



Human Herpes Viruses

Objectives:

- To know the clinically important HHVs.
- To know the common characteristics of HHVs.
- To know the common modes of transmission of different HHVs
- To know the clinical features of these infections, diagnostic methods and treatment

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Human Herpes Virus (HHV)

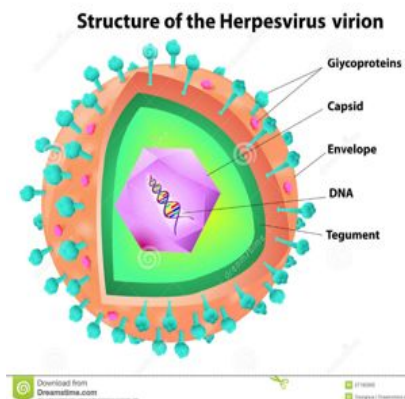
Virus	Infection
Herpes Simplex Virus type 1 (HSV-1)	<ul style="list-style-type: none"> ● Herpes labialis ('cold sores') ● Keratoconjunctivitis ● Finger infection ('whitlows') ● Encephalitis ● Primary stomatitis (inflammation of the mouth and lips, not related to the stomach) ● Genital infection (especially oral sex but type 2 is more common)
Herpes Simplex Virus type 2 (HSV-2)	<ul style="list-style-type: none"> ● Genital infection ● Neonatal infection (acquired during vaginal delivery)
Varicella Zoster Virus	<ul style="list-style-type: none"> ● Chickenpox (العنقز) ● Shingles (الحزام الناري)
Cytomegalovirus (CMV)	<ul style="list-style-type: none"> ● Congenital infection (3rd trimester of pregnancy) ● Disease in immunocompromised patient ● Pneumonitis ● Retinitis ● Colitis ● Systemic infection
Epstein-Barr Virus (EBV)	<ul style="list-style-type: none"> ● Infectious mononucleosis (triad of sore throat, fever, neck lymphadenopathy) ● Burkitt's lymphoma ● Nasopharyngeal carcinoma ● Oral hairy Cell leukoplakia (AIDS patient and post transplant lymphoproliferative disorders)
Human Herpesvirus 6 (HHV-6) and 7 (HHV-7)	<p>Exanthem subitum (Roseola): three day fever Disease in immunocompromised patients and children . Bell's palsy , all other herpes can cause it but HHV-6,7 are the most common</p>
Human Herpesvirus 8 (HHV-8)	<p>Associated with Kaposi's sarcoma , purple papules or plaques around the mouth and swelling in the scrotum.</p>
Herpes simiae (Herpes B or Monkey B Virus)	<p>Fatal human cases of myelitis and hemorrhagic encephalitis have been reported following bites, scratches, or eye inoculation of saliva from monkeys.</p>

-Watch [video](#) lecture overview(10 mins)

- **Common characteristics of herpes Viruses :**
 - All DNA viruses. (when you get infected with a DNA virus it stays forever)
 - All Encapsulated.
 - All Have latency after the initial infection.
 - Mostly Require close contact for transmission.
 - Human is the only reservoir.

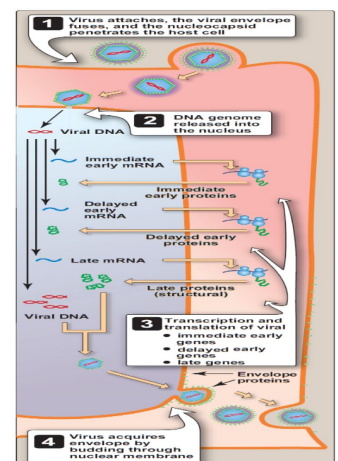
- **Structure:** Herpes viruses have a unique four-layered structure:

- A core containing the large double-stranded DNA genom.
- Genome is enclosed by an icosapentahedral capsid which is composed of capsomers.
- The capsid is surrounded by an amorphous¹ protein coat called the tegument (Between the envelope and the capsid).
- It is encased in a glycoprotein-bearing lipid bilayer envelope (envelope derived from the host's nuclear membrane).



