Human herpesvirus 8, also known as Kaposi sarcoma-associated herpesvirus, is etiologically associated with Kaposi sarcoma and other rare malignancies. Human herpesvirus 8 infection is common in certain areas of Africa and Italy, but occurs in only 0% to 15% of adult populations in North America and Europe. Reports of human herpesvirus 8 prevalence of 3% to over 50% among children in Central Africa, Brazil, and South Texas suggest that horizontal transmission of human herpesvirus 8 occurs among children. Primary human herpesvirus 8 infection in immunocompetent children is associated with a fever and maculopapular rash.

Human herpesvirus 8 (HHV8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), is a human gammaherpesvirus recognized primarily by its association with several human tumors (Table 1). Analysis of HHV8 terminal repeats shows clonal expansion in Kaposi sarcoma (KS) [1]. Establishment of stable HHV8 monoinfected cell lines suggests that cells are immortalized and possibly transformed by HHV8 [2–5]. These cell lines can grow in semi-soft agar [6], suggesting that they have lost contact inhibition and are indeed transformed. Both subcutaneous and intravenous inoculations of HHV8-infected cell lines into nude mice cause tumors, further demonstrating HHV8 tumorigenicity [6,7]. Recently, stable and direct cellular transformation of human primary endothelial cells by HHV8 has been achieved [8,9], providing direct evidence of the oncogenic nature of HHV8.

HHV8 and human cancers

Human herpesvirus 8 was initially discovered by representational difference analysis of KS from a patient with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) [10]. Since the discovery of HHV8, many studies indicate an etiologic role of HHV8 in the development of KS [11,12]. Human herpesvirus 8 DNA is detected in all clinical forms of KS and is specifically localized to KS lesions [10,13–18]. The epidemiology of HHV8 is very similar to that previously established for KS. In North America and Europe, anti-HHV8 antibodies are primarily found in persons with KS or at high-risk for KS, such as homosexual men, but rarely in persons at low risk for KS, such as sexually transmitted disease-free general blood donors [2,19–21]. The geographic distribution of HHV8 infection in the general populations is also very similar to the incidence described for KS: low in North America and Europe, moderate in the Mediterranean and Eastern Europe, and high in Africa [21–23]. Seroconversion to HHV8 has been detected in AIDS-KS prior to disease development [2], further supporting an etiologic role for HHV8 in the development of KS.

In addition to KS, HHV8 is consistently found in primary effusion lymphoma (PEL), also known as body cavity-based lymphoma (BCBL), a distinct type of non-Hodgkin lymphoma (NHL) [10,24–38]. Patients with PEL also frequently develop KS, and the epidemiology of the two diseases is very similar [11]. The AIDS-related PEL is commonly but not exclusively coinfected with Epstein-Barr virus (EBV). Both EBV/HHV8-coinfected

Department of Pediatrics and Center for Pediatric Research, Eastern Virginia Medical School, and Children's Hospital of The King's Daughters, Norfolk, Virginia, USA.

Address correspondence to Hal B. Jenson, MD, Department of Pediatrics, 601 Children's Lane, Norfolk, VA 23507, USA; e-mail: Hal.Jenson@EVMS.edu

Current Opinion in Pediatrics 2003, 15:85–91

Abbreviations

BCBL body cavity-based lymphoma
EBV Epstein-Barr virus
HHV8 human herpesvirus 8
KSHV Kaposi sarcoma-associated herpesvirus
MCD multicentric Castleman disease
NHL non-Hodgkin lymphoma
PEL primary effusion lymphoma

ISSN 1040–8703 © 2003 Lippincott Williams & Wilkins, Inc.
and HHV8-infected, EBV-negative cell lines have been established from PEL, allowing the propagation and characterization of the virus [2–4,24,39–43].

Human herpesvirus 8 has also been found in almost all cases of multicentric Castleman disease (MCD) occurring in patients with AIDS and in approximately half of the cases of MCD occurring in HIV-seronegative patients [44–46]. Patients with MCD frequently develop malignancies, most commonly KS and NHL [11]. In patients with HIV, MCD is usually observed in men infected with HIV by sexual contact and is closely linked to the development of KS. The identification of HHV8 in PEL and MCD suggests a role for HHV8 in the pathogenesis of these diseases.

