported for HIV-1 infection (Ref. 12).

Non-permissive and latent infection of host cells by HHV-6 remains less well understood than productive infection, and there is currently no adequate *in vitro* model for *in vivo* latency. However, one study has suggested that HHV-6 might be capable of establishing a reactivatable latent state in cultured monocytes (Ref. 13). In addition, targeted integration of HHV-6 genomes has been reported in freshly isolated PBMC from three patients with lymphoproliferative disorders, who had unusually high copy numbers of viruses in their PBMC (Ref. 14). It should be noted, however, that the integration of herpesviruses into host genomes is generally considered to be a rare event, which does not represent a mechanism for herpesvirus latency. Thus, the significance of integrated forms of the HHV-6 genome remains uncertain; although viral reactivation from an integrated latent state has been demonstrated for Marek's disease virus, which is a T-cell tropic herpesvirus that infects birds (Ref. 15).

Effect on T cells

Productive HHV-6 infection has a variety of effects on T cells, in addition to the induction of apoptosis. These include virally induced changes in the production of several cytokines, as well as changes in the expression of cell surface proteins involved in T-cell signalling. For example, HHV-6 (both variants HHV-6A and HHV-6B) has been reported to cause the *de novo* expression of CD4 on cells of haematopoietic lineage that are 'normally' $CD4^-$, such as NK cells, $CD8^+$ T cells and lymphomyeloid progenitor cells (Refs 16, 17, 18). In addition, the U1102 and GS strains of HHV-6A have been demonstrated to cause downregulation of cell surface CD3 expression (Refs 19, 20). This might contribute to the reported immunosuppressive effects of HHV-6, including its ability to suppress T-cell proliferation and T-cell function (Refs 21, 22). However, it remains unclear whether HHV-6B also down-modulates CD3, because the Z29 strain of HHV-6B failed to inhibit CD3 expression (Ref. 20). Studies of other strains of HHV-6B will be needed, in order to determine if this result is true for all isolates of HHV-6B, or whether it is a strain-specific anomaly, unique to Z29.

Genetics and molecular biology

The genetics of HHV-6 are discussed below, and are summarised in Table 1 (tab001sdr) [and tab002sdr, in the html version only].

Genome organisation and relationship to other herpesviruses

HHV-6 is a beta herpesvirus that is co-linear with HCMV over most of its genome. However, Karlin and co-workers have noted that the virus also shares a number of genetic properties with the alpha-herpesviruses, and have concluded that the HHV-6 genome might be closest to a 'progenitor herpesvirus', among the currently known herpesviruses of vertebrates (Ref. 23). The conservation of genetic features between HHV-6 (a beta-herpesvirus) and alpha-herpesviruses, such as HSV-1, might provide an explanation for some of the observed biologic properties of HHV-6, including its relatively broad host range and its ability to cause neurologic disease.

The genome of the U1102 strain of HHV-6A has been completely sequenced and consists of a unipartite double-stranded DNA molecule of roughly 159 kb in length, which comprises a long unique region (143 kb) bounded at both ends by a direct repeat (DR) element of approximately 8 kb (Ref. 5). This is shown schematically in Figure 1 (fig005sdr), which also summarises some of the other salient features of the HHV-6 genome (note that the HHV-6A and HHV-6B genomes appear to be essentially identical in terms of their overall organisation and structure; Ref. 24).

The HHV-6 genome is co-linear over much of its length with the genome of HCMV (Ref. 5). This region of overall co-linearity is interspersed with genes found only in HHV-6 (and not in HCMV), but can be broadly divided into two major sequence 'blocks'. These comprise a central core region (core, on Fig. 1) that contains genes found

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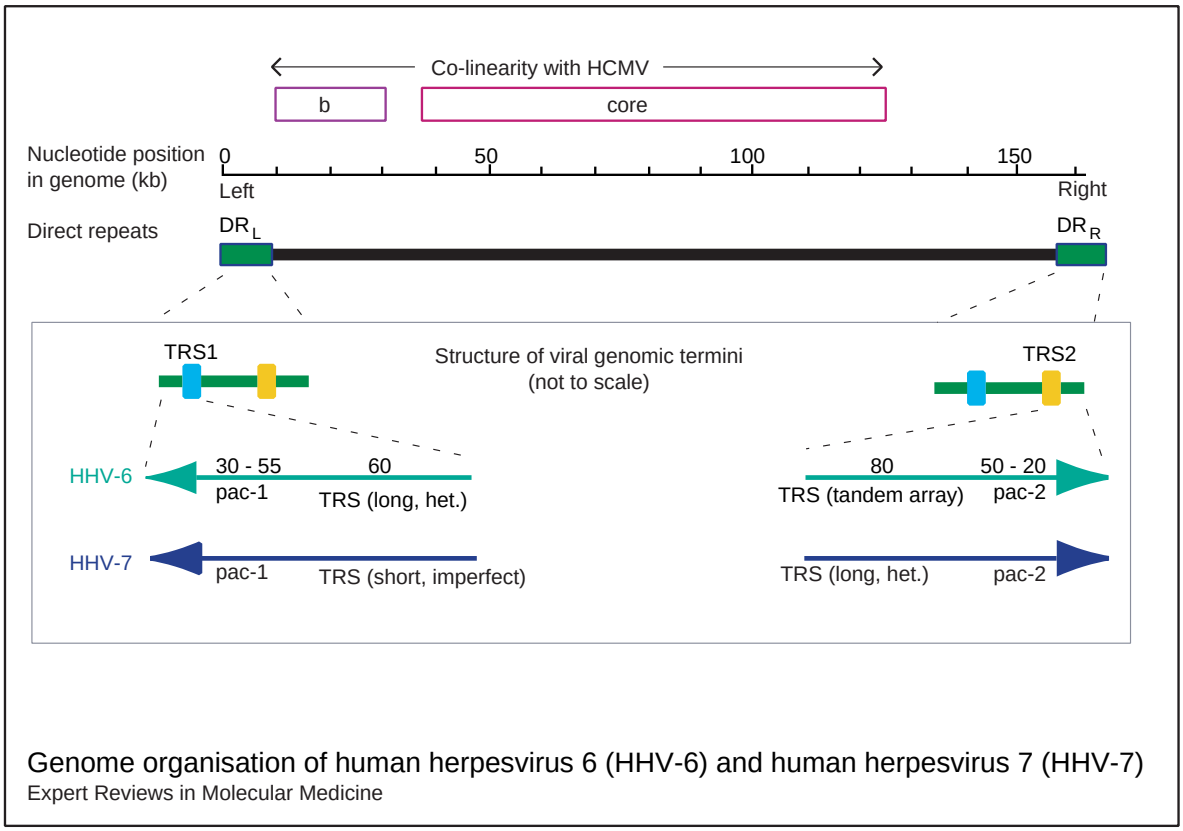