- **Replication:**

- Upon entry into the host cell nucleus, three distinct phases of gene transcription and protein synthesis are initiated producing the immediate-early, early, and late proteins.
- Viral nucleocapsid assembly occurs within the host cell nucleus.
- The virus acquires its final envelope by budding into cytoplasmic vesicles







★ **Types of HHV** (Incubation period 2-12 days after exposure, lesions last 3-4 weeks)

Viruses	HSV-1	HSV-2
General features	Non-genital herpes infection oral	Genital herpes infection
	Primary and recurrent infection	Primary and Recurrent infection
Transmission	Transmission of both HSV types is by close direct contact with body secretions	

¹ without a clearly defined shape

<p>Characteristics: both viruses can cause either genital or oral lesions</p>	<p>HSV-1 typically associated with lesions of the <u>oropharynx</u> (non-sexual contact) ,can be transmitted in oral sex.</p>	<p>HSV-2 typically associated with lesions of the <u>genitalia</u>(sexual contact)</p>
	<p>it's mostly the cause of encephalitis</p>	<p>HSV-2 known to cause Neonatal infection (vertical transmission at time of delivery) is associated with congenital malformations, intrauterine growth retardation (IUGR), chorioamnionitis (AKA <u>intra-amniotic infection</u>), and even neonatal death.</p>
<p>both of them can cause Primary disease as well as Recurrent infections . <u>primary infection</u> is more severe and causes systemic manifestations : fever, malaise ...</p>		
<p>Pathophysiology</p>	<ol style="list-style-type: none"> 1. Exposure to HSV at mucosal surfaces or abraded skin sites → permits entry of the virus and initiation of its replication in cells of the epidermis and dermis 2. After initial infection the virus infects the sensory and autonomic nerves and becomes dormant in the ganglion (<u>latent infection</u>) 	
	<p>on the ganglion Of trigeminal nerve for HSV-1 that's why it usually reactivates in the face .</p>	<p>on the ganglion Of sacral root for HSV-2. reactivates in the genital area</p>
<p>Clinical features of primary infection</p> <p>HSV 1 is very common in children especially daycare and schools</p>	<p>Primary infection is usually asymptomatic and unnoticed, but When <u>symptomatic primary infection</u> is associated with:</p> <ul style="list-style-type: none"> → Systemic manifestations (e.g., fevers, sore throat, tender cervical lymphadenopathy, malaise) → As well as oral lesions: • Oral lesions involve groups of vesicles on patches of erythematous skin (painful blisters around mouth and in oral mucosa) • Pharyngitis & Gingivostomatitis are the most frequent clinical manifestations of <u>first-episode HSV-1 infection</u>. <p>(Gingivostomatitis refers to inflammation of the gum and mouth+lips)</p>	<p>lasting up to 3 weeks:</p> <p>First attack: Very painful genital vesicles or pustules Other findings are tender inguinal lymphadenopathy and vaginal and/or urethral discharge ,myalgias,itching, and dysuria +Constitutional symptoms (e.g., fever, headache, malaise,pain) Recurrent attack: no systemic symptoms .</p>

