

Antiviral Drugs (Lecture 20)

Dr. Wary

Knowledge Objectives

1. Know which antiviral agents are used to treat influenza, herpes or HIV. Within each class, the drugs are listed in order of their relative importance.
2. Know which antiviral agents are **not** analogs of nucleosides.
3. Know the rationale for using nucleoside analogs and their mechanisms as antiviral agents.
4. Know the most common side effects.

Drug List

amantadine
rimantadine
acyclovir
valcyclovir
famciclovir
penciclovir
ganciclovir
foscarnet
sorivudine
idoxuridine
vidarabine
trifluridine
ribavarine

Anti- HIV Agents

NRTI's

retrovir
didanosine
zalcitabine
stavudine
lamivudine
abacavar
tenofovir
emtricitabine

NNRTI's

nevirapine
delavirdine
efavirenz

Protease Inhibitors

saquinavir
ritonavir
indinavir
nelfinavir
amprenavir

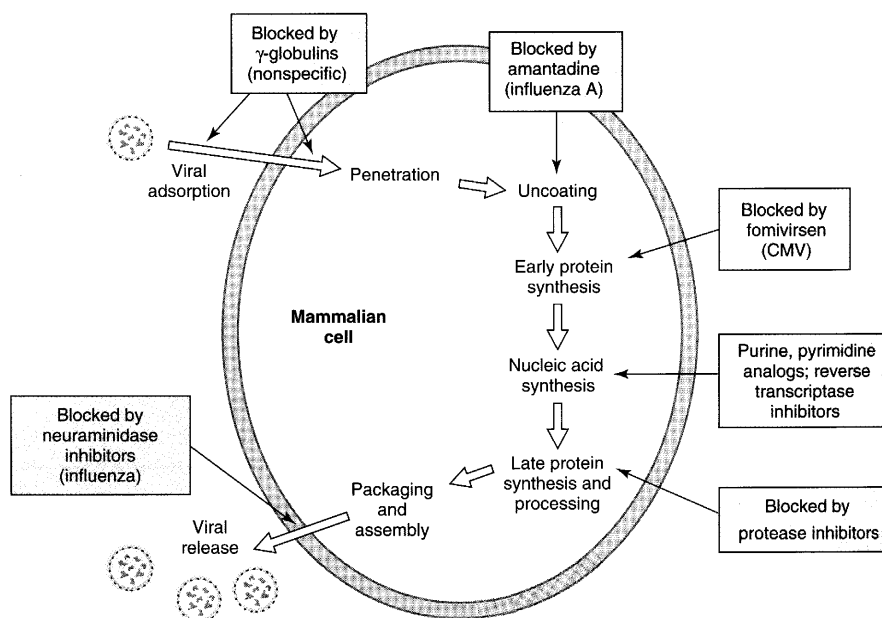
PHARMACOLOGY OF THE ANTIVIRAL AGENTS

A. Background

Three approaches to antiviral therapy:

1. Immunological control
2. Chemotherapy
3. Stimulation of natural host resistance mechanisms

B. Viral infection and replication



C. Anti-influenza Agents

1. Amantadine and Rimantadine

- a. Primary use: Prevention and treatment of influenza A respiratory infections
- b. Mechanism of action: inhibits viral uncoating
- c. Rapid development of resistance, up to 50%
- d. Good oral absorption; excreted by kidney unmetabolized; reduce dose in patients with renal insufficiency or over 65 years old
- e. Side effects: Minor dose-related CNS effects (less with Rimantadine) and GI effects
- f. Not effective against influenza B

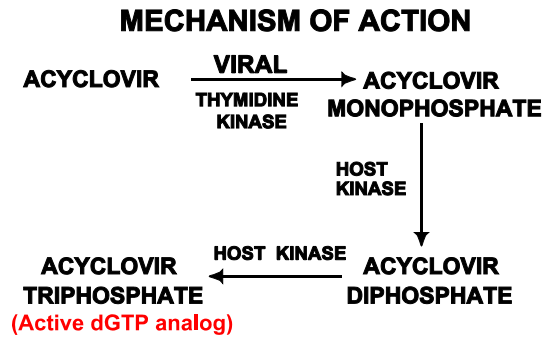
2. Zanamivir & Oseltamivir

1. Primary use: Treatment of uncomplicated influenza infection; types A & B
2. Mechanism of action: Inhibit neuraminidase which is required for viral replication and release
3. Side effects: Well tolerated

D. Anti-herpes and anti-CMV Agents

Nucleoside Analogs:

- Analogs of naturally occurring nucleosides
- Must be converted to the triphosphate analog in order to be active
- Triphosphate competes with native nucleoside for incorporation into viral DNA
- Triphosphate inhibits viral DNA polymerase
- Frequently cause DNA chain termination



