Medical Virology for 2nd Year M.D. Students

Herpesviruses
Part II

University of Jordan
School of Medicine
Section of Microbiology & Immunology
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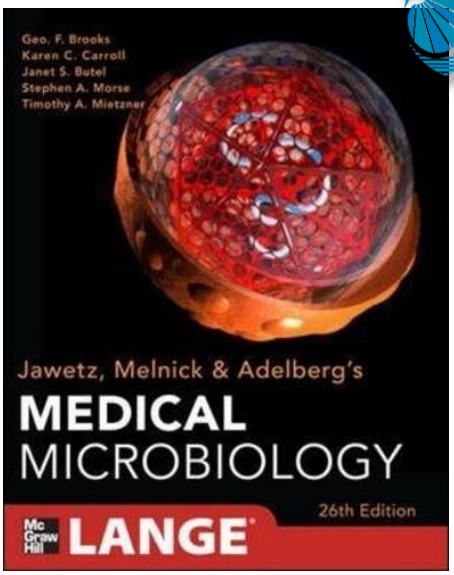
Important Note:
The Required Material for the Exams:
Section IV (Virology) in the provided textbook: Jawetz Medical Microbiology



References

- Jawetz, Melnick & Adelberg's Medical Microbiology. 26th edition. New York : London: McGraw-Hill Medical ; McGraw-Hill, 2013.
- Recent original and review articles in high impact and well renowned scientific journals

Epstein-Barr virus (EBV)

- EBV is the causative agent of IM and is associated with nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin and non-Hodgkin lymphomas, other lymphoproliferative disorders in immunodeficient individuals, and gastric carcinoma.
- The EBV DNA genome contains about 172 kbp, and encodes about 100 genes.
- The major target cell for EBV is the B lymphocyte.
- When human B lymphocytes are infected with EBV, continuous cell lines can be established, indicating that cells have been immortalized by the virus. Very few of the immortalized cells produce infectious virus.

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Epstein-Barr virus (EBV)

- EBV initiates infection of B cells by binding to the viral receptor, which is the receptor for the C3d component of complement (CR2 or CD21).
- EBV directly enters a latent state in the lymphocyte without undergoing a period of complete viral replication.
- The hallmarks of latency are viral persistence, restricted virus expression, and the potential for reactivation and lytic replication.

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Epstein-Barr virus (EBV)

- EBV-immortalized B lymphocytes express differentiated functions, such as secretion of Ig.
- B-cell activation products (e.g., CD23) are also expressed.
- Several patterns of latent viral gene expression are recognized based on the spectrum of proteins and transcripts expressed. These include EBV nuclear antigens (EBNA1, 2, 3A-3C, LP), latent membrane proteins (LMP1, 2), and small untranslated RNAs (EBERs).
- At any given time, very few cells (<10%) in an immortalized population release virus particles.

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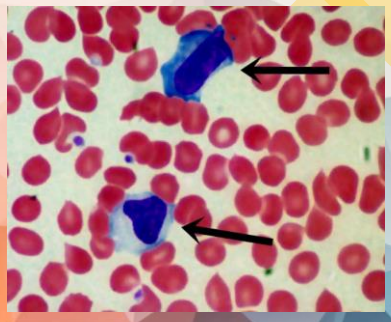
EBV Pathogenesis and Pathology - Primary Infection

- EBV is transmitted by infected saliva and initiates infection in the oropharynx
- Viral replication occurs in epithelial cells (or surface B cells)
- Infected B cells spread infection throughout the body.
- Most virus-infected cells are eliminated, but small numbers of latently infected lymphocytes persist for the lifetime of the host (one in 10^5–10^6 B cells)
- Primary infections in children are usually subclinical, but if they occur in young adults, acute infectious mononucleosis often develops
- Auto-Abs are typical of the disease, with heterophil antibody that reacts with antigens on sheep erythrocytes the classic Auto-Abs