Figure 1. Genome organisation of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7). The overall genome organisation of HHV-6 is shown, and the structure of the genomic termini of HHV-6 and HHV-7 is also presented. Numbers in the upper portion of the figure refer to nucleotide position, in kilobases (kb), within the HHV-6 genome, while numbers in the lower portion of the figure refer to nucleotide position, in base pairs (bp), relative to the viral genomic terminus (left or right), which is indicated by the arrowheads. The region of co-linearity between HHV-6 and human cytomegalovirus (HCMV) is indicated at the top of the figure, and the conserved sequence blocks (b, core) are discussed in the main text. Other indicated DNA motifs include the viral direct repeats (DR), located at the left (L) and right (R) genome ends, as well as consensus sequence motifs (pac-1, pac-2) involved in the cleavage and packaging of replicated viral DNA. TRS motifs refer to blocks of human telomeric repeat sequences ([GGGTTA]n). Distinct iterations of these motifs occur close to the genome ends of HHV-6 and HHV-7 (TRS1, TRS2), including long, heterogeneous arrays (long, het.), perfect tandem repeats (tandem array) or short, imperfect arrays (short, imperfect) **(fig005sdr).**

in all known members of the herpesvirus family (approximately 86 kb in length), and a DNA segment (b, on Fig. 1) that contains genes, thus far, found only in the beta-herpesviruses (i.e. in human and murine cytomegalovirus, and in HHV-6 and HHV-7). The DNA segment at the right end of the long unique component of the HHV-6 genome is more divergent, and encodes a number of proteins that might be relevant to the biological properties of these viruses, including the gp105 glycoprotein (see below) and the major immediate-early transactivating proteins.

The direct repeats that bracket the unique segment of the HHV-6 genome are also specific to HHV-6 and HHV-7, and represent regions of genetic divergence from the other beta-herpesviruses. The first (non-coding) exon and putative promoter elements for the gp105 glycoprotein map to the DR elements, but relatively few other genes appear to be encoded here (Refs 5, 25, 26). However, the DRs contain a number of important *cis*-acting DNA elements. The viral genomic termini (left and right ends of the DRs) merit special mention because they

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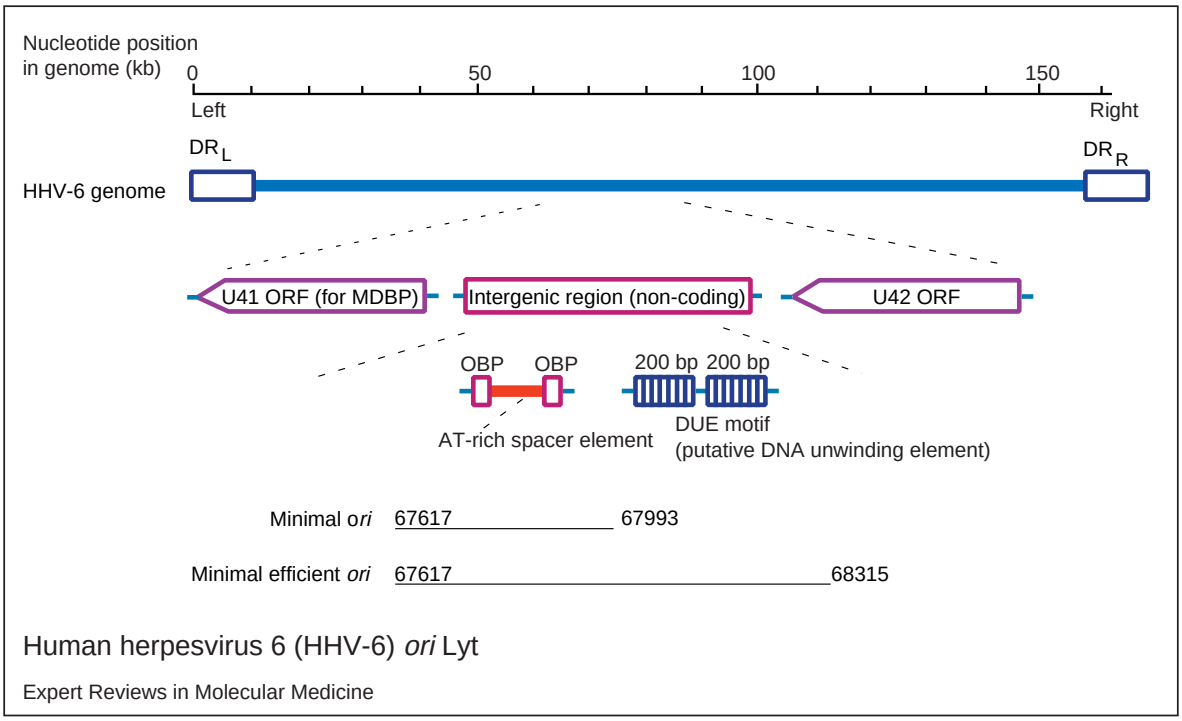