SPECIFICITY:

HERPES VIRUS SPECIFIC BECAUSE PHOSPHORYLATION OF ACYCLOVIR OCCURS 30-300 TIMES FASTER IN HERPES INFECTED CELLS (DUE TO PRESENCE OF HERPES-SPECIFIC THYMIDINE KINASE)

Guanosine analogs:

1. Acyclovir (Zovirax)

- a. A guanosine derivative used against herpes simplex virus (HSV) 1 or 2 and varicella-zoster virus (VZV)
- b. Mechanism: Must be converted to the dGTP analog; inhibits viral DNA polymerase and causes viral DNA chain termination
- c. Primary uses:
 - Topically: Primary mucocutaneous herpes; genital herpes (less effective than systemic); ineffective in recurrent herpes simplex
 - Orally: Severe primary and recurrent genital herpes; mucocutaneous herpes (immuno-compromised patients); varicella and/or zoster (children)
 - Intravenous: Treatment of choice for herpes encephalitis and neonatal herpes; in severe cases can be used for mucocutaneous herpes (immuno-compromised patients) as well as prophylaxis of herpes simplex and herpes zoster
- d. Side effects: Local irritation with topical use; headache, nausea and vomiting with oral use; and nephrotoxicity & neurotoxicity with intravenous use (normally can be avoided with proper treatment)
- e. Resistance: Lack of thymidine kinase that is required for activation

2. Valacyclovir: Analog of acyclovir; converted to acyclovir in the body

3. Ganciclovir

- a. Structurally related to acyclovir
- b. Mechanism of action: Same as acyclovir
- c. Primary uses: Approximately 100x more active than acyclovir against cytomegalovirus (CMV); used for chronic suppression of CMV retinitis in AIDS patients; prevention of CMV in transplant patients; also active against HSV, VZV, Epstein-Barr virus (EBV) and human herpes virus -6,-8 (HHV-6,-8)
- d. Side effects: Can produce serious myelosuppression

4. **Penciclovir and Famciclovir**

- a. Mechanism: Penciclovir is converted to the triphosphate form which inhibits viral DNA polymerase; does not cause DNA chain termination
- b. Penciclovir is used topically for genital herpes
- c. Famciclovir is given orally and is converted to the active agent penciclovir in the body
- d. Primary uses: recurrent genital herpes, localized herpes zoster (immunocompromised patients) and acute zoster
- e. Side effects: headache, diarrhea and nausea; generally well tolerated

Other Nucleoside Analogs:

5. **Cidofovir**

- a. Cytosine analog
- b. Mechanism: Must first be phosphorylated to triphosphate derivative; unlike acyclovir, phosphorylation is not virus specific
- c. Primary uses: I.V. use approved for CMV retinitis
- d. Side effects: Nephrotoxicity (decreased by probenecid)

6. **Idoxuridine**

- a. Iodinated thymidine analog
- b. Mechanism: Must first be phosphorylated to triphosphate which inhibits herpes DNA synthesis
- c. Primary use: herpes keratitis (topically)
- d. Side effects: Pain, inflammation

7. **Vidarabine**

- a. Adenosine analog
- b. Mechanism: Must first be phosphorylated to triphosphate derivative which inhibits viral DNA polymerase
- c. Primary uses: I.V. use approved for herpes encephalitis, neonatal herpes, herpes zoster or varicella in immunocompromised patients (most of these uses have been replaced by acyclovir)
- d. Side effects: Nephrotoxicity

8. **Trifluridine**

- a. Fluorinated pyrimidine nucleoside analog
- b. Mechanism: Monophosphate form inhibits thymidylate synthetase and triphosphate is incorporated into host and viral DNA
- c. Primary use: Topically effective against HSV-1 & -2 to treat keratoconjunctivitis and recurrent epithelial keratitis
Side effects: local irritation

Other Derivatives:

9. Foscarnet

- Synthetic non-nucleoside analog of pyrophosphate
- Mechanism: Inhibits herpes DNA polymerase, RNA polymerase and HIV reverse transcriptase by directly binding to the pyrophosphate binding site; does not require prior activation
- Primary uses: Given I.V. for acyclovir resistant herpes; CMV retinitis (synergism with ganciclovir)
- Side effects: Nephrotoxicity, CNS toxicity

10. Fomivirsen

- Antisense oligonucleotide
- Mechanism: Binds to mRNA; inhibits protein synthesis and viral replication
- Primary use: Intravitreal injection for CMV retinitis in AIDS patients
- Side effects: Increased ocular pressure, iritis & vitritis