	<p>→ NON-GENITAL HSV-1(Gingivostomatitis):</p> 	<p>→ GENITAL HSV-2:</p> 
	<ul style="list-style-type: none"> ● Recurrent herpes labialis (cold sore) is the most frequent clinical manifestation of reactivation HSV infection ● Disease usually less severe than first episode ● symptoms typically include a burning pain followed by small blister or sores  <p>usually at the area where mucosa of lips meets skin. recurrent disease is less severe , it could be multiple recurrences and usually pts can predict when sores are coming(prodrome) they feel tingling around their lips , as soon as tingling sensation starts pts are infectious even before sores appear .</p>	<p>recurrent is less severe and without systemic manifestations , only rash so a lot of women get the vesicles of the recurrent attack and they don't even realise it's there , that's why it's important when a pregnant woman comes in labor that the OB should examine her for active herpetic lesions</p>
	<p>inoculation lesion on the finger gives rise to a paronychia termed a 'whitlow'→ in contacts of patients with herpetic lesions. It was formerly seen in health-care workers and dentists, but is prevented by protective gloves. HSV-1 is the cause in 60% of cases of herpetic whitlow, and HSV-2 is the cause in the remaining 40%</p> 	
<p>Diagnosis</p>	<ul style="list-style-type: none"> ● Can be made clinically when characteristic lesions are recognized. ● Serology: diagnostic test: Direct fluorescent assay and ELISA <ul style="list-style-type: none"> a. IgM(+ after 1 to 2 weeks of infection) b. IgG(+ 3-4 weeks after infection and stays forever) ● Viral culture: Not used ● Cytology ● PCR of CSF(only if presented with meningoencephalitis) 	
<p>Treatment Don't memorize doses</p>	<ul style="list-style-type: none"> ● start treatment with prodrome symptoms (tingling/burning) before lesions appear ● FIRST LINE: Acyclovir (PO,IV,topical) 400mg PO 5 x/ day (q4h while awake) x 5 day ● Famciclovir 500 mg PO BID x 7 days ● Valacyclovir 2 mg PO Q12h x 1 day ● Topical treatment (mild cases): 	

	<p>a. Penciclovir 1% cream Q2h during day x 4 days b. acyclovir 5% cream 6x/day (Q3h) x 7 days</p> <p>for mild disease or recurrent : topical Acyclovir or Penciclovir systemic antivirals should be started as the pt develops the tingling sensation bc it shortens the duration of disease if you start early Master the boards: Foscarnet is used in acyclovir resistant herpes)</p>
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Herpes Encephalitis

-Watch this [video](#) (2.47mins)

- **Clinical Setting:**

- HSV-1 is most common cause of sporadic encephalitis
- Risk factor: use of natalizumab for treatment of multiple sclerosis or Crohn's disease
- Survival and recovery from neurological sequelae are related to mental status at time of initiation of therapy. elderly , dementia and previous CVA pts are unlikely to recover
- Early diagnosis and treatment imperative

- **Etiologies:**

- HSV-1
- HSV-2 causes occasional cases

- **Diagnosis:** it has a tendency to infect the **temporal lobe**

- **PCR analysis of CSF for HSV-1 DNA** is 100% specific and 75–98% sensitive. sensitivity depends on the timing of the lumbar puncture
- 25% CSF samples drawn before day 3 are negative by PCR. if you're still suspicious repeat the LP after 3 days and it'll come back positive .
- Negative PCR is associated with decreased protein and <10 WBC/mm³ in CSF . you should always examine their oral mucosa and if they have active herpes sore that's a very strong clue that they have Herpes Encephalitis.

- **Treatment:** Acyclovir **IV** 12.5 mg/kg IV (infuse over 1 hr) q8h x**21 days (prolonged therapy)** , make sure it's IV and prolonged course!

Varicella Zoster Virus (VZV)

★ Characteristics

- I. Primary infection: Chickenpox(العنقر)
- II. Recurrent infection: Herpes zoster (shingles)(الحزام الناري)

★ Clinical syndromes:

- chickenpox
- shingles (single dermatomal or multiple dermatomes)
- Disseminated VZV disease/organ involvement
- Emerging data suggests VZV may cause vasculopathy of cerebral , temporal, and other arteries
- Suggested as possible cause of Giant Cell arteritis