Figure 2. Schematic diagram of human herpesvirus 6 (HHV-6) *ori*Lyt. The location and structural arrangement of the HHV-6 *ori*Lyt element are shown; all numbers refer to the nucleotide position within the HHV-6 genome. As indicated in the upper portion of the figure, HHV-6 *ori*Lyt is located in an intergenic region between the U41 and U42 open reading frames (ORFs) of the virus (U41 encodes the putative major DNA-binding protein of the virus, MDBP). The intergenic region, containing the origin, is shown in detail in the lower portion of the figure. This region includes two binding sites for the HHV-6 origin-binding protein (OBP), separated by an adenine–thymine (AT)-rich spacer. Together, these elements comprise the minimal essential origin element (minimal *ori*). Immediately adjacent to this domain lie two copies of a repetitive sequence block of roughly 200 base pairs in length, which corresponds to a putative DNA unwinding element (DUE). This larger domain (minimal efficient *ori*) replicates with markedly higher efficiency than the minimal essential origin element **(fig002sdr).**

contain consensus sequence motifs (pac-1, pac-2), which have been shown to be involved in the cleavage and packaging of replicated herpesvirus genomes (Ref. 27). In addition, human telomeric repeat sequences (TRS; [GGGTTA]n) have been mapped close to, but not at, the viral genome ends (Ref. 27). These TRSs are present either as perfect tandem hexameric repeats (right terminus of HHV-6), or as interrupted imperfect repeat arrays (left terminus of HHV-6), which can exhibit significant inter-strain heterogeneity. The functional significance of these TRS arrays remains uncertain.

Viral origin of DNA replication

The origin of lytic-phase DNA replication (*ori*Lyt) in HHV-6 is located at the same locus as the HCMV *ori*Lyt element, immediately downstream of the gene coding for the major DNA binding protein (Ref. 28). Despite this common location, HHV-6 *ori*Lyt has almost no genetic similarity to its HCMV counterpart.

The structure of HHV-6 *ori*Lyt is shown schematically in Figure 2 (fig002sdr). It comprises a central region that is essential for DNA replication (minimal *ori*), and which contains two binding sites for a virally encoded homologue of the HSV-1 origin-binding protein (OBP), as well as an adenine–thymine (AT)-rich spacer sequence; this is much like the origins of DNA replication found in all of the alpha-herpesviruses (Ref. 29). HHV-6 *ori*Lyt exhibits additional complexity, however, because the minimal *ori* is flanked by auxiliary sequences that enhance replication efficiency (Ref. 28). The most potent of these lies 3' to the minimal *ori*, and contains two copies of a DR element, approximately 200 base pairs (bp) in length; this is predicted to be helically unstable

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and might be functionally analogous to the DNA-unwinding elements (DUE) found in some eukaryotic origins of DNA replication.

Viral genes

Genes associated with viral DNA replication

HHV-6 contains homologues of the six core herpesvirus replication genes; these encode the viral DNA polymerase (U38), polymerase accessory/processivity protein (U27), single-stranded DNA binding protein (U41), and the three helicase-primase proteins (U43/U74/U77) (see tab002sdr, in the html version only). HHV-6 also possesses a gene (U73) that encodes an OBP that is similar to HSV-1 OBP. The presence of this locus within the HHV-6 genome was somewhat unexpected because HCMV does not encode a similar protein, but its functional relevance became apparent once the structure of HHV-6 *ori*Lyt was known (Ref. 29).

In addition to the genes described above, HHV-6 also contains a number of other loci that might be important for viral DNA replication. These include homologues of three genes that are not found in HSV-1, but which have been shown to play a role in the replication of HCMV [HCMV open reading frames (ORFs) UL84, UL112 and UL113, which correspond to HHV-6 ORFs U55, U79 and U80, respectively; Ref. 30]. HHV-6 also encodes a homologue of the adeno-associated virus 2 (AAV-2) *rep* gene (ORF U94) (Refs 5, 31). This represents a highly unusual example of the 'pirating' of a gene from one virus by another, unrelated virus. Its significance, however, is unclear. In AAV, the Rep protein plays an active role in viral gene regulation and DNA replication; it possesses helicase and endonuclease activities and exhibits sequence-specific DNA binding activity. The HHV-6 Rep homologue can also regulate transcription from a variety of promoter elements, and it can complement the replication of a *rep*-deficient AAV-2 genome (Refs 32, 33). Thus, the HHV-6 *rep* gene product appears to have conserved at least some of the functions of its AAV-2 counterpart, although it remains to be determined whether this gene plays a role in HHV-6 DNA replication.

Viral glycoproteins

In HSV-1, five virion glycoproteins have roles in viral entry: gB, gC, gD, and gH/gL. Of these, only four are essential for virus infection (gC is dispensible). HSV-1 gB binds to cell surface proteoglycans involved in entry, while HSV-1 gD corresponds to the major receptor-binding protein (Ref. 34) and HSV-1 gH/gL are involved in the post-attachment penetration of virus, via a process of membrane fusion. Because HHV-6 encodes homologues of only gB, gH and gL (Ref. 5), it is possible that another, as-yet unidentified, virion component is responsible for receptor binding by HHV-6. A potential candidate for this putative receptor-binding protein is the unique glycoprotein complex, designated gp82-105, which represents a major component of HHV-6 virions and a target for virus-neutralising antibodies (Refs 25, 26); it is encoded by highly spliced mRNAs that derive from the right end of the unique segment of the viral genome (ORFs U96–U100; see tab002sdr, in the html version only).