Human herpesvirus 8 has been found in the dendritic cells from patients with multiple myeloma [47–50]. Increased prevalence of antibodies to HHV8 latent and lytic antigens are reported in patients with multiple myeloma [51]. Patients with progressive multiple myeloma are more likely to have anti-HHV8 antibodies than cancer controls [51]. The role of HHV8 in the development of multiple myeloma remains controversial [20,52–59].

**HHV8 pathogenesis**

Human herpesvirus 8 is closely related to herpesvirus saimiri and EBV [1,60], both lymphotropic-transforming viruses [61,62]. Similar to other herpesviruses, HHV8 latent infection can occur in the hosts years before the development of KS [2]. In KS lesions, HHV8 maintains latency in most spindle cells [63–70], the hallmark cell of KS, suggesting that viral latency is the mechanism of HHV8 cellular transformation. Nonetheless, HHV8 also undergoes lytic replication in a small proportion of KS tumor cells [63,70–76]. Human herpesvirus 8 lytic replication has also been observed in a small proportion of cells in PEL, MCD, HHV8-infected cell lines, and HHV8-transformed human dermal microvascular epithelial cells [3,8,9,30,74,75,77–80]. Although lytic replication is a termination phase for herpesviruses, for HHV8 it also produces oncogenic, angiogenic, and antiapoptotic viral products [60,81–86]. These products include a highly variable viral oncogene (ORF-K1) [86–93], a constitutively active IL-8–like receptor (vGCR) that has oncogenic and angiogenic activity [82,83], antiapoptotic bel-2 [85,94], IL-6 [60,95], and FLICE (Fas-associated death domainlike interleukin 1 beta-converting enzyme)-inhibitory protein (vFLIP) [70,96], functional angiogenic chemokines (vMIP-I and vMIP-II) [60,84,97–101], a complement-binding protein (vCBP) [1], an OX-2 protein [1], and a viral interferon regulatory factor (vIRF) that causes cellular transformation through inhibition of interferon signaling and down-regulation of cyclin-dependent protein kinase inhibitor (CDKI) p21WAF1/CIP1 [81,102–107]. Thus, HHV8 lytic replication produces viral products that can potentially promote cellular proliferation in tumor cells.

**Epidemiology of HHV8 infection**

Like all herpesviruses, HHV8 infection persists for the life of the host following primary infection. The presence of HHV8 antibodies confirms past, and persistent, HHV8 infection. Therefore, HHV8 antibody seroprevalence increases linearly with age and reflects the cumulative incidence of HHV8 infection. The prevalence of HHV8 infection in blood donors and the general population varies substantially by geographic region. Human herpesvirus 8 prevalence in the general population in North America and Europe is relatively low, ranging from 0% to 15% [2,21,108–115], though some studies have reported rates as high as 20% [116]. In Mediterranean and Eastern European countries, regions where there are historically high rates of KS, HHV8 prevalence is substantially higher, ranging from 4% to 24% [2,117–120]. The prevalence of HHV8 infection in certain African regions, where endemic KS has been reported, is reported to have reached rates of 60% and higher [2,57,110,121–124]. Human herpesvirus 8 genotypes isolated from KS patients from South Texas exhibit a distinct distribution pattern from those in other areas in the US, suggesting that HHV8 might have a different epidemiology in this region [125].

Most evidence indicates that sexual contact, particularly among homosexual men, is the primary route of HHV8 transmission in North America and Europe [2,22,109,121,126,127]. Initial studies among children in these geographic regions indicated that HHV8 infection was rare or nonexistent, with prevalence of 0% reported among HIV-infected children from the United States [128] and among HIV-seronegative children from the UK [21].