★ Pathophysiology

- The virus is spread by the respiratory route (airborne and contact) and replicates in the nasopharynx or upper respiratory tract.
- Followed by localized replication at an undefined site, which leads to seeding of the reticuloendothelial system and, ultimately, viremia.
- The virus establishes latency within the dorsal root ganglia. Especially lumbar and sacral spines. (During reactivation which is common in shingles it affect the dermatome of that spine) New researches linked VZV as the cause of idiopathic vasculitis such as Giant cell arteritis .
- Chickenpox incubation period: 10 to 21 days

★ Clinical features of chickenpox even 3 weeks after exposure pt may present w chickenpox

- Overall, chickenpox is a disease of childhood, because 90% of cases occur in children younger than 13 years of age.
- Symptoms include: fever, headache, malaise, Iching ,blisters-like vesicular rash: appears first on chest, back, and face, and then spread over the entire body. the rash lasts for 2 weeks , there are different ages of these rashes ,some of them would be fresh and others are older that would scab over and dry out . pts are considered infectious until all the lesions scab over and dry out

★ Complications: rare and usually in adults

- Pneumonia
- Encephalitis
- Bacterial skin and soft tissue infections



★ Clinical features of Herpes zoster (shingles): Reactivation of VZV leads to VZ

- it could involve a single dermatome or multiple dermatomes it can also cause disseminated VZV with multiple organ involvement in immunocompromised . unilateral distribution most often appears as a single stripe of blisters that wraps around either the left or the right side of your trunk, hence the latency in the lumbar spine.



- Facial infection with VZV can cause **Ramsay hunt syndrome** characterized by:

Painful rash on the outer ear, Lower motor neuron paralysis of the facial nerve, Loss of taste sensation on the anterior two third of the tongue .

- in case of facial infection pt should be immediately referred to ophthalmology and ENT bc it can cause blindness and deafness

★ Investigations

- Clinical picture Very clear
- Serology Most commonly used , IgM(4-6 weeks after infection) positive in chickenpox/ IgG positive in shingles because it happens in reactivated reactivation!
- Viral culture Not used
- PCR

★ Treatment of chickenpox

- **Acyclovir** 800 mg po 5x/day x 5-7 days, start within 24 hrs of rash
- Valacyclovir 1000 mg po TID x 5 days
- Famciclovir 500 mg po TID
- immunocompromised: Acyclovir 10–12 mg/kg IV (infused over 1 hour) q8h x 7 days
- (Acyclovir oral 1st line , IV in immunocompromised at a lesser dose and duration than encephalitis)

★ Prevention

- VZV vaccination at a minimum age of 1 yr: 2 dose series (12-15 months and 4-6 years)
- <5% of cases of varicella but >50% of varicella-related deaths occur in adults >20 yrs of age:
- VZV immunoglobulin (VZIG)(125 units/10 kg) in susceptible persons at greater risk for complications (immunocompromised such as HIV, malignancies, pregnancy, and steroid therapy) as soon as possible after exposure (<96 hrs).If varicella develops, initiate treatment quickly (<24 hrs of rash) with Acyclovir

- If admitted need airborne infection isolation and contact precautions (HCW 'health care worker' with VZV Ab IgG positive or history of chickenpox do not need PPE 'Personal protective equipment') . Rare complications of VZV (pneumonia,superinfection cellulitis,Encephalitis)
- susceptible adults should be vaccinated , check Antibody in adults with negative or uncertain history of varicella (10-30% will be Ab-neg) and vaccinate those who are Ab-negative .

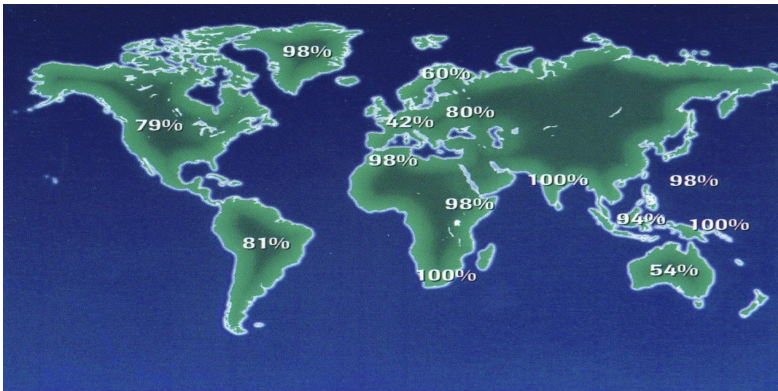
Cytomegalovirus (CMV)