In addition to gp82-105, HHV-6 also contains a number of other unique ORFs that are predicted to encode glycoproteins (tab002sdr, in the html version only). Perhaps the most intriguing of these ORFs is U85. This ORF is also conserved in KSHV and in HHV-7, but not in other human herpesviruses; it is homologous with the cellular *OX-2* gene, which encodes a cell surface protein that has recently been shown to possess co-stimulatory activity for resting (quiescent or unstimulated) T cells (Ref. 35). It is, therefore, possible that the U85 gene product might play a role in viral evasion of host immune responses, although further studies will be required to test this hypothesis.

Other viral genes, including the viral protease

HHV-6 contains two ORFs (U12, U51) that are predicted to encode homologues of G-protein-coupled receptors, as well as a number of genes that represent potential targets for antiviral drugs. These include the viral DNA replication proteins (see above) as well as the following proteins: (1) U69, which encodes a putative phosphotransferase (ganciclovir kinase; a homologue of HCMV UL97), (2) U28, which encodes the large subunit of ribonucleotide reductase and (3) U53, the viral protease. The viral protease is of particular interest, because the crystal structure of the HCMV protease has recently been determined by independent groups of researchers working at four different pharmaceutical companies (Refs 36, 37, 38, 39).

Briefly, all herpesviruses encode serine proteases with similar substrate specificity (they all cleave a peptide bond between a serine and an

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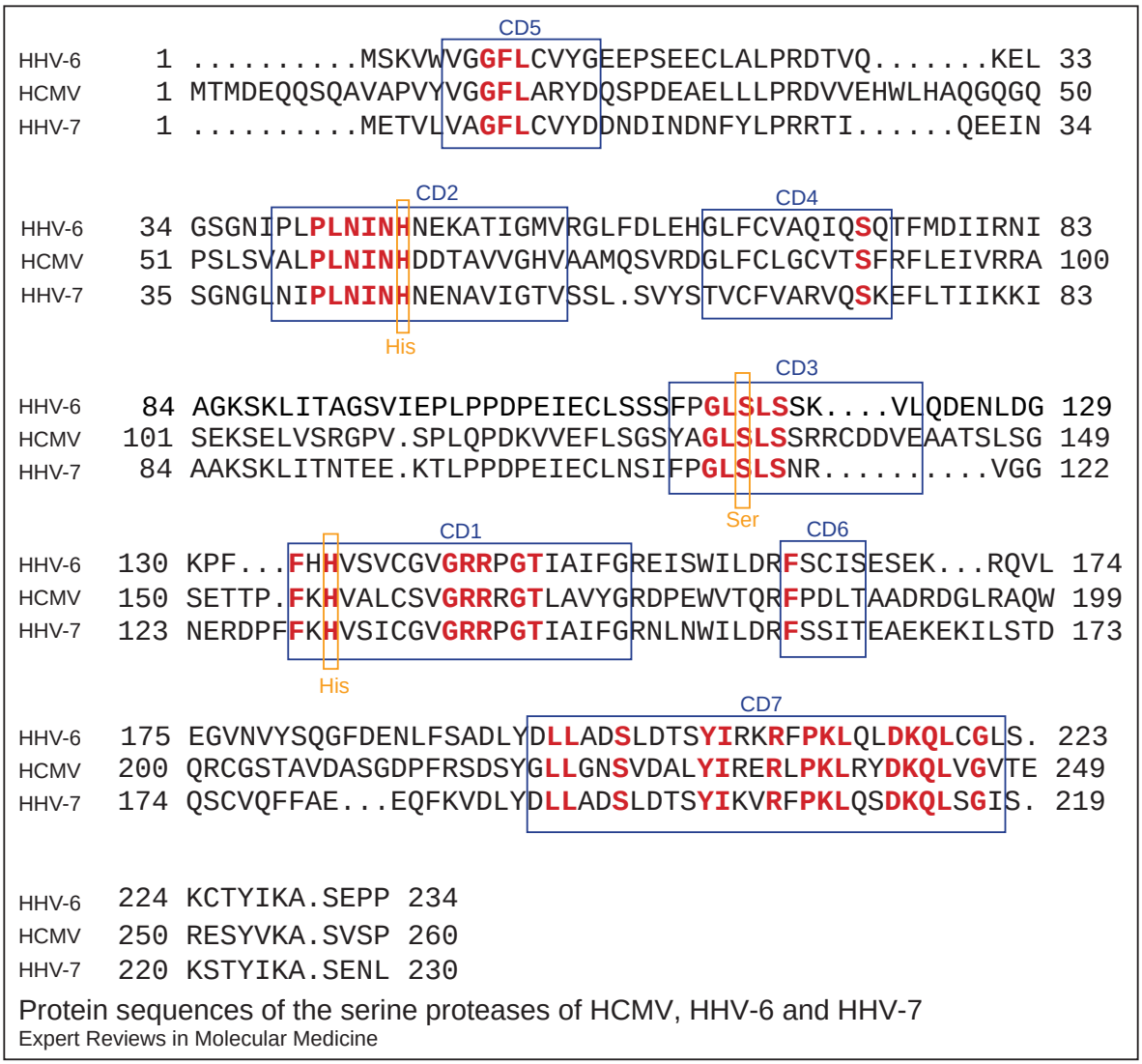

Protein sequences of the serine proteases of HCMV, HHV-6 and HHV-7
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Figure 3. Alignment of the protein sequences of the serine proteases of human cytomegalovirus (HCMV), human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7). The sequence motifs in the boxes represent the conserved domains within herpesvirus proteases that are described in the main text (txt001sdr, txt002sdr). Within these boxed regions, the residues shown in red/bold represent amino acids that are shared by HCMV, HHV-6 and HHV-7. The three active-site residues are 'boxed' in orange (in HCMV: Ser132, His63 and His157; in HHV-6: Ser116, His46 and His135; in HHV-7: Ser115, His47 and His131). Overall, at the amino acid level, the HHV-6 protease is 42% identical to the HCMV protease, and 60% identical to the HHV-7 protease **(fig004sdr)**.

alanine). These enzymes perform a proteolytic cleavage that is essential for virion maturation and, consequently, they represent attractive molecular targets for antiviral drug development.