Recent reports of HHV8 prevalence of 40% to 50% among prepubescent children from Central Africa imply nonsexual horizontal transmission of the virus among children [122,123,129–133]. Human herpesvirus 8 seroprevalence of 3.7% reported among Italian children younger than 11 years of age [134], 41% among Brazilian Amerindian children younger than 10 years of age [135], and exceeding 50% in children in Egypt [136] all suggest horizontal transmission. A 9% seroprevalence was re-
ported among virginal and monogamous women in Sweden [137]. An epidemiologic study of a French Guiana village identified statistically significant mother–child and sibling–sibling correlations of HHV8 infection, suggesting intrafamily spread of HHV8 [138]. A study in Johannesburg, South Africa, found that children born to HHV8 seropositive mothers exhibited a statistically significant increase in HHV8 seroprevalence compared with children of seronegative mothers, with 30% seroprevalence among children younger than 10 years of age born to seropositive mothers [139]. Thus, there appears to be appreciable nonsexual transmission of HHV8. Virus excretion in saliva and saliva exchange is probably a major means of horizontal and intrafamily HHV8 transmission [138,140–142••].

Two studies demonstrate increased HHV8 infection among young children in the United States, in South Texas. The first study reported the absence of an association of HHV8 with the spindle cell disease Langerhan cell histiocytosis [143•]. However, 5 out of 30 (17%) of the healthy children who served as controls, with a mean age of 4.4 years (range 11 months–9 years), showed serologic evidence of HHV8 infection. The second study reported HHV8 seroprevalence among a total of 123 children from 3 study sites in South Texas. In this study, 26% of these children, with an mean age of 7.9 years (range 1–13 years), were positive using immunofluorescent assay (IFA), and 17.1% were positive using methods detecting antibodies to HHV8 ORF65 [144••]. Overall, 10.6% of these children tested positive for HHV8 antibodies using both IFA and ORF65 methods. Correlation of HHV8 infection with sociodemographic factors showed a trend of increased HHV8 prevalence among children 6 years of age or older, with 5 or more members in their household, or with a household income greater than $1,000 per month.

It is possible that environmental conditions in South Texas, particularly among subpopulations in the Texas-Mexico border region, contribute to transmission of HHV8 in ways similar to those of developing countries. These studies in South Texas included children living in colonias, which are rural communities or subdivisions along the U.S.-Mexico border characterized by grossly substandard housing, inadequate roads and drainage, and absent or substandard water and sewage sanitation systems. Flooding is a common problem in many colonias as a result of inadequate surface water drainage systems. The colonias have increased rates of other infections, including hepatitis A [145] and cryptosporidiosis [146]. Nonsexual transmission of HHV8 among children may be more likely to occur in regions with poor public sanitation and overcrowding, particularly in areas where HHV8 infection in the general population is high [136].

Clinical manifestations of primary HHV8 infection
Primary HHV8 infection in immunocompetent children was characterized in a report of 8 children who were identified from among 86 children evaluated for a febrile illness of undetermined origin [142••]. The fever persisted for a mean of 10 days (range 2–14 days). A maculopapular skin rash occurred in 5 of 6 children, with a mean duration of 6 days (range 3–8 days). A case of primary HHV8 infection has been reported in an HIV-infected adult who developed transient angiolympoid hyperplasia with transient fever, arthralgia, cervical lymphadenopathy, and splenomegaly [147•]. Two other cases of primary HHV8 infection have been reported in two patients who each received a kidney from the same HHV8 seropositive cadaveric donor; one recipient developed HHV8 viremia and KS, and the other developed bone marrow failure with plasmacytosis [148•].

Conclusion
There is increasing awareness of the prevalence of HHV8 infection and recognition of the role of horizontal transmission of HHV8 virus among children. There are significant differences in HHV8 prevalence between adult populations and, it now appears, also children from different geographic regions and socioeconomic groups. Intra-family spread, primarily through saliva, may be the primary means of nonsexual HHV8 transmission and the primary mode of spread among children. The ramifications of horizontal spread of HHV8 among family members and potential for wider spread among larger populations remain to be determined.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
•• Of outstanding interest

