Viral Infections: Focus on Human Herpesviruses

Heather E. Vezina, Pharm.D.
University of Minnesota
Laboratory Medicine & Pathology
Experimental & Clinical Pharmacology
wynnx004@umn.edu

Outline

• Pathogenesis
• Clinical Presentations
• Treatment

Characteristics of Herpesviruses

• Family: Herpesviridae
• Approximately 100 known herpesviruses
• 8 recognized human herpesviruses (HHV)
• All 8 are morphologically similar →
  – lipid envelope with glycoprotein protrusions
  – 100-nm icosahedral capsid
  – internal core of linear, double-stranded DNA

Morphology

Nucleocapsid = DNA
Core
Capsid
Protein Matrix = Topography
Envelop
Icosahedral

Genome size: 170-230 kbp
150-200 nm in diameter

Taxonomy

<table>
<thead>
<tr>
<th>Formal Name</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHV 1</td>
<td>Herpes simplex virus 1 (HSV-1)</td>
</tr>
<tr>
<td>HHV 2</td>
<td>Herpes simplex virus 2 (HSV-2)</td>
</tr>
<tr>
<td>HHV 3</td>
<td>Varicella-zoster virus (VZV)</td>
</tr>
<tr>
<td>HHV 4</td>
<td>Epstein-Barr virus (EBV)</td>
</tr>
<tr>
<td>HHV 5</td>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>HHV 6</td>
<td>HHV 6</td>
</tr>
<tr>
<td>HHV 7</td>
<td>HHV 7</td>
</tr>
<tr>
<td>HHV 8</td>
<td>Kaposi’s sarcoma-associated virus</td>
</tr>
</tbody>
</table>

Human Herpesviruses

α
Herpes simplex type 1
Herpes simplex type 2
Varicella-zoster virus

β
Cytomegalovirus
Herpesvirus 6
Herpesvirus 7

γ
Epstein-Barr virus

γ−2 Kaposi sarcoma herpesvirus
HHV Life Cycle: Major Steps

Attachment and Entry:
- Viral envelope proteins bind to receptors on the plasma membrane of the host cell → fusion
- Nucleocapsids enter the cytoplasm of the host cell and are transported to the nucleus
- Linear viral DNA is released into the nucleus and circularizes

HHV Life Cycle: Major Steps

Transcription and Replication:
- Viral genes are transcribed and translated into 3 proteins: immediate-early, early, late
  - Immediate-early proteins participate in further transcription of gene products
  - Early proteins synthesize new viral DNA molecules using circular DNA as a template

HHV Life Cycle: Major Steps

Assembly, Encapsidation and Nuclear Egress:
- Late proteins assemble into capsids, which incorporate newly replicated viral DNA
- Nucleocapsids leave the nucleus by budding through the inner nuclear membrane (envelopment)
- Mature virus particles reach vesicles in the cytoplasm which fuse with the host cell plasma membrane → new virus particles are released into the extracellular space
HHV Life Cycle

Biologic Properties of HHV

- **Primary infection:** (lytic infection)
  - High concentration of replicating virus at infection site
  - Disease manifestations at site appear 2° to viral replication
  - Lasts days to weeks

- **Persistent infection:** (latent infection)
  - Viral replication takes place but there is no expression of genes associated with lytic infection and no production of infectious virus
  - Viral genomes keep hidden from host immune responses
  - Site of viral persistence or latency varies for each HHV

Biologic Properties of HHV

- **Intermittent reactivation:** (lytic infection)
  - Caused by external stimuli (HSV, VZV) or impairment of the host’s immune response (HSV, VZV, EBV, CMV)
  - Results in the emergence of transmissible virus
  - Common sites of periodic viral appearance include:
    - Oral secretions (HSV-1, EBV, CMV, HHV-6)
    - Genital secretions (HSV-2, CMV, HHV-6)
    - Urine (CMV)
    - Mononuclear cells (CMV, HHV-6, HHV-7)
    - Breast milk (CMV, HHV-7)
  - Signs and symptoms of infection may be absent
  - Host immunity influences both the likelihood of reactivation and the severity of clinical illness

