Chapter 49

Antiviral Agents
Antiviral Drugs

1. Characters of Virus
   Viruses are obligate intracellular parasites their replication depends primarily on synthetic processes of the host cell.

2. Classification of virus
   DNA virus
   RNA virus
Viruses

- Obligate intracellular parasites
- Consist of a core genome in a protein shell and some are surrounded by a lipoprotein
- Lack a cell wall and cell membrane
- Do not carry out metabolic processes
- Replication depends on the host cell machinery
Viruses

Steps for Viral Replication

1) adsorption and penetration into cell
2) uncoating of viral nucleic acid
3) synthesis of regulatory proteins
4) synthesis of RNA or DNA
5) synthesis of structural proteins
6) assembly of viral particles
7) release from host cell
The major sites of antiviral drug action

**Viral adsorption**

**Penetration**

**Uncoating**

**Early protein synthesis**

**Nucleic acid synthesis**

**Late protein synthesis and processing**

**Viral release**

**Mammalian cell**

- Blocked by enfuvirtide (HIV); γ-globulins (nonspecific)
- Blocked by amantadine (influenza A)
- Blocked by fomivirsen (CMV)
- Blocked by purine, pyrimidine analogs, reverse transcriptase inhibitors
- Blocked by methisazone (variola); protease inhibitors
- Blocked by rifampin (vaccinia)
I. Agents to Treat Herpes Simplex Virus (HSV) & Varicella Zoster Virus (VZV) Infections

- Acyclovir
- Valacyclovir
- Famciclovir
- Penciclovir
- Docosanol
- Trifluridine
Acyclovir, Overview

Chemistry

-Acyclovir is an acyclic guanosine derivative with clinical activity against Herpes Simplex Virus (HSV-1), HSV-2 and Varicella Zoster Virus (VZV)
Mechanism of action of antiherpes agents

Acyclovir 1st activated by viral kinase to mono-phosphate
Then metabolized by host cell kinases to di- & tri-phosphate
Activated drug ↓ DNA polymerase, chain termination & ↓ viral division
Pharmacokinetics

- The bioavailability of oral acyclovir is 15–20% and is unaffected by food.
- Peak serum concentrations are reached 1.5–2 hours after dosing.
- Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is approximately 3 hours in patients with normal renal function and 20 hours in patients with anuria.
- Topical formulations produce high local concentrations in herpetic lesions, but systemic concentrations are undetectable.
- Acyclovir diffuses into most tissues and body fluids to produce concentrations that are 50–100% of those in serum. CSF: 50% of serum values.
### Clinical uses

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route of Administration</th>
<th>Use</th>
<th>Recommended Adult Dosage and Regimen</th>
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</thead>
<tbody>
<tr>
<td>Acyclovir(^1)</td>
<td>Oral</td>
<td>First episode genital herpes</td>
<td>400 mg tid or 200 mg five times daily</td>
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<tr>
<td></td>
<td></td>
<td>Recurrent genital herpes</td>
<td>400 mg tid or 200 mg five times daily or 800 mg bid</td>
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<td></td>
<td></td>
<td>Genital herpes suppression</td>
<td>400 mg bid</td>
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<tr>
<td></td>
<td></td>
<td>Herpes proctitis</td>
<td>400 mg five times daily</td>
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<tr>
<td></td>
<td></td>
<td>Mucocutaneous herpes in the immunocompromised host</td>
<td>400 mg five times daily</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>Varicella</td>
<td>20 mg/kg (maximum 800 mg) four times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoster</td>
<td>800 mg five times daily</td>
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<tr>
<td></td>
<td></td>
<td>Severe HSV infection</td>
<td>5 mg/kg q8h</td>
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<tr>
<td></td>
<td></td>
<td>Herpes encephalitis</td>
<td>10–15 mg/kg q8h</td>
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<tr>
<td></td>
<td></td>
<td>Neonatal HSV infection</td>
<td>20 mg/kg q8h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicella or zoster in the immunosuppressed host</td>
<td>10 mg/kg q8h</td>
</tr>
</tbody>
</table>
Resistance

- Resistance to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase
  - Agents such as foscarnet, cidofovir, and trifluridine do not require activation by viral thymidine kinase and thus have preserved activity against the most prevalent acyclovir-resistant strains