1. Russo JJ, Behendy RA, Chien MC, et al.: Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proc Natl Acad Sci USA 1996, 93:14862–14867.
2. Gao SJ, Kingsley L, Hoover DR, et al.: Seroconversion to antibodies against Kaposi’s sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi’s sarcoma. N Engl J Med 1996, 335:239–241.
3. Gao X, Tajima M, Sairenji T: Nitric oxide downregulates Epstein-Barr virus reactivation in epithelial cell lines. Virology 1999, 258:375–381.
4. Renne R, Zhong W, Herndier B, et al.: Lytic growth of Kaposi’s sarcoma-associated herpesvirus (human herpes virus 8) in culture. Nat Med 1996, 2:342–346.
5. Arvanitakis L, Mesri EA, Nadar RG, et al.: Establishment and characterization of a primary effusion (body cavity-based) lymphoma cell line (BC-3) harboring Kaposi’s sarcoma-associated herpesvirus (KSHV/HHV-8) in the absence of Epstein-Barr virus. Blood 1996, 88:2648–2654.
6. Boshoff C: Kaposi’s sarcoma. Coupling herpesvirus to angiogenesis [news; comment]. Nature 1998, 391:24–25.
7. Picchio GR, Sabbe RE, Gulizia RJ, et al.: The KSHV/HHV-8-infected BCBL-1 lymphoma line causes tumors in SCID mice but fails to transmit virus to a human peripheral blood mononuclear cell graft. Virology 1997, 238:22–29.
8. Flore O, Rafi S, Elia S, et al.: Transformation of primary human endothelial cells by Kaposi’s sarcoma-associated herpesvirus. Nature 1998, 394:588–592.
9 Moses AV, Fish KN, Ruhl R, et al.: Long-term infection and transformation of dermal microvascular endothelial cells by human herpesvirus 8. J Virol 1999, 73:8982–8992.

10 Chang Y, Cesarman E, Pessin MS, et al.: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi’s sarcoma. Science 1994, 266:1865–1869.

11 Cesarman E, Knowles DM: Kaposi’s sarcoma-associated herpesvirus: a lymphoedematous human herpesvirus associated with Kaposi’s sarcoma, primary effusion lymphoma, and multicentric Castleman’s disease. [published erratum appears in Semin Diagn Pathol 1997, 14:161–162], Semin Diagn Pathol 1997, 14:54–66.

12 Chang Y, Moore PS: Kaposi’s Sarcoma (KS)-associated herpesvirus and its role in KS. Infectious Diseases and Immunization 1996, 5:215–222.

13 Boshoff C, Schulz TF, Kennedy MM, et al.: Kaposi’s sarcoma-associated herpesvirus infects endothelial and spindle cells. Nat Med 1995, 1:1274–1278.

14 Chang Y, Ziegler J, Wabinga H, et al.: Kaposi’s sarcoma-associated herpesvirus and Kaposi’s sarcoma in Africa. Uganda Kaposi’s Sarcoma Study Group. Arch Intern Med 1996, 156:202–204.

15 Dupin N, Grandadam M, Calvez V, et al.: Herpesvirus-like DNA sequences in patients with Mediterranean Kaposi’s sarcoma. Lancet 1995, 345:761–762.

16 Lebbe C, de Cremoux P, Rybojad M, et al.: Kaposi’s sarcoma and new herpesvirus. Lancet 1995, 345:1180.

17 Moore PS, Chang Y: Detection of herpesvirus-like DNA sequences in Kaposi’s sarcoma in patients with and without HIV infection. N Engl J Med 1995, 332:1181–1185.

18 Schalling M, Ekman M, Kaaya EE, et al.: Antibodies to butyrate-inducible antigens of Kaposi’s sarcoma-associated herpesvirus in patients with HIV-1 infection. N Engl J Med 1996, 334:1292–1297.

19 Miller G, Riggsby MO, Heston L, et al.: Antibodies to butyrate-inducible antigens of Kaposi’s sarcoma-associated herpesvirus in patients with HIV-1 infection. N Engl J Med 1996, 334:1292–1297.

20 Parravicini G, Lauri E, Baldini L, et al.: Kaposi’s sarcoma-associated herpesvirus infection and multiple myeloma. Science 1997, 278:1969–1970.

21 Simpson GR, Schulz TF, Whitby D, et al.: Prevalence of Kaposi’s sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 1996, 348:1133–1138.

22 Gao SJ, Kingsley L, Li M, et al.: KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi’s sarcoma. Nat Med 1996, 2:925–928.

23 Gao SJ, Moore PS: Molecular approaches to the identification of unculturable infectious agents. Emerg Infect Dis 1996, 2:159–167.