Seroprevalence & Transmission

<table>
<thead>
<tr>
<th>Virus</th>
<th>Seroprevalence Among Young, U.S. Adults (%)</th>
<th>Mode of Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>50</td>
<td>secretions, especially oral</td>
</tr>
<tr>
<td>HSV-2</td>
<td>25</td>
<td>secretions, especially genital</td>
</tr>
<tr>
<td>VZV</td>
<td>100</td>
<td>infected skin lesions; respiratory route (chickenpox)</td>
</tr>
<tr>
<td>EBV</td>
<td>75</td>
<td>oral secretions, blood, transplanted organs</td>
</tr>
<tr>
<td>CMV</td>
<td>50</td>
<td>oral or genital secretions, urine, breast milk, blood, transplanted organs</td>
</tr>
<tr>
<td>HHV-6</td>
<td>100</td>
<td>oral secretions</td>
</tr>
<tr>
<td>HHV-7</td>
<td>100</td>
<td>oral secretions, breast milk</td>
</tr>
<tr>
<td>HHV-8</td>
<td>&lt;10</td>
<td>bodily secretions</td>
</tr>
</tbody>
</table>

Adapted from: Prober C. NEJM 2005;352(8):753-5

Persistence & Infection

<table>
<thead>
<tr>
<th>Virus</th>
<th>Site of Latency</th>
<th>Common Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV-1</td>
<td>neuronal cells, especially trigeminal ganglia</td>
<td>herpes labialis, herpes whitlow, herpetic keratitis, herpes simplex encephalitis</td>
</tr>
<tr>
<td>HSV-2</td>
<td>neuronal cells, especially sacral dorsal root ganglia</td>
<td>herpes genitalis, herpes proctitis, neonatal herpes</td>
</tr>
<tr>
<td>VZV</td>
<td>neuronal cells, especially posterior root ganglia</td>
<td>chickenpox, herpes zoster (shingles)</td>
</tr>
<tr>
<td>EBV</td>
<td>B lymphocytes</td>
<td>infectious mononucleosis, prolonged fever, multiorgan manifestations</td>
</tr>
<tr>
<td>CMV</td>
<td>monocytes, macrophages</td>
<td>infectious mononucleosis, prolonged fever</td>
</tr>
<tr>
<td>HHV-6</td>
<td>T lymphocytes</td>
<td>febrile illness, roseola</td>
</tr>
<tr>
<td>HHV-7</td>
<td>T lymphocytes</td>
<td>febrile illness, roseola</td>
</tr>
<tr>
<td>HHV-8</td>
<td>not established</td>
<td>Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

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HSV-1 & -2: Clinical Presentations

- **Localized Infection**
  - Gingivostomatitis
  - Keratoconjunctivitis
  - Cutaneous herpes
  - Genital herpes
- **Central nervous system involvement - encephalitis**
- **Visceral dissemination (immunocompromised host)**
  - Esophagitis
  - Pneumonitis
  - Hepatitis
HSV-1 & -2: Localized Infection

- Primary infection
  - Incubation period: 4 to 6 days
  - Cell lysis, local inflammation → vesicles
  - Regional lymphatics and lymph nodes drain infected secretions → disseminated disease in susceptible hosts
  - Infectious period: 10 to 14 days
  - Virus establishes latent infection
- Reactivation disease
  - External stimuli – stress, menstruation, UV light
  - Impaired immunity - HIV infection
  - Prodromal symptoms – tingling, itching, burning
  - Usually milder than primary infection or asymptomatic