Unusual aspects of herpesvirus proteases include the fact that these enzymes are catalytically inefficient compared with archetypal serine proteases. They are also only weakly inhibited by common serine protease inhibitors, such as phenylmethylsulphonyl fluoride (PMSF) and *N*-tosyl-L-leucine chloromethyl ketone (TLCK). These biochemical characteristics might be related to the unique structural properties of this class of enzyme, as exemplified by the novel polypeptide backbone fold and active site found in HCMV protease (see mol001sdr the three-dimensional structure of the serine protease of HCMV, in the html version only. This was produced and is viewed using CHIME software).

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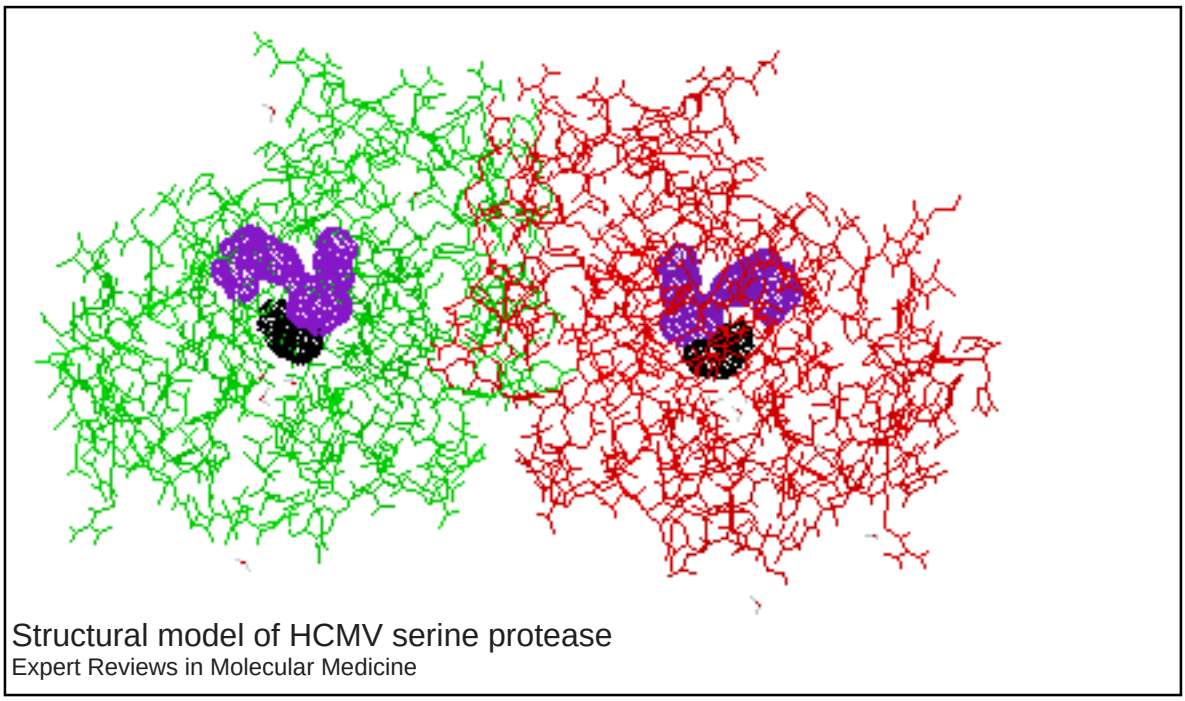

Figure 4. Structural model of human cytomegalovirus (HCMV) serine protease. The individual protease monomers within the homodimeric enzyme are coloured red and green. The catalytic triad representing the active site of the enzyme is represented by van der Waals dot surfaces around its component atoms (to help visualise them) and is coloured black (Ser132; the catalytic nucleophile) or purple (His63, His157). This molecular representation was generated using RasMol software (http://www.glaxowellcome.co.uk/netscape/software), using the PDB database file 1CMV.PDB (http://www.pdb.bnl.gov/cgi-bin/pdbmain); residues within the protease backbone are shown in the 'wireframe' format **(fig007sdr)**.

Similarities between the serine proteases of HHV-6 and HCMV include an overall level of 42% amino acid identity, as well as the conservation of the His–Ser–His catalytic triad, represented by amino acid residues His63, Ser132 and His157 of HCMV protease, and by residues His46, Ser116 and His135 of the HHV-6 protease (Fig. 3; fig004sdr; Refs 40, 41). A structural representation of HCMV protease is shown in Figure 4 (fig007sdr), with the catalytic nucleophile (Ser132) coloured in black and the other active-site residues coloured purple; note that the enzyme is a homodimer, and that the two monomer subunits are coloured red and green in this figure (see mol001sdr, the dynamic molecular model of HCMV serine protease in the html version only; produced and viewed using CHIME software).

