# ANTIVIRAL AGENTS
Therapeutics (PHMPR 732)
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**Which of the following drugs is most convenient for patient use in the treatment of influenza?**

1. Acyclovir  
2. Zanamivir  
3. Osteltamivir  
4. Amantidine

## By which route is acyclovir least effective in treatment of recurrent episodes of labial herpes?

1. Intravenous  
2. Intramuscular  
3. Oral  
4. Topical

## Which of the following are indicated for treatment of hepatitis B?

1. Adefovir  
2. Entecavir  
3. Lamivudine  
4. Interferon alfa
Classification of Viruses

DNA-viruses

RNA-viruses: 1

RNA-viruses: 2
**Purine Nucleotides**
- Acyclovir (Zovirax)
- Valacyclovir (Valtrex)
- Famciclovir (Famvir)
- Penciclovir (Denavir)
- Ganciclovir (Cytovene)
- Valganciclovir (Valcyte)
- Cidofovir (Vistide)
- Most often used to treat HSV and CMV

**Acyclovir**
- Converted to monophosphate form by thymidine kinase, and then to active triphosphate form by viral enzymes
- Incorporates into viral DNA resulting in premature chain termination
- Resistance arises due to:
  - Deficient or mutant viral thymidine kinase or
  - Mutant viral DNA polymerase

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**Acyclovir**
- Spectrum of activity:
  - Herpes simplex virus 1 (HSV 1)
  - Herpes simplex virus 2 (HSV 2)
  - Varicella zoster virus (VZV)
  - Epstein Barr virus (EBV)
  - Cytomegalovirus (CMV)
- Relative activity:
  - HSV 1 > HSV 2 > VZV > EBV >> CMV
- Usage:
  - HSV orolabial & genital infections, encephalitis, zoster

**Acyclovir**
- Elimination: chiefly by kidneys
- Available as:
  - Capsules, oral suspension, ointment, powder for injection
- Drug interactions:
  - Zidovudine (↑ CNS effects)
  - Nephrotoxic drugs
- These drugs do not prevent transmission of HSV
### Acyclovir

**Adverse Reactions**
- Most commonly HA, N, V, D
- Infusion site reactions with IV form
- Transient burning sensation with topical form
- Reversible renal dysfunction (5%)
  - Crystalline nephropathy
- Lethargy, confusion, hallucinations, seizures (< 4 %)

### Valacyclovir

**Prodrug of acyclovir**
- Converted during 1st pass metabolism
- Available as capsules
- Chiefly eliminated by kidneys (as acyclovir)
- Used in HSV genital infections and zoster
  - Recently approved (2003) to reduce heterosexual transmission of genital herpes
- Drug interactions:
  - Nephrotoxic drugs
  - ↑ CNS effects with zidovudine
  - Cimetidine and probenecid ↓ rate of conversion to acyclovir

### Valacyclovir

**Adverse Reactions**
- More common:
  - HA, N, V, D
- Contraindicated in immunocompromised
  - ↑ risk of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)
    - Reported in small numbers of advanced AIDS, BMT, and renal transplant patients.

### Penciclovir

**Spectrum of activity/relative potency:**
- HSV 1 > HSV 2 > VZV
- Available as a topical cream
- Indicated for topical treatment of recurrent orolabial HSV in immunocompetent adults
**Famciclovir**

- Prodrug of penciclovir
- Available as tablets
- Metabolized in liver to penciclovir which is then converted, intracellularly to its active triphosphate form
- Chiefly eliminated (>90%) by kidneys as penciclovir
- Indicated in genital HSV and zoster
- Common side effects: headache & nausea

**Famciclovir**

- Adverse Reactions:
  - More common:
    - HA, N, V, D
  - < 4%: Lethargy, dizziness
- Drug Interactions:
  - ↑ CMAX of digoxin (19%)
  - ↑ concentrations with probenecid