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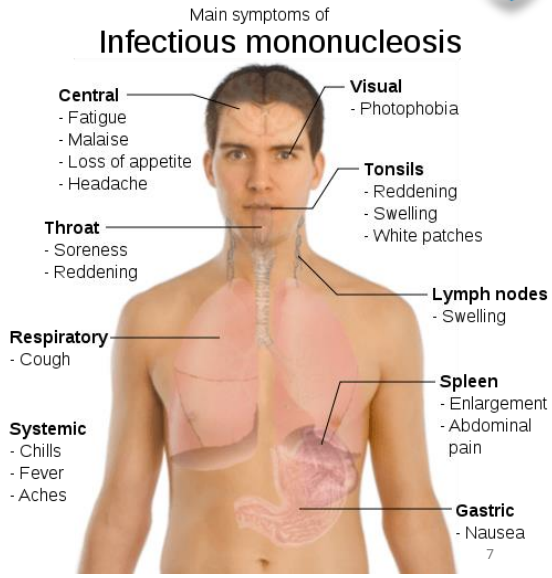
EBV Clinical Findings - Infectious Mononucleosis

- After an incubation period of 30–50 days, symptoms of headache, fever, malaise, fatigue, and sore throat occur. Enlarged lymph nodes and spleen are characteristic. Some patients develop signs of hepatitis.
- The typical illness is self-limited and lasts for 2–4 weeks.
- During the disease, there is an increase in the number of circulating white blood cells, with a predominance of lymphocytes.
- Many of these are large, atypical T lymphocytes.
- Low-grade fever and malaise may persist for weeks to months after acute illness. Complications are rare in normal hosts.



EBV Clinical Findings - Cancer

- EBV is associated with Burkitt lymphoma, nasopharyngeal carcinoma, Hodgkin and non-Hodgkin lymphomas, and gastric carcinoma.
- Burkitt lymphoma is a tumor of the jaw in African children and young adults. Most African tumors (>90%) contain EBV DNA.
- In other regions, only about 20% of Burkitt lymphomas contain EBV DNA.
- Malaria, may foster enlargement of the pool of EBV-infected cells. Finally, there are characteristic chromosome translocations that involve immunoglobulin genes and result in deregulation of expression of the *c-myc* proto-oncogene.

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EBV Clinical Findings - Cancer

Nasopharyngeal carcinoma is a cancer of epithelial cells and is common in males of Chinese origin.

EBV DNA is regularly found in nasopharyngeal carcinoma cells, and patients have high levels of antibody to EBV.

Genetic and environmental factors are believed to be important in the development of nasopharyngeal carcinoma.

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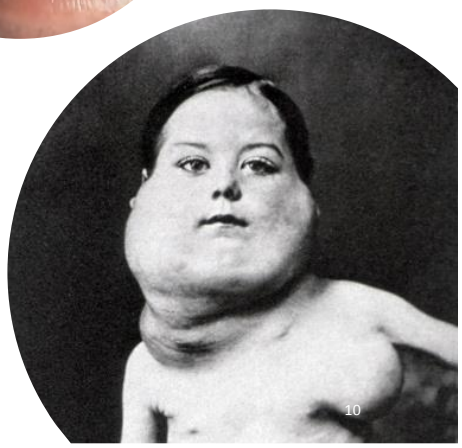
EBV Clinical Findings

- AIDS patients are susceptible to EBV-associated lymphomas and oral hairy leukoplakia, a wart-like growth that develops on the tongue; it is an epithelial focus of EBV replication.
- Virtually all CNS non-Hodgkin lymphomas are associated with EBV, but fewer than 50% of systemic lymphomas are EBV positive.
- In addition, EBV is associated with classic Hodgkin disease, with the viral genome detected in the malignant Reed-Sternberg cells in up to 50% of cases.



EBV - Immunity

- EBV infections elicit an intense immune response consisting of antibodies against many virus-specific proteins, a number of cell-mediated responses, and secretion of lymphokines.
- Cell-mediated immunity and cytotoxic T cells are important in limiting primary infections and controlling chronic infections.
- Serologic testing to determine the pattern of specific antibodies to different classes of EBV antigens is the usual means of ascertaining a patient's status with regard to EBV infection.