Adverse effects

- Acyclovir is generally well tolerated. **Nausea, diarrhea, and headache** have occasionally been reported
- I.v. infusion may be associated with reversible renal dysfunction due to crystalline nephropathy or neurologic toxicity (e.g., tremors, delirium, seizures); however, these are uncommon with adequate hydration and avoidance of rapid infusion rates
- Chronic daily suppressive use of acyclovir for more than 10 years has not been associated with untoward effects
II. Agents to Treat Cytomegalovirus (CMV) Infections

- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
Ganciclovir

An acyclic guanosine analog

- requires triphosphorylation for activation
- monophosphorylation is catalyzed by a phosphotransferase in CMV and by thymidine kinase in HSV cells

- **Mechanism: Similar to acyclovir**
  - Activated by viral kinase to mono-phosphate, then by host cell kinases to di- & tri-phosphate
  - Activated drug \( \downarrow \) DNA polymerase & \( \downarrow \) viral division

- **Pharmacokinetics:**
  - Given orally, IV & intra-ocularly
Clinical uses:
• Treatment of CMV retinitis, esophagitis, colitis & pneumonitis
• Reduces risk of CMV in AIDS & transplant recipients

Adv. effects:
• Bone marrow: Myelosuppression
• Nausea, diarrhea, fever, rash, headache, insomnia, peripheral neuropathy and retinal detachment in patients with CMV retinitis.
III. Antiretroviral Agents

There are four classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are:

1. Nucleoside & Nucleotides Reverse Transcriptase Inhibitors
2. Non-Nucleoside Reverse Transcriptase Inhibitors and Nucleotides
3. Protease Inhibitors
4. Fusion Inhibitors
Combination therapy

• Combination therapy with maximally efficacious and potent agents reduces viral replication to the lowest level and decrease likelihood of resistance

• Standard of Care: HAART
  (highly active antiretroviral therapy)
  3-4 agents (NRTIs+NNRTIs+PI+Fusion Inhibitors) → tailored to patient (e.g. 2 NRTIs +PI)
Figure 49-4. Life cycle of HIV. Binding of viral glycoproteins to host cell CD4 and chemokine receptors precedes fusion and entry into the cell. After uncoating, reverse transcription copies the single-stranded HIV RNA genome into double-stranded DNA, which is integrated into the host cell genome. Gene transcription by host cell enzymes produces messenger RNA, which is translated into proteins that assemble into immature noninfectious virions that bud from the host cell membrane. Maturation into fully infectious virions is through proteolytic cleavage.
1. Antiretroviral Agents:
Nucloside/nucleotide Reverse Transcriptase Inhibitors (NRTIs)

- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zalcitabine
- Stavudine
- Zidovudine
Zidovudine, Overview

- Zidovudine (azidothymidine; AZT) is a deoxythymidine analog
- Zidovudine is the first licensed antiretroviral agent. It is the first drug approved for treatment of HIV

**Mechanism of action**

- Intracellularly, zidovudine is phosphorylated to its active 5-triphosphate metabolite, zidovudine triphosphate (AZT-TP)
- Zidovudine acts by competitive inhibition of HIV-1 reverse transcriptase (RT; the enzyme that HIV uses to make a DNA copy of its RNA)
  - The RT uses zidovudine triphosphate instead of thymidine triphosphate for making DNA, and it is the zidovudine triphosphate that interferes with the RT
- Zidovudine can also be incorporated into the growing viral DNA chain to cause termination
Pharmacokinetics

- It is well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid
- Plasma protein binding is approximately 35%
- The serum half-life averages 1 hour, and the intracellular half-life of the phosphorylated compound is 3-7 hours
- Zidovudine is eliminated primarily by renal excretion following glucuronidation in the liver
Clinical Uses

- Zidovudine decreases the rate of clinical disease progression and prolongs survival in HIV-infected individuals.

- In pregnancy, a regimen of oral zidovudine beginning between 14 and 34 weeks of gestation, i.v. zidovudine during labor and zidovudine syrup to the neonate from birth through 6 weeks of age has been shown to reduce the rate of vertical (mother-to-newborn) transmission of HIV by up to 23%.
 résistance, plus les niveaux de résistance étaient associés à un nombre plus élevé de mutations.

