**Human Herpesviruses - subtypes**

Herpes Simplex I (HSV I) -
*herpes labialis* (cold sores)
*herpes keratitis* (eye infections)

HSVII - *herpes genitalis* (genital herpes)

Varicella Zoster virus (VZV)
Chicken pox (primary infection)
Shingles (recurrence, esp. elderly)

Cytomegalovirus (CMV) - retinitis
Epstein-Barr Virus (EBV) - mononucleosis

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**Herpesvirus structure:**

- **Envelope**
- **Icosahedral capsid**
- 35 proteins in virus particle

**Large genome**
- **Linear DNA**
- Double-strand
- 100,000-200,000 bases

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**HSV DNA replication**

“Rolling circle” mechanism.
Unlike cell DNA replication.
Numerous virus-specific factors
Virus-specific DNA polymerase

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**Latency and Chemotherapy**

- In general, antiherpes chemotherapy can suppress or reduce the severity of recurrences, but it cannot cure latent infection.

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**Herpesvirus Latency**

**Acyclovir (acycloguanosine) {Zovirax}**
Acyclovir Selectivity

Nearly 1000x more inhibitory toward HSV-I replication than toward cell (VERO) replication

Acyclovir selectivity

1. Only phosphorylated in HSV-infected cells, by HSV-TK (thymidine kinase, a salvage enzyme) to form acycloGTP

Acyclovir selectivity

2. AcycloGTP is a selective competitive inhibitor of HSV DNA polymerase but not human DNA polymerase

HSV-I DNA pol, $K_i = 0.08$ uM

Human DNA pol alpha, $K_i = 2$ uM

Acyclovir selectivity

3. Incorporated into viral (but not cellular) DNA blocking further synthesis (chain terminator)

Acyclovir selectivity

4. Can't be removed from DNA by HSV polymerase once incorporated
Acyclovir selectivity
5. HSV DNA polymerase binds 100x more tightly to acyclovir-terminated DNA end than to normal DNA end

Result: dead-end complex
Can't polymerize on acyclovir-terminated end
Can't remove acyclovir
Can't dissociate

Acyclovir - resistance
- Mutant HSV thymidine kinase (TK)
  - Doesn’t phosphorylate acyclovir
- Most common resistance mechanism
- Mutant HSV DNA polymerase
  - Doesn’t bind to or incorporate acycloGTP
  - Less common

Acyclovir - Clinical Use
**Oral** for
- Genital herpes (treatment & suppression)
- Varicella, Zoster
- CMV prophylaxis (organ transplant)

**Intravenous** for
- CMV retinitis
- Varicella or Zoster in immunocompromised

**Pharmacokinetics**
- Short half-life in serum: 3-4 hr ➔
- 4-5x daily administration

**Tox:** well-tolerated, occasional CNS

Other “cyclovirs”
- Famiclovir
- Penciclovir
- Ganciclovir
- Valacyclovir
- All guanosine analogues
- All lack sugar ring
- All phosphorylated by HSV TK
- All DNA pol inhibitors
- Different degrees of chain termination

Penciclovir {Denavir}
Topical treatment of *herpes labialis*
Triphosphate has much longer (10-20 hr) half-life in cells than AcycloGTP

Famiclovir {Famvir}
Prodrug - converted to Penciclovir
- Genital herpes treatment & suppression
- *herpes labialis* in immunocompromised Zoster
- Administration: (2x/day oral)
Ganciclovir {Cytovene}
Particularly effective vs. CMV retinitis (100x vs. Acyclovir)
Oral, Intravenous, or ocular implant
More effective chain terminator than Penciclovir

Valacyclovir {Valtrex}
Prodrug (L-valyl ester) of acyclovir
Increased serum levels relative to acyclovir
Less frequent dosage
Similar usage, oral for HSV, VZV, CMV

Cidofovir {Vistide}
Structure: nucleotide (already phosphorylated) cytidine analogue

Cidofovir
Polymerase inhibitor & partial chain terminator
mono-P to di-P to tri-P by cellular kinases
Resistance:
Mutation in HSV DNA polymerase
HSV TK not needed ->
Acyclovir-resistant strains with mutant TK will still be sensitive to cidofovir
Those with mutant polymerase often cross-resistant

Cidofovir - Clinical Use
Given IV for CMV retinitis
Pharmacokinetics:
Phosphocholine metabolite has 87-hr half-life -> weekly or biweekly IV
Tox: primarily renal, hydration required

Idoxuridine (iododeoxyuridine)
Thymidine analogue
Not a chain terminator
Topical for herpes keratitis
Phos. by cell enzymes
Gets into viral DNA
Inhibits transcription
Trifluridine - CF3 instead of iodine, similar usage
Bromovinydeoxyuridine (BVDU) - bromovinyl group instead of iodine - phos. by HSV TK
Vidarabine (adenine arabinoside)

**Mechanism:** DNA pol inhibitor and partial chain terminator

**Clinical Use:**
- HSV encephalitis (IV)
- & keratitis (topical)

**Tox:** CNS: inc. tremor, ataxia, psychosis

Carcinogen?

Don’t confuse with Ribavirin (RSV drug)

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Foscarnet {Foscavir}

![Foscarnet structure]

**Mechanism:**
- Binds to pyrophosphate site on polymerase, blocks replication

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**Foscarnet - Clinical Use**

CMV Retinitis
- Acyclovir resistant VZV or HSV

**Administration:** intravenous, 6-8 hr half-life

**Tox:**
- Renal (minimize w/ infusion pump)
- CNS (headache, seizures)
- Phosphate or calcium imbalances

**Resistance:** Mutant HSV DNA pol
- Generally not cross-resistant with nucleosides

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**Summary - anti-herpes mechanisms**

DNA polymerase inhibitors: Acyclovir, Valacyclovir, Ganciclovir, Penciclovir, Ganciclovir, Cidofovir, Vidarabine

Other nucleosides (incorporated into viral DNA): Bromovinyldeoxyuridine, Vidarabine, Trifluridine

Pyrophosphate analogue: Foscarnet

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**Drug activation (phosphorylation)**

nucleoside -> monophosphate nucleotide

Substrates for cellular kinase:
- Vidarabine, Idoxuridine, Trifluridine

Require HSV thymidine kinase:
- Acyclovir, Valacyclovir, Ganciclovir, Penciclovir, Ganciclovir

Already phosphorylated:
- Cidofovir

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**Summary - clinical uses**

For *herpes genitalis:*
- Acyclovir, Valacyclovir, Famciclovir

For *herpes keratitis:*
- Trifluridine, Vidarabine, Idoxuridine (topical)

For *herpes encephalitis:*
- Vidarabine (IV)

Fov CMV retinitis: Acyclovir, Foscarnet, Cidofovir

For varicella, zoster:
- Acyclovir, Valacyclovir, Famciclovir