HSV-1 & -2 Primary Infection

HSV-1 & -2 Latency & Reactivation

Oral Herpes Simplex

Cutaneous Herpes Simplex

VZV: Clinical Presentations

- Primary infection = varicella (chickenpox)
  - ~ 14 day incubation period
  - Characterized by generalized fever and vesicular lesions
  - Usually self-limiting in normal children
  - More severe in adults and immunocompromised persons
  - Mechanism of latency not as well understood as for HSV
- Reactivation in adults = zoster (shingles)
  - Painful unilateral vesicular rash
  - Dermatomally distributed (T3-T12; L1-L2; V1)
  - Vesicles usually resolve in 2-3 weeks – scarring possible
  - Most common complication: post-herpetic neuralgia
  - More severe, often disseminated in immunocompromised persons → encephalitis
CMV: Clinical Presentations

Normal host:
• Primary infection - CMV mononucleosis
  – Occurs in late childhood or adulthood
  – Incubation period: 20 to 60 days
  – Illness lasts 2 to 6 weeks
    • fever, chills, myalgia, malaise, lethargy, leukopenia, mild dyspnea
  – Most patients recover without sequelae
  – Postviral asthenia may persist for months
• Other primary infections: hepatitis, congenital
• Reactivation infection not well understood

Immunocompromised host:
• Primary & reactivation infection - invasive disease
  – Pneumonitis, esophagitis, colitis, hepatitis, pancreatitis, retinitis (can lead to blindness)
• Lethal Syndrome
  – Severe hypoxia, respiratory failure, hypotension, GI hemorrhages, superinfections, MSOF
• Both begin with prolonged fever, malaise, fatigue, night sweats, arthralgias, myalgias
• Most common life- & sight-threatening opportunistic viral infection in patients with AIDS
CMV Retinitis: “Cotton Wool Spots”

EBV: Clinical Presentations

Normal host:
- Primary infection - infectious mononucleosis
  - Frequently seen in adolescents & adults
  - Infants & children usually asymptomatic/nonspecific sx
  - 7-day prodromal illness; 4-day to 3-wk acute illness
  - Fever, lymphadenopathy, pharyngitis (> 50%)
  - Splenomegaly, hepatomegaly (> 10%)
  - Leukocytosis is common
  - Most symptoms are attributed to proliferation and activation of CD4/CD8 cells responding to infection
- Other primary infections: hepatitis, encephalitis
- Reactivation infection not well understood

EBV: Infectious Mononucleosis

EBV: Clinical Presentations

Immunocompromised host:
- Primary & reactivation infection
  - Polyclonal & monoclonal lymphoproliferative disorders (post-transplantation)
  - Oral Hairy Leukoplakia - nonmalignant hyperplastic lesion of epithelial cells (tongue) usually seen in HIV/AIDS

Association with human cancers:
- Burkitt’s lymphoma, nasopharyngeal carcinoma, Non-Hodgkin’s lymphoma, CNS lymphoma

Antiviral Therapies for HHV Infections

HHV Antiviral Therapies

- Nearly all clinically useful antiviral drugs are nucleoside analogues
  - Target = viral DNA polymerase
- Most require intracellular phosphorylation (by viral and/or cellular kinases) to become active moieties
- Individual drugs exhibit a narrow antiviral spectrum of activity
- Maximum efficacy → treatment must be initiated early during primary or recurrent infection
  - No activity against latent infection
Nucleoside Analogues

• Acyclovir (IV, oral, or topical) (HSV, VZV)
  - Intracellular phosphorylation → triphosphate moiety mimics natural deoxyguanosine triphosphate (dGTP) → binds viral DNA polymerase → terminates DNA elongation
  - Low oral bioavailability (15-30%)
  - Primarily eliminated renally (dose adjustments)
  - Fairly well tolerated – GI upset, headache possible
  - May crystalize in renal tubules (rapid IV; dehydration)

• Valacyclovir (oral) (HSV, VZV)
  - Ester prodrug of acyclovir → > oral bioavailability (3-5 fold); higher plasma concentrations; less frequent dosing

• Famciclovir (oral) (HSV, VZV)
  - Prodrug of penciclovir (topical) → > oral bioavailability (77%)
  - Similar to acyclovir in intracellular phosphorylation requirements and mechanism of action