**Ganciclovir**

- Available as capsules, injection & intra-vitreal implant (Visasert)
- Spectrum of activity/relative potency:
  - CMV >> HSV 1 > HSV 2 > EBV
- Chiefly eliminated unchanged by kidneys
- Indicated in CMV disease including retinitis (treatment and prevention)

**Ganciclovir**

- Adverse Reactions:
  - Bone marrow suppression (reversible)
    - Neutropenia (40%), thrombocytopenia (20%), anemia (20%)
  - HA, Confusion, N, V, D, abdominal pain, rash
  - MUTAGENIC, TERATOGENIC
Antiviral Agents
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### Ganciclovir
- **Drug Interactions:**
  - ↑ myelosuppression with zidovudine, cyto-
    toxic medications
  - ↓ AUC with didanosine
  - ↑ seizure potential with imipenem

### Valganciclovir
- Ganciclovir prodrug
  - Better bioavailability / should be taken with food
  - Plasma concentrations after PO admin similar to IV gan
- Available as tablets
- Chiefly eliminated by kidneys as ganciclovir
- Indicated for treatment of CMV retinitis
- Adverse effects as with ganciclovir
- Drug interactions as with ganciclovir

### Cidofovir
- Available as parenteral injection
  - Usually administered with probenecid
- Spectrum of activity
  - HSV 1, HSV 2, VZV, CMV, EBV
- Indicated for CMV retinitis
- May be active vs acyclovir or ganciclovir-
  resistant strains of CMV
- Chiefly eliminated unchanged by kidneys

### Cidofovir
- Adverse Reactions:
  - Nephrotoxicity
  - N, V, D
  - Myelosuppression
    - Neutropenia, thrombocytopenia
    - Ocular toxicity
    - CARCINOGENIC, MUTAGENIC
- Drug Interactions:
  - Other nephrotoxic agents (contraindication)
## Anti-influenza Agents

- Amantadine (Symmetrel)
- Rimantadine (Flumadine)
- Zanamivir (Relenza)
- Oseltamivir (Tamiflu)
- Your mother’s chicken soup

## Amantidine

- Acts by inhibiting viral uncoating
- Spectrum of activity: influenza type A
- Available as capsules and oral solution
- Indicated in treatment and prophylaxis of influenza A disease
- Chiefly eliminated unchanged by kidneys

### Amantidine

- **Adverse Reactions:**
  - CNS (5-33%)
    - HA, dizziness, insomnia, depression, difficulty concentrating, fatigue, tremor, seizures, coma
  - N, V, D, dry mouth
  - Urinary retention
  - Livedo reticularis, orthostatic hypotension (long term use)

### Amantidine

- **Drug Interactions:**
  - Antihistamines & anticholenergics ↑ CNS side effects
  - Triamterene/HCTZ cause ↓ clearance ↑ CNS side effects
**Ramantadine**

- 4 - 10 X more active than amantadine
- Larger Vd than amantadine with higher nasal mucus concentrations relative to plasma
- Available as tablets and oral syrup
- Chiefly eliminated by hepatic metabolism
- Similar adverse effects but less common

**Ramantadine**

- Drug interactions
  - Cimetidine causes ↑ concentrations
    - 15-20%
  - APAP or ASA cause ↑ concentrations
    - 10%

**Neuraminidase Inhibitors**

Neuramidase:
- Catalyzes viral cleavage of terminal sialic acid from cell surface glycoconjugates
- Consequences:
  - Promotes release of virions
  - Prevents formation of viral aggregates
  - Prevents viral inactivation
  - May contribute of viral pathogenicity
  - Promotes production of pro-inflammatory cytokines

**Oseltamivir**

- Ethyl ester requiring hydrolysis to oseltamivir carboxylate
- Available as 75 mg capsules
- Dose: 75 mg bid for 5 days
- Begin therapy within 48 hr of onset of symptoms
Oseltamivir