24 Cesarman E, Moore PS, Rao PH, et al.: In vitro establishment and characterization of two acquired immunodeficiency syndrome-related lymphoma cell lines (BC-1 and BC-2) containing Kaposi’s sarcoma-associated herpesvirus-like (KSHV) DNA sequences. Blood 1995, 86:2708–2714.

25 Nador RG, Cesarman E, Knowles DM, et al.: Herpes-like DNA sequences in a body-cavity-based lymphoma in an HIV-negative patient. N Engl J Med 1995, 333:943.

26 Nador RG, Cesarman E, Chadburn A, et al.: Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi’s sarcoma-associated herpes virus. Blood 1996, 88:645–656.

27 Pastore C, Gloghini A, Volpe G, et al.: Distribution of Kaposi’s sarcoma herpesvirus sequences among lymphoid malignancies in Italy and Spain. Br J Haematol 1995, 91:918–920.

28 Karcher DS, Alkan S: Herpes-like DNA sequences, AIDS-related tumors, and Castleman’s disease. N Engl J Med 1995, 333:797–798; discussion 798–799.

29 Carbone A, Gloghini A, Zagonel V, et al.: Expression of Epstein-Barr virus-encoded latent membrane protein 1 in nonendemic Burkitt’s lymphomas. Blood 1996, 87:1202–1204.

30 Cesarman E, Nador RG, Aozasa K, et al.: Kaposi’s sarcoma–associated herpesvirus in non-AIDS related lymphomas occurring in body cavities. Am J Pathol 1996, 149:53–57.

31 Ansari MQ, Dawson DB, Nador R, et al.: Primary body cavity-based AIDS-related lymphomas. Am J Clin Pathol 1996, 105:221–229.

32 Karcher DS, Alkan S: Human herpesvirus-8-associated body cavity-based lymphoma in human immunodeficiency virus-infected patients: a unique B-cell neoplasm. Hum Pathol 1997, 28:801–808.
Tisdale JF, Stewart AK, Dickstein B, et al.: Molecular and serological examination of the relation of human herpesvirus 8 to multiple myeloma. Blood 1999, 93:1110–1111.

Biesinger B, Muller-Fleckenstein I, Simmer B, et al.: Stable growth transformation of human T lymphocytes by herpesvirus saimiri. Proc Natl Acad Sci USA 1992, 89:3116–3119.

Staskus KA, Zhong W, Gehbhard K, et al.: Kaposi’s sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. J Virol 1997, 71:715–719.

Rainbow L, Platt GM, Simpson GP, et al.: The 222- to 234-kilodalton latent nuclear protein (LNA) of Kaposi’s sarcoma-associated herpesvirus (human herpesvirus 8) is encoded by orf73 and is a component of the latency-associated nuclear antigen. J Virol 1997, 71:5915–5921.

Sturzl M, Blasig C, Schreier A, et al.: Expression of HHV-8 latency-associated T0.7 RNA in spindle cells and endothelial cells of AIDS-associated, classical and African Kaposi’s sarcoma. Int J Cancer 1997, 72:68–71.

Davis DA, Humphrey RW, Newcomb FM, et al.: Detection of serum antibodies to a Kaposi’s sarcoma-associated herpesvirus-specific peptide. J Infect Dis 1997, 175:1071–1079.

Reed JA, Nador RG, Spaulding D, et al.: Demonstration of Kaposi’s sarcoma-associated herpesvirus cycle D homolog in cutaneous Kaposi’s sarcoma by colormetric in situ hybridization using a catalyzed signal amplification system. Blood 1998, 91:3825–3832.

Dupin N, Marcellin AG, Calvez V, et al.: Absence of a link between human herpesvirus 8 and periphereg. Br J Dermatol 1999, 141:159–160.

Linderoth J, Rambech E, Dictor M: Dominant human herpesvirus type 8 RNA transcripts in classical and AIDS-related Kaposi’s sarcoma. J Pathol 1999, 187:582–587.

Sturzl M, Hohenadl C, Zietz C, et al.: Expression of K13/v-FLIP gene of human herpesvirus 8 and apoptosis in Kaposi’s sarcoma spindle cells. J Natl Cancer Inst 1999, 91:1729–1733.