• Ganciclovir (IV, oral) (CMV)
  - Analogue of acyclovir with > activity against CMV
  - Similar to acyclovir in phosphorylation requirements and mechanism of action
  - Poor oral bioavailability (5-9%) → large oral doses or IV
  - Primarily eliminated renally (dose adjustments)
  - Adverse effects: bone marrow suppression (neutropenia), renal insufficiency; potentially mutagenic

• Valganciclovir (oral) (CMV)
  - Ester prodrug of ganciclovir → > oral bioavailability (60%)

Acyclovir – Mechanism of Action

Nucleoside Analogues


De Clercq E. Clin Microbiol Rev 2003, 16(4):569-96


Resistant virus lacks the functional enzymes TK or UL97 and cannot perform this key step. Resistant virus $\rightarrow$ the structure of viral DNA polymerase is altered and unable to bind or incorporate the TP moiety.

Nucleotide Analogue

- Cidofovir (IV) (CMV)
  - Intracellular phosphorylation $\rightarrow$ diphosphate moiety $\rightarrow$ mimics natural deoxycytidine triphosphate (dCTP) $\rightarrow$ binds viral DNA polymerase $\rightarrow$ terminates DNA elongation
  - Poor oral bioavailability $\rightarrow$ IV
  - Intracellular $t_{1/2} > 48h$ $\rightarrow$ dosed 1x per week
  - Risk of nephrotoxicity (dose adjustments) $\rightarrow$ prehydrate (0.9% saline); prophylaxis with probenecid; slow infusion
  - Other adverse effects: uveitis or iritis, rash, neutropenia, GI intolerance

Pyrophosphate Analogue

- Foscarnet (IV) (HSV, VZV, CMV)
  - Pyrophosphate (ppi) analogue $\rightarrow$ blocks ppi binding site $\rightarrow$ prevents ppi cleavage from incoming natural deoxynucleoside triphosphates (dNTP) $\rightarrow$ blocks incorporation of dNTPs into viral DNA
  - Does NOT require intracellular phosphorylation
  - Active against acyclovir resistant HSV, VZV
  - Primarily eliminated renally (dose adjustments)
  - Risk of nephrotoxicity (dose adjustments) $\rightarrow$ prehydrate (0.9% saline); slow infusion
  - Other adverse effects: hypocalcemia, hypomagnesemia, hypokalemia, hypo- or hyperphosphatemia

Foscarnet – Site of Action

Cidofovir does not rely on viral kinases for phosphorylation and development of resistance may be more difficult.
Other Antiviral Agents

- Limited to topical use:
  - Penciclovir
  - Idoxuridine
  - Trifluridine
  - Vidarabine

- Antisense oligonucleotide:
  - Fomiviren → intravitreal injections for resistant CMV retinitis

Qualitative Antiviral Activity

<table>
<thead>
<tr>
<th></th>
<th>HSV</th>
<th>VZV</th>
<th>EBV</th>
<th>CMV</th>
<th>HHV 6-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Valacyclovir</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gancyclovir</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Valganclovir</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Adapted from: Medical Management of HIV Infection, 2001-2002 edition

Treatment of HSV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>genital</td>
<td>normal</td>
<td>Acyclovir: 5 mg/kg IV q8h for 5d (severe) or 200 mg PO 5x/d or 400 mg PO tid for 10d or topical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir: 1g PO bid for 10d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Famiclovir: 250 mg PO tid for 5-10d*</td>
</tr>
<tr>
<td>recurrent</td>
<td>normal</td>
<td>Acyclovir: 200 mg PO 5x/d or 400 mg PO tid for 5d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir: 500 mg PO bid for 3-5d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Famiclovir: 125 mg PO bid for 5d</td>
</tr>
</tbody>
</table>