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EBV – Laboratory Diagnosis

- Nucleic acid hybridization is the most sensitive means of detecting EBV in patient materials. EBER RNAs are abundantly expressed in both latently infected and lytically infected cells and provide a useful diagnostic target for detection of EBV-infected cells by hybridization.
- Viral antigens can be demonstrated directly in lymphoid tissues and in nasopharyngeal carcinomas.
- During the acute phase of infection, about 1% of circulating lymphocytes will contain EBV markers; after recovery from infection, about one in 1 million B lymphocytes will carry the virus.

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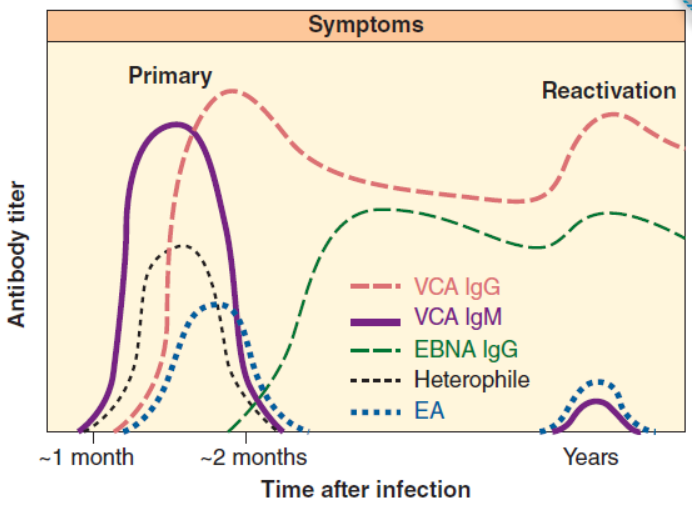
EBV – Laboratory Diagnosis



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EBV – Laboratory Diagnosis

- The less-specific heterophil agglutination test may be used to diagnose EBV infections. In the course of infectious mononucleosis, most patients develop transient heterophil antibodies that agglutinate sheep cells.
- Serologic tests for EBV antibodies require some interpretation. The presence of antibody of the IgM type to the viral capsid antigen is indicative of current infection.
- Antibody of the IgG type to VCA is a marker of past infection and indicates immunity.
- EA antibodies are generally evidence of current viral infection, although such antibodies are often found in patients with Burkitt lymphoma or nasopharyngeal carcinoma.
- Antibodies to the EBNA antigens reveal past infection with EBV, although detection of a rise in anti-EBNA antibody suggests a primary infection. Not all persons develop antibody to EBNA.

EBV – Epidemiology

- EBV is common with more than 90% of adults being sero-positive.
- It is transmitted primarily by contact with oropharyngeal secretions.
- In developing areas, infections occur early in life; more than 90% of children are infected by age 6 years. These infections in early childhood usually occur without any recognizable disease. The inapparent infections result in permanent immunity to infectious mononucleosis.
- In industrialized nations, more than 50% of EBV infections are delayed until late adolescence and young adulthood. In almost half of cases, the infection is manifested by infectious mononucleosis.

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EBV – Treatment and Prevention

- There is no EBV vaccine available.
- Acyclovir reduces EBV shedding from the oropharynx during the period of drug administration, but it does not affect the number of EBV-immortalized B cells.
- Acyclovir has no effect on the symptoms of mononucleosis and is of no proved benefit in the treatment of EBV-associated lymphomas in immunocompromised patients.