-watch this [video](#) (3.16mins)

★ Characteristics

- Worldwide distribution;The largest virus that infects human beings
- Latency after primary infection
- Infection ranges from asymptomatic to severe multisystemic disease

★ CMV Seroepidemiology



★ Clinical features

- Primary infection:
 - Asymptomatic
 - OR
 - Infectious mononucleosis syndrome:
 - clinically identical to that caused by EBV. It is estimated that about 8 percent of infectious mononucleosis (IM) cases are caused by CMV. Persistent fever, Sore throat, and lymphadenopathy are characteristic IM symptoms.
- Secondary infections in Immunocompromised patients esp.solid organ transplant (SOT) and hematopoietic stem cell transplant (HCT) recipients

Cytomegalovirus in Transplant Recipients (The doctor stressed that its important):

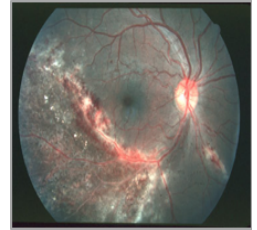
- SOT recipients disease onset was early post-transplant (first 100 days) but with the use of effective prophylaxis disease is now often "late-onset" and occurs following the discontinuation of prophylaxis

★ Risk factors:

- SOT: Seropositive donor (D+) and seronegative recipient (R-) .Lymphocyte depleting antibody therapy (thymoglobulin, ATG, OKT-3,alemtuzumab)
- HCT: Seronegative donor (D-) and seropositive recipient (R+) .T-cell depleted or cord blood transplants , Graft versus host diseases(GVHD)

★ Clinical disease:

- "CMV syndrome" (fever, leukopenia, and thrombocytopenia w/o other end-organ disease)
- Gastrointestinal disease (colitis, esophagitis, enteritis)
- Hepatitis *very high ALT + AST*
- Pneumonitis *multi-lobar patch disease*
- CNS disease (meningoencephalitis, myelitis)
- Retinitis(*Common in AIDS pts should be routinely seen by an ophthalmologist to look specifically for CMV Retinitis bc it can progress without the pt knowing and cause blindness*)
- Multisystem (cystitis, nephritis, etc.)



★ Investigations

- Diagnosis almost always depends on laboratory confirmation and cannot be made on clinical grounds alone.
 - I. **Serologic tests** (antigen detection): Serological tests can identify latent (IgG) or primary (IgM) simple detection of anti-HCMV antibody is not generally useful because the incidence of HCMV infection in the population is so high, and periodic inapparent recurrent infections occur frequently.
 - II. **PCR** (most common test, used on serum, CSF, tissue) from blood , qualitative and quantitative PCR to know the viral load and for follow up after treatment
 - III. **Viral cultures: from blood ,urine*,tissue, lacks specificity. (slowly growing)**
 - IV. pp65 antigen: less commonly used, not recommended in neutropenic patients
 - V. **Histopathology (gold standard to confirm end-organ disease)** bronchoscopy and biopsy in pneumonitis , colonoscopy and biopsy in colitis ,The virus can also be identified in tissues by the presence of characteristic intranuclear ‘owl’s eye’ inclusions (see the fig) . Detection of CMV in urine is not helpful in diagnosing infection, except in neonates, since CMV is intermittently shed in the urine

★ Treatment

- **Ganciclovir** 5 mg/kg IV q12h (*1st line treatment*) OR
- Valganciclovir 900 mg po q12h
- foscarnet (90 mg/kg IV q12h) or cidofovir (5 mg/kg IV once weekly) (*If CMV is resistant to ganciclovir*)
- Treatment duration should be individualized: Continue treatment until:
 - CMV PCR or antigenemia has become undetectable
 - Clinical evidence of disease has resolved . At least 2-3 weeks of treatment