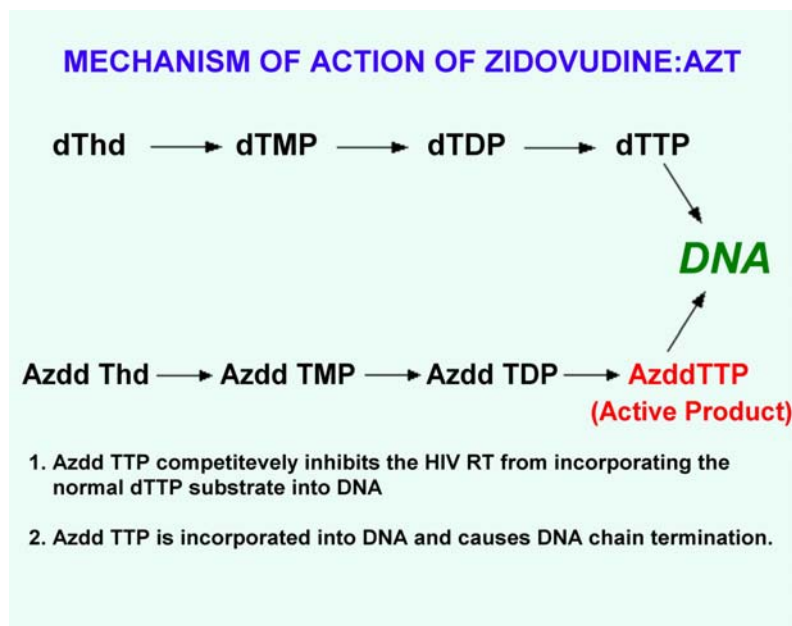
E. Anti-HIV Agents

Nucleoside Reverse Transcriptase Inhibitors (NRTIs):

- Are analogs of naturally occurring nucleotides
- Require phosphorylation to triphosphate form
- Competitively inhibit HIV-1 (and usually HIV-2) reverse transcriptase (RT)
- Are incorporated into viral DNA and cause chain termination
- Net effect is inhibition of viral DNA synthesis
- Block acute infection but are much less active against chronically infected cells
- Usually used in combination with other anti-HIV drugs

1. Zidovudine (Azidothymidine: AZT)

- Deoxythymidine analog



- b. Mechanism: Inhibits HIV RT and causes DNA chain termination
- c. Metabolized in liver
- d. Primary uses: Management of certain adult patients with symptomatic HIV infections, AIDS and advanced AIDS-related complex (ARC); HIV-infected pregnant women; HIV-infected neonates
- e. Resistance: Usually due to viral mutation
- f. Side effects: Bone marrow depression, headache, abdominal pain, fever and insomnia; clearance reduced 50% in uremic patients; toxicity may increase in patients with advanced hepatic insufficiency

2. **Didanosine**

- a. Deoxyadenosine analog
- b. Mechanism: Inhibits HIV RT and causes DNA chain termination
- c. Should be taken on empty stomach to decrease degradation by acidic pH
- d. Primary uses: Advanced HIV in adults and children (over 6 months); patients intolerant or unresponsive to zidovudine; or who have taken zidovudine for over 4 months
- e. Resistance: Viral mutation
- f. Side effects: Dose-dependent pancreatic damage; peripheral neuropathy

3. **Zalcitabine**

- a. Deoxycytosine analog
- b. Mechanism: Inhibits HIV RT and causes DNA chain termination
- c. Bioavailability reduced by food
- d. Primary use: In combination with zidovudine (produces synergistic effects)
- e. Resistance: Viral mutation
- f. Side effects: Peripheral neuropathy; oral & esophageal ulcerations

4. **Stavudine**

- a. Thymidine analog
- b. Mechanism: Inhibits HIV RT and causes DNA chain termination
- c. Bioavailability not reduced by food
- d. Primary use: Advanced HIV in patients unresponsive to other therapies
- e. Resistance: Not frequently observed
- f. Side effects: Peripheral sensory neuropathy

5. **Lamivudine**

- a. Cytosine analog
- b. Mechanism: Inhibits HIV RT and causes DNA chain termination
- c. Bioavailability not reduced by food
- d. Primary uses: Usually used in combination with with other RT inhibitors for HIV-1 treatment; also approved for chronic hepatitis B infection
- e. Resistance: Viral mutation
- f. Side effects: Generally well tolerated

6. **Abacavir**

- a. Guanosine analog
- b. Newer agent that seems to be more effective than earlier NRTIs
- c. Mechanism: Inhibits HIV RT and causes DNA chain termination
- d. Good oral absorption; bioavailability not reduced by food
- e. Resistance: Develops more slowly because it requires three concomitant HIV mutations
- f. Side effects: Hypersensitivity reactions (may be fatal)