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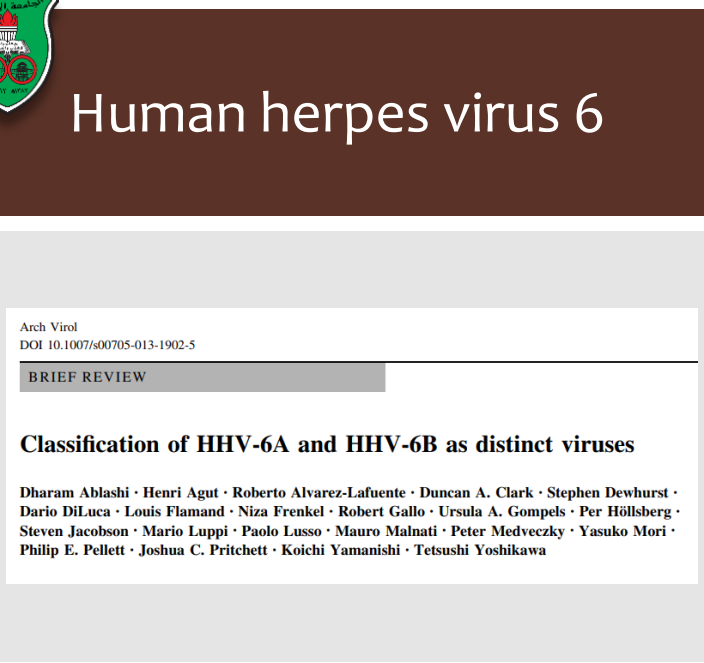
Human herpes virus 6



Arch Virol
DOI 10.1007/s00705-013-1902-5

BRIEF REVIEW

Classification of HHV-6A and HHV-6B as distinct viruses

Dharam Ablashi · Henri Agut · Roberto Alvarez-Lafuente · Duncan A. Clark · Stephen Dewhurst · Dario DiLuca · Louis Flamand · Niza Frenkel · Robert Gallo · Ursula A. Gompels · Per Höllsberg · Steven Jacobson · Mario Luppi · Paolo Lusso · Mauro Malnati · Peter Medveczky · Yasuko Mori · Philip E. Pellett · Joshua C. Pritchett · Koichi Yamanishi · Tetsushi Yoshikawa

- The T-lymphotropic HHV-6 was first recognized in 1986.
- Initial isolations were made from cultures of PBMCs from patients with lymphoproliferative disorders.
- The viral DNA is about 160–170 kbp. The genetic arrangement of the HHV-6 genome resembles that of CMV.
- Isolates of HHV-6 segregate into two closely related but distinct antigenic groups (designated A and B).

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Human herpes virus 6 – General Features

- The virus exhibits a limited cross-reactivity with HHV-7.
- The virus grows well in CD4 T lymphocytes.
- Other cell types also support viral replication, including B cells and cells of glial, fibroblastoid, and megakaryocyte origin.
- Cells in the oropharynx must become infected because virus is present in saliva.
- It is not known which cells in the body become latently infected.
- Human CD46 is the cellular receptor for the virus.

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JOURNAL OF VIROLOGY, May 2004, p. 4385–4388 Vol. 78, No. 9
0022-538X/04/$08.00+0 DOI: 10.1128/JVI.78.9.4385–4388.2004

GUEST COMMENTARY

Four Viruses, Two Bacteria, and One Receptor: Membrane Cofactor Protein (CD46) as Pathogens' Magnet

Roberto Cattaneo*

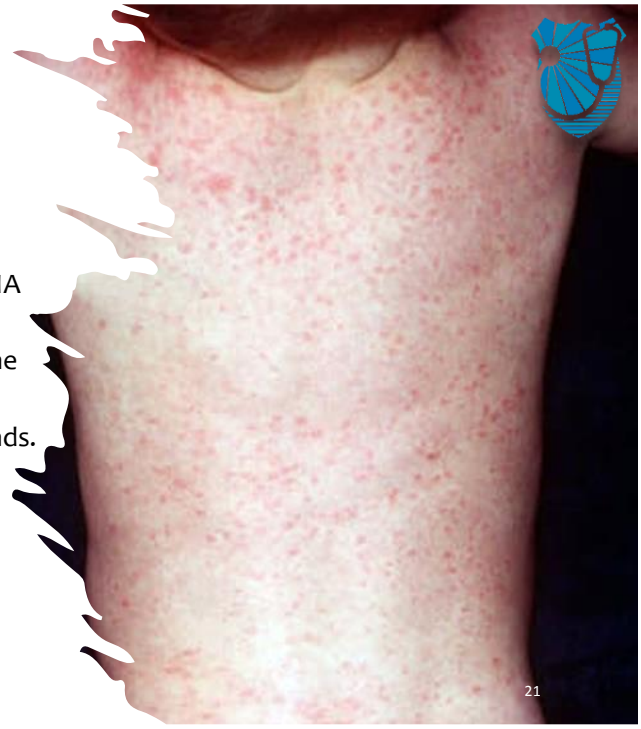
Molecular Medicine Program, Mayo Clinic, and Virology and Gene Therapy, Mayo Clinic College of Medicine, Rochester, Minnesota