Orenstein JM, Alkan S, Blauvelt A, et al.: Visualization of human herpesvirus type 8 in Kaposi’s sarcoma by light and transmission electron microscopy. AIDS 1997, 11:F35–F45.

Sturzl M, Ascherl G, Blasig C, et al.: Expression of the human herpesvirus 8-encoded viral macrophage inflammatory protein-1 gene in Kaposi’s sarcoma lesions. AIDS 1998, 12:1105–1106.

Blasig C, Zietz C, Haar B, et al.: Monocytes in Kaposi’s sarcoma lesions are productively infected by human herpesvirus 8. J Virol 1997, 71:7963–7968.

Parravicini C, Corbellino M, Paulli M, et al.: Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castlemain’s disease. Am J Pathol 1997, 151:1517–1522.

Staskus KA, Sunday R, Miller G, et al.: Cellular tropism and viral interlink-6 expression distinguish human herpesvirus 8 involvement in Kaposi’s sarcoma, primary effusion lymphoma, and multicentric Castleman’s disease. J Virol 1999, 73:4181–4187.

Krisher JR, Staskus K, Haase A, et al.: Expression of the open reading frame 74 (G-protein-coupled receptor) gene of Kaposi’s sarcoma (KS)-associated herpesvirus: implications for KS pathogenesis. J Virol 1999, 73:6006–6014.

Zhong W, Wang H, Henndler B, et al.: Restricted expression of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genes in Kaposi sarcoma. Proc Natl Acad Sci USA 1996, 93:6641–6648.

Sunday R, Lin SF, Staskus K, et al.: Kinetics of Kaposi’s sarcoma-associated herpesvirus gene expression. J Virol 1999, 73:2232–2242.

Teruya-Feldstein J, Zuber P, Setstuda JE, et al.: Expression of human herpesvirus-8 oncogene and cytokine homologues in an HIV-seronegative patient with multicentric Castleman’s disease and primary effusion lymphoma (published erratum appears in Lab Invest 1999, 79:835). Lab Invest 1999, 78:1637–1642.

Zoetewej JP, Eyes ST, Orenstein JM, et al.: Identification and rapid quantification of early- and late-lytic human herpesvirus 8 infection in single cells by flow cytometric analysis: characterization of antiherpervirus agents. J Virol 1999, 73:5894–5902.

Gao Y, Smith PR, Karan L, et al.: Induction of an exceptionally high-level, untranslated, Epstein-Barr virus-encoded polyadenylated transcript in the Burkitt’s lymphoma line Daudi J Virol 1997, 71:84–94.

Arvanitakis L, Geras-Raaka E, Varma A, et al.: Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. Nature 1997, 385:347–350.

Bais C, Santomasso B, Coso O, et al.: G-protein-coupled receptor of Kaposi’s sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator [published erratum appears in Nature 1998, 392:210]. Nature 1998, 391:86–89.

Boshoff C, Moore PS: Kaposi’s sarcoma–associated herpesvirus: a newly recognized pathogen [review]. AIDS Clin Rev 1997, 323–347.

Sarid R, Sato T, Bohenzky RA, et al.: Kaposi’s sarcoma-associated herpesvirus encodes a functional bcl-2 homologue. Nat Med 1997, 3:293–298.

Lee WK, Kim SM, Sim YS, et al.: B-lymphoblastoid cell lines from cancer patients. In Vitro Cell Dev Biol Anim 1998, 34:97–100.

Muralidhar S, Pumfrey AM, Hassani M, et al.: Identification of Kaposin (open reading frame K12) as a human herpesvirus 8 (Kaposi’s sarcoma-associated herpesvirus) transforming gene [published erratum appears in J Virol 1999, 73:2568]. J Virol 1999, 72:4980–4988.

Lagounoff M, Majetj W, Weiss A, et al.: Deregulated signal transduction by the K1 gene product of Kaposi’s sarcoma-associated herpesvirus. Proc Natl Acad Sci USA 1999, 96:5704–5709.

Zong JC, Metroka C, Reitz MS, et al.: Strain variability among Kaposi’s sarcoma–associated herpesvirus (human herpesvirus 8) genotypes: evidence that a large cohort of United States AIDS patients may have been infected by a single common isolate. J Virol 1997, 71:2505–2511.