- Absorption & Bioavailability:
  - Well absorbed from GI tract
  - 75% of dose reaches systemic circulation as oseltamivir carboxylate
  - Administration with food decreases side effects but not bioavailability
- Plasma Protein Binding: low
- Metabolism:
  - Oseltamivir converted to the carboxylate by hepatic esterases
  - Carboxylate not further metabolized

Oseltamivir

- Elimination:
  - Oseltamivir carboxylate eliminated entirely by renal elimination ($Cl_k >$ glomerular filtration)
  - Elimination half-life: 6-10 hours
  - Half-life prolonged with renal impairment
    - Dosage adjustment needed with $CrCl < 30$ ml/min
  - Exposure (AUC) increased in elderly without a change in half-life ($Cl$ and $V$ increased)
- Drug interactions: unlikely
- ADRs: N, V, D
  - New ('06) labeling: patients with influenza, especially children, may be at increased risk of self-injury and confusion

Zanamivir

- Available as Relenza Rotadisks
  - Each disk has 4 blisters containing 5 mg
  - Contents of blister inhaled using breath-activated Diskhaler
  - Patient instruction important
- Dose: 10 mg bid for 5 days
- Begin therapy within 48 hr of onset of symptoms

Zanamivir

- 4 - 17% of inhaled dose absorbed systemically
- Elimination:
  - Unchanged by kidneys
    - Decreased clearance with impaired renal function
  - Unabsorbed drug eliminated in feces
- Drug Interactions: unlikely
- ADRs: local nasal irritation, GI, broncho-constriction
**Neuraminidase Inhibitors**
*Other considerations*
- Approved for pediatric use
  - Oseltamivir: ≥ 1 year (treatment), ≥ 13 year (prophylaxis)
  - Zanamivir: ≥ 7 year
- Not a substitute for influenza vaccination
- Only oseltamivir approved for prophylaxis
- Ultimate utility affected by diagnostic issues, cost, and difficulty in administration (zanamivir)
- Costs for 5 day course of therapy (AWP):
  - Tamiflu: $53.00
  - Relenza: $44.40

**Your mother’s chicken soup**
- Actually has no antiviral activity
- Improvement probably based on psychological benefits
- Some hydration
- Can cause hypernatremia & hyperlipidemia
- “It couldn’t hurt”

**Ophthalmic Antivirals**
- Vidarabine (Viar-A)
- Idoxuridine (Herplex)
- Trifluridine (Viroptic)
- Used to treat HSV keratoconjunctivitis and/or epithelial keratitis

**Vidarabine**
- Adenosine analog; blocks DNA polymerase
- Spectrum and relative potency
  - HSV 1&2, VZV >> CMV, EBV
- Available as ophthalmic ointment
- Adverse Reactions:
  - Burning sensation, lacrimation, photophobia
Idoxuridine

- Thymidine analog which incorporates into viral DNA causing mutations and inhibition of replication
- Spectrum: HSV 1 & 2
- Available as ophthalmic solution
- Adverse Reactions:
  - Burning sensation, lacrimation, photophobia, pruritis, corneal edema

Trifluridine

- Thymidine analog
- Spectrum: HSV 1&2, CMV
- Indicated for acyclovir-resistant HSV keratoconjunctivitis
- Available as ophthalmic solution
- Adverse Reactions:
  - Burning sensation, photophobia

Anti-RSV Antivirals

- Ribavirin (Virazole)
  - Inhibits viral RNA & DNA replication
  - Spectrum: respiratory syncitial virus (RSV), HSV, adenovirus, myxovirus
  - Available as powder for reconstitution administered as inhaled solution capsules
  - Eliminated 40% by kidneys
  - Indicated for treatment of RSV bronchiolitis & pneumonia
  - Esp. compromised infants (congenital heart disease, chronic lung disease, immuno compromised)