Epstein-Barr Virus (EBV)

-Watch this [video](#) (4.45 mins)

★ Characteristics

- Ubiquitous human herpes virus.
- By adulthood 90 to 95% of most populations are positive.
- Spread occurs by intimate contact between susceptible individuals and asymptomatic shedders of EBV. **even cheek to cheek kisses can transmit it**
- Mostly causes asymptomatic infections.
- Carcinogenic: Strong association with African **Burkitt's lymphoma & Nasopharyngeal carcinoma.**

★ Clinical features

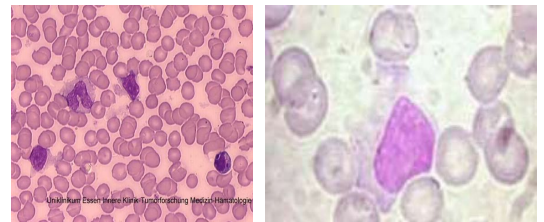
- **Infectious mononucleosis**, symptoms include:
 - Fever
 - Sore throat
 - Lymphadenopathy **tender**



★ Investigations

-Watch this [video](#)(2.33 mins)

- **Serologic:**
 - Transient appearance of **heterophile antibodies (weak antibodies)** 70-92% sensitivity and 96-100% specificity ↑ **diagnostic test** which is detected by the Paul-Bunnell or 'Monospot' test, (heterophile AB is weak antibodies produced by non specific B cells)
 - later on, Permanent emergence of antibodies to EB
- **Hematologic Findings: in peripheral blood smear**
 - **>50% mononuclear cells**
 - Lymphocytosis (**>10% atypical lymphocytes**)
as demonstrated in the pics.)
 - neutropenia
 - thrombocytopenia
 - EBV specific antibodies



★ Treatment

- Treatment of infectious mononucleosis is largely supportive because more than 95% of the patients recover uneventfully without specific therapy.
- Corticosteroids(**In patients who are unable to swallow and severe cases**)

cases from the doctor

Case 1

36 Y/O Indian professor presents to ID clinic with recurrent oral vesicular lesions that lasts for 10 to 14 days, 4 to 5 lesion around his lip, slightly painful, interferes with his lecturing, No fever, no oral cavity lesions, Gets these episodes almost on a monthly basis, Previously diagnosed with HSV-1, took acyclovir on occasion with good results, Brought on occasionally with stress but he's is still annoyed by the recurrency of the disease

- **You recommend ?** Chronic suppressive therapy with acyclovir
The treatment of recurrent HSV-1 infection (herpes labialis) is ACYCLOVIR, but if it was not responding well, we give it with steroids.

Case 2

32 Y/O 40 weeks pregnant lady who is in labor, O.B. found her to have genital vesicular lesions suspected to be HSV-2, She had similar genital lesions twice in the past 4 years, O.B. calls for medical opinion.

- **You recommend?**
 - C-Section if possible with
 - IV acyclovir till delivery
 - Refer baby to neonatal ID once born. to start him on acyclovir