Association with disease

The pathogenesis and epidemiology of HHV-6 infection are discussed below, and are summarised in Table 2 (tab003sdr).

Ubiquity and persistence

Serologic surveys have shown that HHV-6 infection occurs in most children by the age of three years (Ref. 2). It is generally assumed that this childhood infection is followed by lifelong persistence of the virus, and that this accounts for the very high (>90%) seroprevalence of HHV-6 in otherwise healthy adults.

HHV-6 DNA can be detected in saliva and in PBMC from 90% of healthy individuals (Ref. 42); in one study of healthy European adults, HHV-6B was the predominant variant detected (Ref. 43). Quantitative measurements of virus load have shown that HHV-6 DNA typically persists in immunocompetent adults at a level of approximately 100–4000 viral DNA genome equivalents for every one million (1×10^6) PBMCs (Refs 42, 44). However, some healthy individuals can 'tolerate' much higher virus loads without apparent ill effects; for example, one person examined by Clark and colleagues had a stable

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Table 2. Pathogenesis and epidemiology of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) (tab003sdr)

	HHV-6	HHV-7
Paediatric infection	Infects most children at 6–24 months of age (somewhat earlier than HHV-7).	Infects most children by 3 years of age.
Primary infection (infants and children under three years of age)	HHV-6B infection usually manifests as a febrile illness, with or without a rash; presentation with a rash is usually diagnosed as roseola (exanthem subitum). HHV-6A can also cause roseola.	HHV-7 can cause roseola.
Oropharyngeal persistence	DNA can be found in salivary glands and in saliva of a high proportion of adults.	DNA can be found in salivary glands and saliva of a high proportion of adults; infectious virus is readily isolated from saliva of almost all adults.
Neurological involvement (children and adults)	Primary HHV-6B infection in infants is associated with seizures, particularly in the 12–15-month age range, and with some cases of encephalitis. In adults, HHV-6 DNA has been detected in biopsy samples from some cases of focal encephalitis, and viral antigens have been detected in active CNS lesions from persons with multiple sclerosis.	In two Japanese children, primary HHV-7 infection has been associated with exanthem subitum complicated by acute hemiplegia.
Infection in immunocompromised adults	HHV-6A and HHV-6B can be pathogenic; the viruses can cause pneumonitis, bone marrow suppression and encephalitis.	Effects of HHV-7 are uncertain and might be complicated by reactivation of HHV-6.
Role in AIDS	Its role is uncertain, both in adults and in children. *In vitro*, HHV-6 can induce CD4 expression on some $CD4^-$ cells; it can also up-regulate HIV-1 gene expression.	Its role is uncertain, both in adults and in children. *In vitro*, HHV-7 can compete for CD4 binding and inhibit HIV-1 infection.
Other diseases	HHV-6 has been proposed to play a role in CFIDS, but evidence for this is currently equivocal.	Unknown.
	Shared properties of HHV-6 and HHV-7	
Prevalence	Over 90% of all adults are infected with both HHV-6 and HHV-7.	
Reactivation (children)	Children who have previously been infected with HHV-6 can experience reactivation of HHV-6 in conjunction with primary HHV-7 infection; HHV-7 can also reactivate HHV-6 *in vitro*.	

Abbreviations used: AIDS = acquired immunodeficiency syndrome; CFIDS = chronic fatigue immunodeficiency syndrome; CNS = central nervous system; HHV = human herpesvirus; HIV = human immunodeficiency virus.
Other details, including citations, are described in the main text.

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burden of roughly 10 x 10^6 copies of HHV-6 DNA for every 1 x 10^6 PBMCs (Ref. 44).

The presence of HHV-6 DNA in saliva, and in salivary glands and bronchial glands, as well as the finding that infectious HHV-6 can be isolated from specimens of saliva, strongly suggest that the virus might be spread horizontally (from one person to another) via oral secretions (Ref. 2). In contrast, vertical transmission of virus (from mother to fetus), if it occurs, is rare; perinatal acquisition (infection at or around birth) remains a possibility, in light of studies showing that HHV-6 DNA can be detected in secretions from the cervix (Ref. 2).

Primary infection and association with exanthem subitum (roseola)

Yamanishi and co-workers provided the first compelling evidence that primary HHV-6 infection might be associated with human disease, when they showed that HHV-6 could be isolated from the PBMC of 4/4 Japanese infants with exanthem subitum (commonly known as roseola) (Ref. 45). Subsequent studies confirmed this association, but also noted that primary HHV-6 infection frequently occurs in the absence of the diffuse rash that is diagnostic for roseola (Fig. 5; fig001sdr; Ref. 46). Complications of primary viral infection can include otitis media (inflammation of the middle ear) and seizures, as well as occasional, more serious, disorders such as hepatitis, encephalitis (inflammation of the brain substance) and very rare cases of fatal, disseminated infection (Ref. 47).

Awareness of the existence of two distinct viral variants prompted a re-examination of the association between HHV-6 and febrile disease of children. In North American, European and Japanese infants, the predominant viral variant isolated from peripheral blood at the time of acute illness has been HHV-6B (Ref. 2), although at least one case of roseola as a result of primary HHV-6A infection has been reported in a Japanese infant (Ref. 48). Further studies will be needed to determine the timing, presentation and sequelae of primary infection with HHV-6A.

Association with neurologic disease

Several studies have noted that primary HHV-6 infection is a frequent cause of febrile convulsions in young children (Ref. 2), and HHV-6 infections have been shown to account for as much as one-third of all febrile seizures in children up to the age of two years (Ref. 49). More serious neurologic complications of acute HHV-6 infection can include encephalitis, which has also been described in healthy and immunosuppressed adults (Refs 50, 51, 52). Demyelinating central nervous system (CNS) disease can also occur in some cases (Refs 53, 54).