Ribavirin

- Combination tx with oral ribavirin and interferon alfa may be more effective than IV ribavirin alone (Rebetron)
- Adverse Reactions:
  - Rash, wheezing, eye irritation
  - In health care workers:
    - HA (51%), conjunctivitis (32%), lacrimation, rhinitis, dizziness, nausea
    - MUTAGENIC, TERATOGENIC; pregnant women should not receive or give care
Palivizumab (Synagis)

- A monoclonal antibody directed against RSV
- Available as powder for reconstitution and IM administration
- Indicated for prophylaxis of respiratory infection with RSV in pediatric patients at high risk
- Adverse Reactions:
  - V, D, rash, pain

Miscellaneous Agents

Foscarnet

- Inhibitor of viral RNA & DNA polymerases and HIV reverse transcriptase
- Spectrum of activity:
  - HSV, HIV, CMV
  - Often active vs acyclovir or ganciclovir-resistant strains
- Available as injectable solution
- Indicated for CMV retinitis and acyclovir resistant HSV

Foscarnet

- Resistance through mutant viral DNA polymerase or reverse transcriptase
- Chiefly eliminated unchanged by kidneys
  - Sequestered preferentially in bone with terminal $t_{1/2}$ of as long as 90 hr
**Foscarnet**

- **Adverse Reactions**:
  - Nephrotoxicity (≤ 50%)
  - Electrolyte imbalances (can lead to seizures)
    - K, Ca, Mg, P
  - Fever (65%), HA, seizures (10%)
  - N, V, D (30-40%)
  - Anemia (30%)
  - Myelosuppression

- **Drug Interactions**
  - Other nephrotoxic agents
  - Hypocalemia with pentamidine
  - ↑ seizures with ciprofloxacin

- Dosage adjustment necessary with renal impairment

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**Fomivirsen (Vitravene)**

- An antisense oligonucleotide
- Indicated for intravitreal tx of CMV retinitis in HIV-infected patients intolerant of other drugs
- More common ADRs: iritis, vitritis, ↑ intra-ocular pressure and vision changes

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**Adefovir Dipivoxil (Hepsera)**

- A nucleotide reverse transcriptase inhibitor
- A prodrug converted to active form intracellularly
- Indicated for chronic hepatitis B
- Eliminated chiefly by active tubular secretion
- Unremarkable ADR profile; few if any DIs
### Entecavir (*Baraclude*)
- A nucleoside analog
- Indicated for chronic hepatitis B
- Once-a-day, monotherapy
- Available as tablets and oral solution
- Most common side effects:
  - Headache, fatigue, dizziness, nausea
- Not a substrate, inhibitor or inducer of CYP450 system

### Telbivudine (*Tyzeka*)
- A nucleoside analog for treatment of active chronic hepatitis B
  - In patients ≥ 16 years of age
- 600 mg oral tablet
- At least as effective as lamivudine in treatment-naïve patients but cross-resistance is an issue
- ADRs:
  - Lactic acidosis with steatosis have occurred with other nucleoside analogs
  - Creatine kinase elevations
  - Pregnancy category B

### Interferon alfa
- Alfa-n3 (*Alferon N*)
- Alfa-2a (*Roferon-A*)
- Alfa-2b (*Intron A*)
- Alfa-2b & ribavirin (*Rebetron*)
- Pegylated alfa-2b (*PEG-Intron*)
- Pegylated alfa-2a (*Pegasys*)
- Consensus interferon alfa (*Infergen*)
  - Interferon alfacon-1

### Interferon alfa
- Used in treatment of hepatitis (esp B & C)
- Combination of interferon alfa and ribavirin more effective than either alone (HCV)
- Adverse Reactions:
  - Influenza-like syndrome, bone marrow suppression, fatigue, myalgia, weight loss, rash, cough, ↑ susceptibility to bacterial infections, psychiatric sx, alopecia, hypo- or hyperthyroidism, tinnitus, hearing loss, retinopathy
  - Injection site reactions more common with pegylated forms