Viruses	HSV-1	HSV-2
Characteristics: both viruses can cause either genital or oral lesions	HSV-1 typically associated with lesions of the oropharynx (non-sexual contact)(can be transmitted in oral sex)	HSV-2 typically associated with lesions of the genitalia (sexual contact)
	both of them can cause Primary disease as well as Recurrent infections	
Pathophysiology	on the ganglion Of trigeminal nerve for HSV-1	on the ganglion Of sacral rout for HSV-2
Clinical features of primary infection	usually asymptomatic and unnoticed, but When <u>symptomatic primary infection</u> is associated with: <ul style="list-style-type: none"> ● Pharyngitis & Gingivostomatitis are the most frequent clinical manifestations of <u>first-episode HSV-1 infection</u>. ● Recurrent herpes labialis (mcq?) ‘cold sore’ is the most frequent clinical manifestation of <u>reactivation HSV infection</u> 	More severe and prolonged symptoms, lasting up to 3 weeks: <ul style="list-style-type: none"> ● Very painful genital vesicles or pustules ● Other findings are tender inguinal lymphadenopathy and vaginal and/or urethral discharge ,myalgias,itching, and dysuria ● Constitutional symptoms (e.g., fever, headache, malaise) often present in primary infection. :
Investigations	<ol style="list-style-type: none"> 1. clinically 2. Serology 3. Cytology 4. PCR 	
Treatment	<ol style="list-style-type: none"> 1. FIRST LINE: Acyclovir (PO,IV,topical) 	

virus	VZV	CMV	EBV
characteristic	<p>1-Primary infection: Chickenpox(العنقز)</p> <p>2-Recurrent infection: Herpes zoster (shingles)</p>	<ul style="list-style-type: none"> · Latency after primary infection 	<ul style="list-style-type: none"> · Mostly causes asymptomatic infections. · Strong association with African Burkitt's lymphoma & Nasopharyngeal carcinoma.
Clinical features	<p>-Chickenpox: children younger than 13</p> <p>-Herpes zoster: most often appears as a single stripe of blisters that wraps around either the left or the right side of your trunk can cause Ramsay hunt syndrome</p>	<p>Primary infection:</p> <ul style="list-style-type: none"> · Asymptomatic · Infectious mononucleosis syndrome <p>Secondary infections in Immunocompromised patients</p>	<p>Infectious mononucleosis, symptoms include:</p> <ul style="list-style-type: none"> · Fever · Sore throat · Lymphadenopathy
Investigation	<ul style="list-style-type: none"> · Serology (Most commonly used) · Clinical picture · PCR 	<ul style="list-style-type: none"> · Serologic tests (antigen detection) · PCR · Viral cultures: from blood urine,tissue · Histology 	<p>Serologic: Transient appearance of heterophile antibodies (diagnostic test)</p>
treatment	<ul style="list-style-type: none"> · Acyclovir (1st line) (IV in immunocompromised patients) · Valacyclovir · Famciclovir 	<ul style="list-style-type: none"> · ganciclovir (1st line treatment) · foscarnet or cidofovir(If CMV is resistant to ganciclovir) 	<ul style="list-style-type: none"> · Supportive in 98% of cases · corticosteroids

Questions

1-which of the following is not true regarding HSV ?

- a) HSV-1 typically associated with lesions of the oropharynx
- b) HSV-1 is more likely to cause Neonatal infection than HSV-2
- c) After initial infection the virus becomes dormant in the nerves
- d) transmission is through direct contact with body secretions

2-After initial infection HBV-1 becomes dormant in which of the following ?

- a) sacral ganglion
- b) trigeminal ganglion
- c) optic ganglion
- d) facial ganglion

3- 34 years old sexually active female presented to clinic with fever ,multiple painful genital vesicles and dysuria what is your next step?

- a) start ganciclovir IV
- b) serology
- c) start Acyclovir oral
- d) PCR

4-A 38-year-old woman has undergone allogeneic bone marrow transplantation for acute myelogenous leukemia in second remission from a matched unrelated donor; she now develops pneumonia , what is the most likely causative organism ?

- a) pneumococcus
- b) EPV
- c) Haemophilus influenzae
- d) CMV

5-EPV is usually associated with which of the following malignancies ?

- a) esophageal carcinoma
- b) multiple myeloma
- c) Burkitt's lymphoma
- d) small cell carcinoma of the lung

6-what is the most accurate test for diagnosing infectious mononucleosis?

- a) heterophile antibodies
- b) ELISA
- c) serum antigen
- d) culture

1b ,2b ,3c ,4D ,5c ,6a