Human herpes virus 6 – Epidemiology and Clinical Findings

- The mode of transmission of HHV-6 is presumed to be via oral secretions.
- Infections persist for life. Reactivation appears to be common in transplant patients and during pregnancy. The consequences of reactivated infection remain to be determined.
- HHV-6 reactivation occurs in close to half of patients who undergo hematopoietic stem cell transplantation. Those reactivations occur soon after transplant and have been associated with delayed engraftment, CNS dysfunction, and increased mortality.

Human herpes virus 7

- A T-lymphotropic virus, first isolated in 1990 from activated T cells recovered from PB lymphocytes.
- HHV-7 is immunologically distinct from HHV-6, although they share about 50% homology at the DNA level.
- Most infections occur in childhood but later than the very early age of infection noted with HHV-6.
- Persistent infections are established in salivary glands.
- In a longitudinal study of healthy adults, 75% of subjects excreted infectious virus in saliva one or more times during a 6-month observation period.
- Similar to HHV-6, primary infection with HHV-7 has been linked with roseola infantum in infants and young children. Any other disease associations of HHV-7 remain to be established.



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Detection of Human Herpesvirus-6 in Cerebrospinal Fluid of Patients with Encephalitis

Karen Yao, MS,[1,2] Somayeh Honarmand, MS,[3] Alex Espinosa, BS,[3] Nahid Akhyani, BS,[1] Carol Glaser, MD,[3] and Steven Jacobson, PhD[1]

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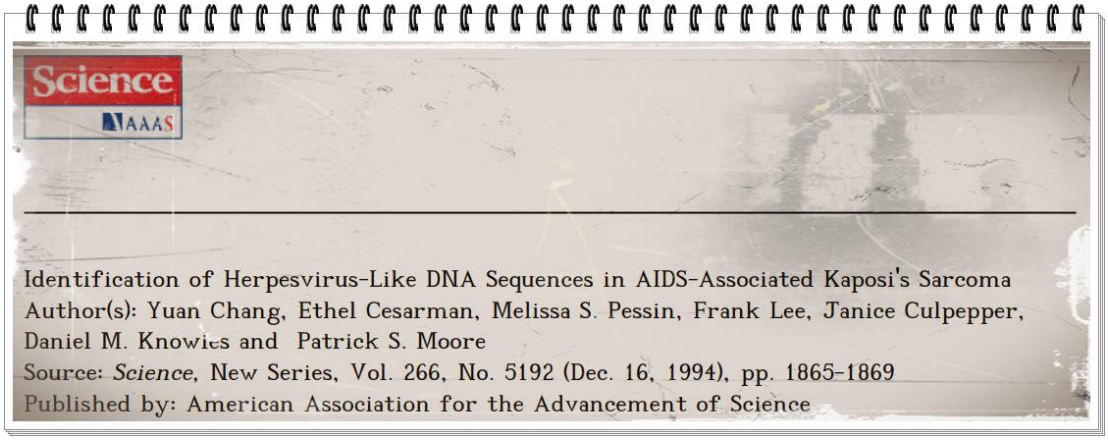
Human herpes virus 6 – Epidemiology and Clinical Findings

- Sero-epidemiologic studies using IF tests for serum antibodies or PCR assays for viral DNA in saliva or blood cells have shown that HHV-6 is widespread in the population. It is estimated that more than 90% of children older than age 1 year and adults are virus positive.
- Infections with HHV-6 typically occur in early childhood.
- This primary infection causes exanthem subitum (roseola infantum, or "sixth disease"), the mild common childhood disease characterized by a high fever and skin rash.
- The 6B variant appears to be the cause of this disease. The virus is associated with febrile seizures in children.