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- Bind to RT at a different site than nucleoside reverse transcriptase inhibitors (NRTIs)
- Do not require phosphorylation to inhibit the HIV RT
- Do not compete with nucleoside triphosphates for incorporation into DNA
- Bind to RT's active site and block RNA- and DNA-dependent DNA polymerase
- No cross resistance with NRTIs or protease inhibitors (below)
- Rapid development of resistance by viral mutation
- Used in combination antiretroviral therapy
- Metabolized by cytochrome P450 enzyme complex
- Interactions with drugs which are metabolized by certain cytochrome P450 enzymes
- Frequently require dosage reduction in patients with compromised liver function

1. **Nevirapine**

- a. Excellent oral bioavailability not reduced by food therapy
- b. Side effects: Severe rash, hepatic damage, fever, nausea

2. **Delavirdine**

- a. Good oral bioavailability; reduced by antacids
- b. Side effects: Skin rash, can be teratogenic (avoid pregnancy during therapy)

3. **Efavirenz**

- c. Good oral bioavailability with long half-life
- a. Side effects: Generally well tolerated; CNS effects, skin rash

Protease Inhibitors:

- HIV requires specific protease to generate essential structural proteins of the mature virion core as well as RT itself
- Protease inhibitors block this enzyme and consequently the development of mature infectious virions during HIV replication
- Are effective in both acutely and chronically infected cells
- High potential for resistance through viral mutation
- Produce synergistic effects when used in combination with RT inhibitors
- Metabolized by cytochrome P450 enzyme complex
- Interactions with drugs which are metabolized by certain cytochrome P450 enzymes
- Frequently require dosage reduction in patients with compromised liver function

1. **Saquinavir**

- a. Poor to adequate oral bioavailability
- b. Side effects: Fairly well tolerated with mild GI discomfort
- c. Usually used in combination with Ritonavir (see below)

2. **Ritonavir**

- a. Good oral bioavailability when given with food
- b. Side effects: GI disturbances, peripheral or oral sensations, elevated serum triglycerides and aminotransferase levels

3. **Indinavir**

- a. Excellent oral bioavailability when given on empty stomach
- b. Side effects: Hyperbilirubinemia and nephrolithiasis (crystals forming in the kidneys)

4. **Nelfinavir**

- a. Oral bioavailability increased with food
- b. Side effects: Diarrhea

5. **Amprenavir**

- a. Good oral bioavailability when given with or without food
- b. Efficacy increases when combined with two nucleoside RT inhibitors
- c. Side effects: GI disturbances & rashes

F. Combination therapy for HIV

1. **Atripla**

- a. New combination HIV therapy that combines three different anti-HIV drugs in a single pill.
- b. Emtricitabine: an NRTI analog of cytosine
- c. Tenofovir: an NRTI analog of adenosine monophosphate
- d. Efavirenz: a NNRT

G. Interferons

- a. A family of small antiviral proteins produced as earliest response of body to viral infections
- b. Three classes: alpha, beta and gamma
- c. Alpha and beta are produced by all body cells in response to various stimuli, e.g., viruses, endotoxins, bacteria, cytokines, etc.
- d. Gamma produced by T-lymphocytes and natural killer cells
- e. Mechanism: inhibits viral protein synthesis by blocking the translation of viral messenger RNA; other actions include inhibition of viral penetration, uncoating or synthesis of mRNA as well as inhibition of virion assembly and release
- f. Primary uses: chronic hepatitis C; Kaposi's sarcoma (in HIV infected patients); hairy cell leukemia, chronic myelogenous leukemia, malignant melanoma, papillomavirus; herpes simplex, varicella, herpes keratitis
- g. Side effects: Bone marrow suppression, acute influenza-like syndrome

H. Miscellaneous Agents

1. Ribavirin

- a. Guanosine analog
- b. Mechanism: Phosphorylated to triphosphate by host enzymes, and inhibits RNA-dependent RNA polymerase, viral RNA synthesis, and viral replication
- c. Primary uses: severe RSV (respiratory syncytial virus) bronchiolitis and pneumonia in hospitalized children; chronic hepatitis C (plus interferon)
- d. Side effects: conjunctival irritation, rash (in aerosol form); dose-related hemolytic anemia (systemically); teratogenic and mutagenic potential

2. Palivizumab

- a. Humanized monoclonal antibody
- b. Mechanism: Targets F glycoprotein on surface of RSV
- c. Primary use: Approved for prevention of RSV in high-risk infants and children
- d. Side effects: Elevation in serum aminotransferase levels