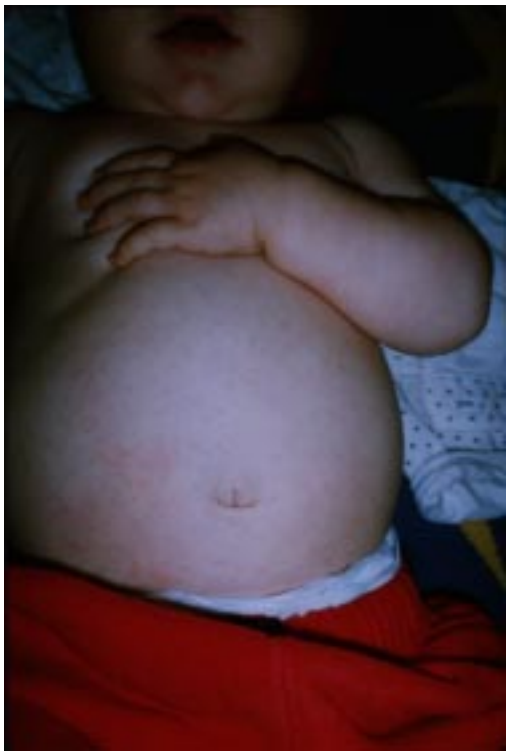

Figure 5. Photograph of a child with exanthem subitum (roseola). There is a disseminated, fine, macular rash on the trunk of this 12-month-old infant. The rash typically appears when the elevated temperature has abated, and can last for only a few hours before subsiding **(fig001sdr)**.

The propensity for HHV-6 to cause febrile seizures and other neurologic illnesses might be linked to the neurotropic and neuroinvasive properties of the virus, characteristics that HHV-6 shares with HSV-1. HHV-6 DNA has been found at a high frequency in brain tissue from apparently healthy adults and in cerebrospinal fluid from children during and after acute infection with HHV-6, which suggests that the virus may be capable of persisting in the CNS (Refs 55, 56).

In most cases examined to date, HHV-6B appears to be the predominant viral variant found in the CNS (Refs 43, 49). However, these studies have focused principally on Japanese, North American or European children. Thus, the

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relatively infrequent detection of HHV-6A in the CNS could simply reflect the scarcity of this viral variant in these countries (Ref. 7). Further studies will be needed to examine this issue.

Viral infection of oligodendrocytes and association with multiple sclerosis

The issue of CNS infection by HHV-6 has been studied further using DNA *in situ* hybridisation and immunohistochemical staining methods, to determine which cell type(s) in the CNS harbour the virus. These studies have shown that HHV-6 DNA is frequently localised to oligodendrocytes, at least in the CNS of HIV-1-infected children (Ref. 57). In adults with multiple sclerosis (MS), structural antigens of the virus have also been localised to oligodendrocytes, with expression levels being highest within active disease plaques (Ref. 56). These findings, combined with the absence of HHV-6 antigen in oligodendrocytes from control brains (i.e. brains from non-MS affected humans), have led to the suggestion that HHV-6 might be associated with the aetiology or pathogenesis of MS (Ref. 56). However, additional studies will be required to determine whether HHV-6 is causally linked to MS.

Association with malignancies

HHV-6 DNA sequences have been identified in a number of human malignancies, including Hodgkin's disease and non-Hodgkin's lymphoma, as well as some cases of T-cell acute lymphoblastic leukaemia and T-cell chronic lymphoproliferative disease (Ref. 2). In addition, whole HHV-6 DNA, or cloned fragments of the viral genome have been shown to be capable of oncogenically transforming cultured cells (Refs 58, 59). Despite these observations, the hypothesis that HHV-6 might have a direct or aetiologic role in human malignancy remains unproved, in large part because the virus might simply be a 'passenger' in most, or even all, of the tumour tissues in which it has been detected (Ref. 2).

Association with disease in immunocompromised individuals

Role in post-transplant disease

Given the fact that HCMV is probably the most important viral pathogen in the post-transplantation setting, it would seem likely that a closely related virus such as HHV-6 might also lead to post-transplant complications. Several studies have demonstrated that this is indeed the case.

HHV-6 has been linked, most frequently, to disease in bone marrow transplant (BMT) recipients, although complications in renal and liver transplant recipients have also been described (Ref. 2). In BMT recipients, HHV-6 was isolated from approximately 40% of individuals (6/16 cases examined) who developed idiopathic febrile illness (fever of unknown origin) following bone marrow engraftment (Ref. 60). The isolation of HHV-6 from PBMC was frequently associated with idiopathic bone-marrow suppression, and HHV-6 could also be isolated directly from the bone marrow of such individuals (Ref. 60). These findings, together with the ability of HHV-6 to suppress the *in vitro* maturation of bone-marrow precursor cells, suggest that the virus might be a cause of bone-marrow suppression in BMT recipients.

HHV-6 antigens and DNA have also been detected in the lung tissue from BMT patients with otherwise idiopathic pneumonitis (inflammation of the lung of unknown origin; Refs 61, 62), although, the overall frequency of HHV-6 related pneumonias in recipients of BMTs remains rather unclear, as does the overall importance of HHV-6 as a pathogen in the post-transplantation setting.

Role in chronic fatigue immunodeficiency syndrome

The notion that HHV-6 might play a role in the pathogenesis of chronic fatigue syndrome (also known as chronic fatigue immunodeficiency syndrome, CFIDS) has existed in the literature for many years. However, data concerning the relationship, if any, between CFIDS and HHV-6 are, at best, conflicting. For example, Patnaik and colleagues reported an increase in the prevalence of IgM antibodies to HHV-6 in people with CFIDS (Ref. 63), while several other groups have concluded that there is no evidence of any relationship between anti-HHV-6 antibody titres and CFIDS (Refs 64, 65, 66). It, therefore, seems unlikely that HHV-6 is involved in the pathogenesis of CFIDS, although additional studies might be warranted (Ref. 2).