**Adverse Effects**

- L'effet indésirable le plus commun de zidovudine est l'aplasie médullaire, entraînant une anémie ou une neutropénie.
- La tolérance gastroduodénale, les maux de tête et l'insomnie peuvent survenir mais tendent à s'améliorer pendant le traitement.
2. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Bind to site on viral reverse transcriptase, different from NRTIs
- Do not require phosphorylation for activation and do not compete with nucleoside triphosphates
- No cross-resistance with NRTI
- Rapid resistance with monotherapy
NNRTIs

🌟 Nevirapine - prevents transmission of HIV from mother to newborn when given at onset of labor and to the neonate at delivery

• Delavirdine - teratogenic, therefore cannot be given during pregnancy

• Efavirenz - teratogenic, therefore cannot be given during pregnancy
3. Protease Inhibitors:

- Amprenavir
- Atazanavir
- Fosamprenavir
- **Indinavir**
- Lopinavir /Ritonavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir
Indinavir

- **Mechanism of action:**
  - Specific inhibitors of the HIV-1 protease enzyme

- **Mechanism of resistance:**
  - Mediated by expression of multiple and variable protease amino acid substitutions

- **Adverse effects:**
  - Nephrolithiasis due to crystallization
  - thrombocytopenia, hypoprothrombinemia, GI-upset (nausea, vomiting & diarrhoea)

- **Contraindications:**
  - Inhibitor/substrate for CPY3A4, do **not** give with antifungal azoles
4. Fusion Inhibitors

*Enfuvirtide*

- Blocks entry into the cell
- A peptide, resembles a segment of HIV protein (gp41); given s.c. twice daily
- Can cause more allergic reactions
IV. Antihepatitis Agents

- Interferon Alfa
- Lamivudine - Nucleoside Reverse Transcriptase Inhibitor (NRTI)
- Adefovir - Nucleotide Inhibitor
- Pegylated Interferon Alfa
- Ribavirin
Interferon Alfa

- Interferons are naturally occurring small proteins that exert complex antiviral, immunomodulatory, and antiproliferative activities through cellular metabolic processes involving synthesis of both RNA and protein
- Interferons belong to the large class of glycoproteins known as cytokines

**Mechanism of action**

- Bind to membrane receptors on cell surface
- May also inhibit viral penetration, uncoating, mRNA synthesis, and translation, and virion assembly and release
- They stimulate the cytotoxic activity of lymphocytes, natural killer cells, and macrophages
- Enhance MHC I and II and thus presentation of foreign peptides to T cells

**Pharmacokinetics**

- Maximum serum concentrations occur approximately 4 hours after intramuscular administration and approximately 7 hours after subcutaneous administration
- Elimination half-life is 2–5 hours depending on the route of administration.
- Alfa interferons are filtered at the glomeruli and undergo rapid proteolytic degradation during tubular re-absorption, such that detection in the systemic circulation is negligible
- Liver metabolism and subsequent biliary excretion are considered minor pathways.
**Clinical uses**
- Treatment of both HBV and HCV virus infections.
  - Interferon alfa-2b is the only preparation licensed for treatment of HBV and HCV infections
- Treatment of Hairy cell leukemia
- As an adjuvant to surgical treatment of malignant melanoma
- Treatment of clinically aggressive follicular lymphoma
- Treatment of AIDS-Related Kaposi’s Sarcoma

**Adverse effects**
A flu-like syndrome within 6 hours after dosing in more than 30% of patients that tends to resolve upon continued administration
Other potential A.E. include:
- Thrombocytopenia and granulocytopenia
- Neurotoxicity (fatigue, sleepiness, confusion, seizures) (after high doses)
- Cardiotoxicity (cardiac failure)(after high doses)
- Hepatotoxicity (after high doses)
- Interstitial nephritis (after high doses)
- Hypersensitivity reactions (rare)
- Impairment of fertility
V. Anti-Influenza Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
Amantadine and Rimantadine

- cyclic amines
- inhibit the uncoating of viral RNA therefore inhibiting replication
- resistance due to mutations in the RNA sequence coding for the structural M2 protein
- used in the prevention and treatment of Influenza A
Zanamivir and Oseltamivir

- Inhibits the enzyme neuraminidase
- interfere with release of progeny influenza virus from infected to new host cells, thus halting the spread of infection within the respiratory tract
- inhibit the replication of influenza A and Influenza B
- treats uncomplicated influenza infections
- administered intranasally
VI. Other Antiviral Agents

(1) Ribavirin (virazole):
- Board antiviral spectrum
- Effective to DNA or RNA virus
- Type A, B Infl., HSV, adnoviral pneumonia

(2) Palivizumab

(3) Imiquimod

(4) Interferons