Human herpes virus 8 (KSHV)



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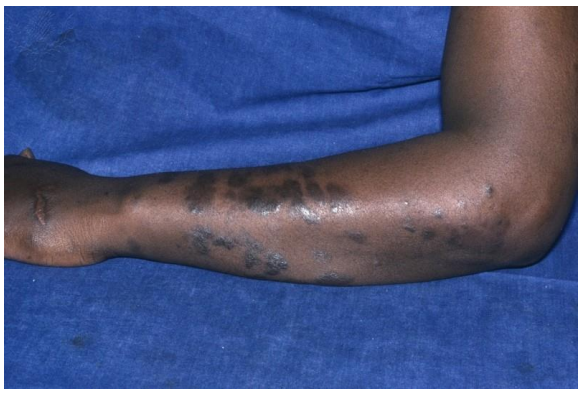
Human herpes virus 8

- KSHV is lymphotropic and is more closely related to EBV.
- The KSHV genome (~165 kbp) contains numerous genes related to cellular regulatory genes that presumably contribute to viral pathogenesis.
- KSHV is the cause of Kaposi sarcomas (angio-proliferative multifocal tumors of the skin, mucosa and less frequently the viscera), and is involved in the pathogenesis of body cavity-based lymphomas occurring in AIDS patients (Primary effusion lymphoma) and of multicentric Castleman disease.



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KS clinical presentation

Source: Douglas JL, Gustin JK, Moses AV, Dezube BJ, Pantanowitz L. Kaposi Sarcoma Pathogenesis: A Triad of Viral Infection, Oncogenesis and Chronic Inflammation. Transl Biomed. 2010;1(2):172.

Classic (sporadic) KS

Primarily affects older non-HIV infected men of Mediterranean and Jewish origin

Patients present with multifocal mucocutaneous lesions, typically as violaceous lesions on the legs, but may infrequently present solely with KS of the mucosa, genitalia and gastrointestinal tract

Visceral and lung involvement portends a poor prognosis

African (endemic) KS

Causes lymphadenopathy in young males, but manifests in adults with deeply ulcerating tumors of the lower extremity

Presently, it is difficult to differentiate between true endemic KS and AIDS-associated KS

AIDS-related (epidemic) KS

May cause minimal disease or manifest with widespread lesions resulting in significant morbidity and mortality

Skin lesions vary from small papules to large plaques and exophytic or fungating nodules

Lymphedema may be extensive and disproportionate to the extent of the cutaneous disease

Extracutaneous disease is common, and typically involves the oral cavity, gastrointestinal tract, lymph nodes, and lungs

Transplant (iatrogenic) KS

KSHV infection can be associated with fatal KS in this setting

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KSHV Epidemiology

- KSHV is less prevalent compared to other herpesviruses; about 5% of the general population in the US and northern Europe have serologic evidence of KSHV infection.
- Contact with oral secretions is likely the most common route of transmission. The virus can also be transmitted sexually, vertically, by blood, and through organ transplants. Viral DNA has also been detected in breast milk samples in Africa.
- Infections are common in Africa (>50%) and are acquired early in life.

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KSHV Epidemiology

- Viral DNA can be detected in patient specimens using PCR assays. Direct virus culture is difficult and impractical.
- Serologic assays are available to measure persistent antibody to KSHV using indirect immunofluorescence, Western blot, and ELISA formats.
- Foscarnet, famciclovir, ganciclovir, and cidofovir have activity against KSHV replication.
- The level of KSHV replication and rate of new Kaposi sarcomas are markedly reduced in HIV-positive patients on effective ART, probably reflecting reconstituted immune surveillance against KSHV-infected cells.