Relationship between HHV-6 and HIV-1

The interplay between HHV-6 and HIV-1 has been studied extensively, at least *in vitro*. HHV-6 infection can induce *de novo* expression of CD4 on some cells of haematopoietic lineage (Refs 16, 18), rendering such cells susceptible to infection by HIV-1 (Ref. 17). In addition, HHV-6 and HIV-1 can co-infect the same cells, and HHV-6 gene products

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can trans-activate the long terminal repeat (LTR) of HIV-1 (Ref. 2). However, *in vivo* studies of the role of HHV-6 in disease progression in AIDS have yielded somewhat contradictory results, at least in adults.

Several investigators have suggested that HHV-6 might enhance HIV-1 replication and broaden the *in vivo* host-cell range of HIV-1 (Refs 10, 67), but others have found no correlation between antibody titres to HHV-6, or numbers of copies of HHV-6 DNA in saliva, and progression of HIV-1 related disease (Refs 68, 69). Nonetheless, it appears likely that HHV-6 might be reactivated in people infected with HIV-1 (Refs 44, 70), and that the virus can, at least occasionally, cause serious disease in immunosuppressed individuals, including pneumonitis and encephalitis (see above). It might, therefore, be important to examine the role that HHV-6 plays in disease progression in HIV-1-infected infants, in whom primary HHV-6 infection might occur, resulting in HHV-6 viraemia and immune activation, possibly leading to extensive replication of HIV-1.

Clinical implications/applications

Primary infection

Acute childhood infection with HHV-6 is usually self-limiting, but can be associated with more severe complications, which have both medical and economic impact. In one large prospective study of viral complications and reactivation, approximately 13% of children with primary viral infection developed seizures and a similar number required hospitalisation (Ref. 49). Furthermore, primary HHV-6B infection accounted for 20% of all emergency department visits for febrile illnesses in children 6–12 months old, in one large university hospital in North-Eastern USA (Ref. 42).

The strikingly high fevers (> 40°C) and frequent neurologic symptoms, which are associated with HHV-6 infection, often elicit time-consuming and expensive clinical laboratory tests to rule out more serious diseases, such as bacterial infections of the CNS. This suggests the need for rapid, sensitive and specific diagnostic tests for HHV-6, which could be applied in a clinical setting.

An anti-HHV-6 vaccine might have medical and societal value; the frequency of HHV-6-related acute disease, the duration of illness, and the possibility for complications are, in extremely broad terms, similar in scope and magnitude to the corresponding parameters for varicella zoster virus (VZV), which is the causative agent of chicken pox and shingles. Cost–benefit analyses and medical considerations have provided a compelling rationale for routine vaccination of all children in the USA and Japan against VZV, and similar analyses of the potential benefits of immunisation for HHV-6 might, therefore, be warranted.

Management of severe complications of infection, including neurologic disease

The association of HHV-6 with severe complications such as encephalitis or pneumonitis, particularly in immunocompromised individuals, suggests the need to identify effective antiviral drugs. *In vitro* studies have shown that HHV-6 is relatively resistant to acyclovir, which is consistent with the fact that the virus does not encode a thymidine kinase. In contrast, the virus is sensitive to ganciclovir and phosphonoformic acid (foscarnet). *In vivo* evaluation of antiviral strategies for HHV-6 has not, however, been reported, and it is also uncertain whether the novel inhibitors of HSV-1 ribonucleotide reductase that under development will be effective in blocking the replication of HHV-6.

Research in progress and outstanding research questions

Delineation of the relationship between HHV-6 and multiple sclerosis

The association of productive HHV-6 replication with active demyelinating lesions in the CNS is provocative, and has important implications for the therapeutic management of patients with MS, but only if the virus can be causally linked to this disease.

Deciphering the pathobiological significance and distribution of HHV-6A

It remains unclear whether the two HHV-6 variants (HHV-6A and HHV-6B) exhibit important differences in terms of their biological properties, propensity for disease or distribution. Further study of HHV-6A, in particular, is needed to resolve these issues.

Analysis of the role that the adeno-associated virus (AAV) **rep** *homologue plays in the biological properties and lifecycle of HHV-6*

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The acquisition of a parvoviral replication gene by a herpesvirus is intriguing, but its significance can be examined only through the generation and analysis of mutants of HHV-6 in which this gene has been deleted.

Understanding the long-term consequences of HHV-6-associated seizures

Studies are needed to determine whether children who experience febrile seizures related to their primary HHV-6 infection are at risk for the development of future neurological disorders.

Understanding the role (if any) of HHV-6 in chronic fatigue immunodeficiency syndrome

The notion that HHV-6 may play a role in the progression or aetiology of CFIDS is a subject for speculation in the popular media. Definitive scientific studies are therefore needed, in order to resolve this issue, once and for all.

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Further reading, other resources and other contacts

A genome database that includes the complete genome of HHV-6
http://www3.ncbi.nlm.nih.gov/Entrez/Genome/org.html

Tables

Table 1. Genetics and cell infection of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7), (tab001sdr).

Table 2. Pathogenesis and epidemiology of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7), (tab003sdr).

Coding capacity of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7)(tab002sdr); in an html version only).

Schematic figures

Figure 1. Genome organisation of human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7) (fig005sdr).

Figure 2. Schematic diagram of human herpesvirus 6 (HHV-6) *ori*Lyt (fig002sdr).

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