*Not FDA approved

Treatment of HSV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>mucocutaneous</td>
<td>compromised</td>
<td>Acyclovir: 5 (or 10 in children) mg/kg IV q8h (severe) or 400 mg PO 5x/d* for 7-14d or topical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valacyclovir: 1 gm PO tid for 7d*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Famiclovir: 500 mg PO bid for 7d</td>
</tr>
<tr>
<td>mucocutaneous (ACY resistant)</td>
<td>compromised</td>
<td>Foscarnet: 40 mg/kg IV q8h or q12h for 2-3 wks or until healed (Cidofovir gel being evaluated as alternative*)</td>
</tr>
</tbody>
</table>

*Not FDA approved

Treatment of HSV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>encephalitis</td>
<td>any</td>
<td>Acyclovir: 10 (or 20 in children) mg/kg IV q8h for 10-14d (may see out to 21d in compromised host)</td>
</tr>
<tr>
<td>neonatal</td>
<td>any</td>
<td>Acyclovir: 10 mg/kg IV q8h for 10-14d (may see 15 or 20 mg/kg)</td>
</tr>
</tbody>
</table>

*Not FDA approved
### Treatment of VZV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varicella</td>
<td>normal</td>
<td><strong>Acyclovir</strong>: children ≥ 2 yrs old → 20 mg/kg/dose PO qid (80 mg/kg/d) for 5d; adults and children &gt; 40 kg → 800 mg PO qid for 5-7d</td>
</tr>
<tr>
<td></td>
<td>compromised</td>
<td><strong>Foscarnet</strong>: 40 mg/kg IV q8h or 60 mg/kg IV q12h for 2-3 wks or until healed* (Cidofovir IV may serve as an alternative*)</td>
</tr>
<tr>
<td>Zoster</td>
<td>compromised</td>
<td><strong>Foscarnet</strong>: 60 mg/kg IV q12h for 2-3 wks; maintenance: 90-120 mg/kg/d IV</td>
</tr>
</tbody>
</table>

*Not FDA approved

### Treatment of VZV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoster</td>
<td>normal</td>
<td><strong>Acyclovir</strong>: 800 mg PO 5x/d for 7-10d</td>
</tr>
<tr>
<td></td>
<td>compromised</td>
<td><strong>Valacyclovir</strong>: 1 g PO tid for 7d</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Famiclovir</strong>: 500 mg PO tid for 7d</td>
</tr>
<tr>
<td></td>
<td>compromised</td>
<td><strong>Acyclovir</strong>: 10 mg/kg IV q8h (severe) or 800 mg PO 5x/d* for 7-10d</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Valacyclovir</strong>: 1 g PO tid for 7-10d*</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Famiclovir</strong>: 500 mg PO tid for 7-10d*</td>
</tr>
</tbody>
</table>

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### Treatment of CMV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ganciclovir</td>
<td>compromised</td>
<td>**5 mg/kg IV q12h for 14-21d; maintenance: 5 mg/kg IV qd 7d/wk or 6 mg/kg IV qd 5d/wk or 1 g PO tid</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Valganciclovir</strong>: 900 mg PO bid for 21d; maintenance: 900 mg PO qd</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>compromised</td>
<td><strong>6 mg/kg IV qd 5d/wk</strong></td>
</tr>
<tr>
<td></td>
<td>compromised</td>
<td><strong>Cidofovir</strong>: 5 mg/kg IV once weekly x 2 weeks; maintenance: 5 mg/kg IV every 2 weeks (both with probenecid - 4 gm total)</td>
</tr>
</tbody>
</table>

### Treatment of CMV Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Host</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinitis</td>
<td>compromised</td>
<td><strong>Foscarnet</strong>: 60 mg/kg IV q8h or 90 mg/kg IV q12h for 2-3 wks; maintenance: 90-120 mg/kg/d IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ganciclovir</strong>: 5mg/kg IV q12h for 14-21d; maintenance: 5 mg/kg IV qd 7d/wk or 6 mg/kg IV qd 5d/wk or 1 g PO tid</td>
</tr>
</tbody>
</table>

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