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eports first human death from Monkey B Virus. All
know
-based veterinarian started experiencing nausea and vomiting and
later, fever and neurological symptoms followed.
Herpes B virus of Old World monkeys
A Beijing-based veterinary surgeon was infected with the virus after he dissected two
in early March (Raj K Raj / HT Photo)
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Herpes B virus of Old World monkeys

- Herpes B virus is highly pathogenic for humans.
- It is designated cercopithecine herpesvirus 1.
- Transmissibility of virus to humans is limited, but infections that do occur with **a high mortality rate (~60%)**.
- B virus disease of humans is **an acute ascending myelitis and encephalomyelitis**.
- B virus is a typical herpesvirus that is indigenous in macaques, Old World monkeys in Asia.
- Animal workers and persons handling macaque monkeys, including medical researchers, veterinarians, pet owners, and zoo workers, are at risk of acquiring B virus infection. Individuals having intimate contact with animal workers exposed to the monkeys are also at some risk.

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Herpes B virus of Old World monkeys

- There is no specific treatment after the clinical disease is manifest. However, treatment with acyclovir is recommended immediately after exposure.
- γ-Globulin has not proved to be effective treatment for human B virus infections. No vaccine is available.
- The risk of B virus infections can be reduced by proper procedures in the laboratory and in the handling and management of macaque monkeys. This risk makes macaques unsuitable as pets.

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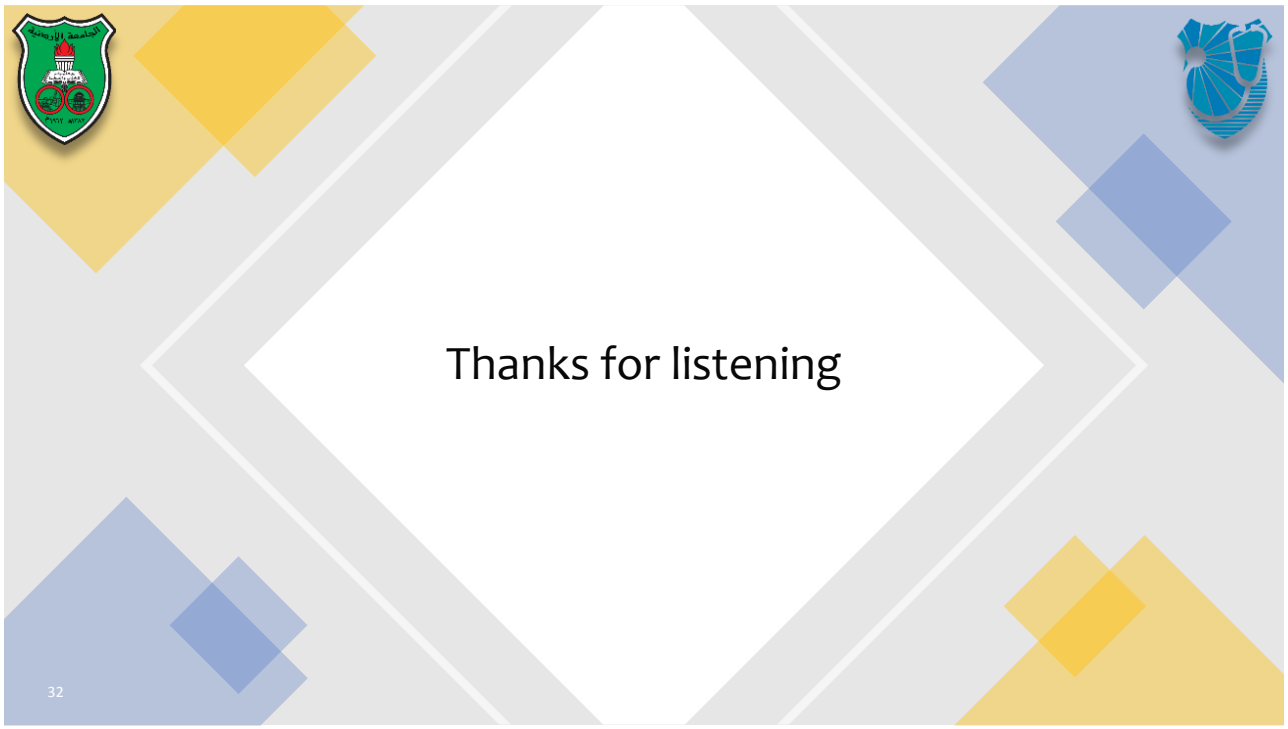
Thanks for listening
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