Nicholas J, Zong JC, Alendar DJ, et al.: Novel organizational features, captured cellular genes, and strain variability within the genome of KSHV/HHV8. J Natl Cancer Inst Monogr 1998, 79:88–98.

Poole Li, Zong JC, Cufo DM, et al.: Comparison of genetic variability at multiple loci across the genomes of the major subtypes of Kaposi’s sarcoma-associated herpesvirus reveals evidence for recombination and for two distinct types of open reading frame K1 alleles at the right-hand end. J Virol 1999, 73:6646–6660.

Zong JC, Cufo DM, Alendar DJ, et al.: High-level variability in the ORF-K1 membrane protein gene at the left end of the Kaposi’s sarcoma-associated herpesvirus genome defines four major virus subtypes and multiple variants or clades in different human populations. J Virol 1999, 73:4156–4170.

Hayward QS: KSHV strains: the origins and global spread of the virus. Semin Cancer Biol 1999, 9:187–199.

Cheng EH, Nicholas J, Bellows DS, et al.: A Bcl-2 homolog encoded by Kaposi sarcoma-associated herpesvirus, human herpesvirus 8, inhibits apoptosis but does not heterodimerize with Bax or Bak. Proc Natl Acad Sci USA 1997, 96:690–694.

Nicholas J, Ruvolo V, Zong J, et al.: A single 13-kilobase divergent locus in the Kaposi’s sarcoma-associated herpesvirus (human herpesvirus 8) genome contains nine open reading frames that are homologous to or related to cellular proteins. J Virol 1997, 71:1963–1974.

Thome M, Schneider P, Hofmann K, et al.: Viral FLICE-inhibitory proteins (FLIPs) prevent apoptosis induced by death receptors. Nature 1997, 386:517–521.

Kedal TN, Rosenkilde MM, Coulin F, et al.: A broad-spectrum chemokine antagonist encoded by Kaposi’s sarcoma-associated herpesvirus. Science 1997, 277:1656–1659.

Geras-Raaka E, Arvanitakis L, Bais C, et al.: Inhibition of constitutive signaling of Kaposi’s sarcoma-associated herpesvirus G protein-coupled receptor by protein kinases in mammalian cells in culture. J Exp Med 1998, 187:801–806.

Dairaghi DJ, Fan RA, McMaster BE, et al.: HHV8-encoded vMIP-I selectively engages chemokine receptor CCR5. Agonist and antagonist profiles of viral chemokines. J Biol Chem 1998, 273:21569–21574.

Endres MJ, Garlisi CG, Xiao H, et al.: The Kaposi’s sarcoma–related herpesvirus (KSHV)-encoded chemokine vMIP-I is a specific agonist for the CC chemokine receptor (CCR)8. J Exp Med 1999, 189:1993–1998.

Sozanni S, Luini W, Bianchi G, et al.: The viral chemokine macrophage inflammatory protein-II is a selective Th2 chemoh attractant. Blood 1998, 92:4036–4039.
145 Leach CT, Frantz C, Head DR, et al.: Human herpesvirus-8 (HHV-8) associated with small non-cleaved cell lymphoma in a child with AIDS. Am J Hematol 1999, 60:215–221.

146 Leach CT, Koo FC, Kuhls TL, et al.: Prevalence of Cryptosporidium parvum infection in children along the Texas-Mexico border and associated risk factors. Am J Trop Med Hyg 2000, 62:656–661.

147 Oksenhendler E, Cazals-Hatem D, Schulz TF, et al.: Transient angiolymphoid hyperplasia and Kaposi’s sarcoma after primary infection with human herpesvirus 8 in a patient with human immunodeficiency virus infection. N Engl J Med 1998, 338:1585–1590.

148 Luppi M, Barozzi P, Schulz TF, et al.: Bone marrow failure associated with human herpesvirus 8 infection after transplantation. N Engl J Med 2000, 343:1378–1385.

A report of two cases of primary HHV8 infection in two patients who each received a kidney from the same HHV8 seropositive cadaveric donor; one recipient developed HHV8 viremia and KS, and the other developed bone marrow failure with plasmacytosis.