ANTIVIRAL AGENTS
Many viruses infect a specific host cell

Many viral infections are self-limiting and require no medical treatment—ex. Rhinoviruses that cause common cold

Common viral infections such as the influenza, mumps, or chicken pox are usually overcome by the body's immune system

Other viruses cause serious and even fatal disease & require aggressive therapy
Principles of antiviral therapy

- Viruses are obligate intracellular parasites
- They do not have a metabolic machinery of their own – use host enzymes
- Difficulty in obtaining selective toxicity against viruses
Anti-Viral drugs

• Many antiviral drugs are Purine or Pyrimidine analogs

• Many antiviral drugs are Prodrugs. They must be phosphorylated by viral or cellular enzymes in order to become active.

• Anti-viral agents inhibits active replication so the viral growth resumes after drug removal
• Antiviral therapy is challenging:

1. Rapid replication of viruses makes it difficult to develop effective antiviral

2. Viruses can rapidly mutate – drug resistant viral mutants

3. They are active only against replicating viruses and do not affect latent virus
Structure of viruses

Virus particles (virions) consist of following parts:

Nucleic acid core:
- DNA or RNA

Contain virus-specific enzymes

Surrounded by “capsid”

An outer lipid “envelope”
The Life Cycle of Viruses

1. Attachment of the virus to receptors on cell surface
2. Entry of the virus through the host cell membrane
3. Uncoating of viral nucleic acid
4. Replication
   - Synthesis of early regulatory proteins, e.g., nucleic acid polymerases;
   - Synthesis of new viral RNA or DNA;
   - Synthesis of late, structural proteins;
5. Assembly (maturation) of viral particles;
6. Release from the cell
1. Viral attachment and entry
2. Penetration
3. Uncoating
4. Early protein synthesis
5. Nucleic acid synthesis
6. Late protein synthesis and processing
7. Packaging and assembly
8. Viral release

Mammalian cell

- Blocked by interferon-alfa (HBV, HCV)
- Blocked by neuraminidase inhibitors (influenza)
- Blocked by enfuvirtide (HIV), maraviroc (HIV), docosanol (HSV), palivizumab (RSV)
- Blocked by amantadine, rimantadine (influenza)
- Blocked by NRTIs (HIV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV), entecavir (HBV)
- Blocked by protease inhibitors (HIV)
• Antiviral drugs work by:

1. Altering the **cells genetic material** so that the virus cannot use it to multiply, i.e. acyclovir (inhibiting Viral enzymes, Host expression of viral proteins & Assembly of viral proteins)

2. Preventing new virus formed from **leaving the cell**, i.e. amatadine.
Inhibition of Viral Nucleic acid
Acyclovir

- Acyclovir is a Guanosine analogue
- Active primarily against HSV1,2 and VZV
- No activity against CMV
- Valacyclovir is a prodrug, with better availability
- mostly taken up by the virus infected cells and has low toxicity for host cells

1. Incorporated into DNA and terminates synthesis
2. Inhibition of herpes virus DNA polymerase
Other Topical drugs for HSV

- **Penciclovir**
  - Similar to acyclovir
  - Treatment of recurrent orolabial herpes simplex

- **Docosanol**
  - Active against a broad range of lipid-envelop viruses
  - MOA: interferes with viral fusion to host cell

- **HSV Keratoconjunctivitis**
  - **Trifluridine** Active against acyclovir resistant strains
    - Also active against vaccinia virus and smallpox
Ganciclovir

- Mechanism like Acyclovir
- Active against all Herpes viruses & CMV
- Activated by a CMV-encoded phosphokinase
- Low oral bioavailability given I.V.
- Most common adverse reaction: bone marrow suppression (leukopenia, thrombocytopenia) and CNS effects (headache, psychosis, convulsions).
- 1/3 of patients have to stop because of adverse effects
Cidofovir

- A nucleoside analogue of cytosine
- Incorporation into viral DNA chain results in reductions of the rate of viral DNA synthesis
- A/E: nephrotoxicity
- Must be administered with high-dose probenecid & adequate hydration
**Foscarnet**

- A non-nucleoside inhibitor
- An inorganic pyrophosphate analogue
- Does not have to be phosphorylated
- Active against Herpes (I, II, Varicella, CMV), including those resistant to Acyclovir and Ganciclovir
- IV only
- Direct inhibition of DNA polymerase
- A/E: Nephrotoxicity, electrolyte abnormalities, CNS toxicity
- Foscarnet should only be given during pregnancy when benefit outweighs risk
Antihepatitis Agents
Viral Hepatitis B

• Acute hepatitis B infection does not usually require antiviral drug treatment. Early antiviral treatment may only be required in patients, with a very aggressive "fulminant hepatitis" or who are immunocompromised.

For people with chronic hepatitis B, antiviral drug therapy used to slow down liver damage and prevent complications (cirrhosis and liver cancer)

Alpha interferon
Pegylated alpha interferon
Lamivudine
INTERFERONs

• A family of small antiviral proteins produced as earliest response of body to viral infections
• Both DNA and RNA viruses induce interferon but RNA viruses tend to induce higher levels
• Currently grouped into: IFN-α, IFN-β, and IFN-γ
• Administered Intrallesionally, S.C, and I.V
• Distribution in all body tissues, except CNS and eye
• Pegylated interferons are modified interferons with improved pharmacokinetic properties
**Lamivudine**

- A potent nucleoside analogue
- Inhibits HBV **DNA polymerase** and both types (1 and 2) of HIV **reverse transcriptase**
- It is prodrug-needs to be phosphorylated
- **Adverse Effects:**
  - CNS: paresthesias and peripheral neuropathies
  - Pancreatitis
  - Neutropenia
Treatment of Chronic Viral Hepatitis C

- Interferon alpha
- Pegylated interferon alpha
- Ribavirin
Ribavirin

• Guanosine analogue
• Mechanism: Phosphorylated to triphosphate by host enzymes
• Inhibits RNA-dependent RNA polymerase, viral RNA synthesis, and viral replication
• Ribavirin aerosol is used clinically to treat pneumonitis caused by RSV in infants
• A/E: Hemolytic anemia, Conjunctival and bronchial irritation
Antiretroviral Agents

Figure 1

- Nucleoprotein (RNA)
- Lipid Envelope
- Capsid
- Hemagglutinin
- Neuraminidase (Sialidase)
- Influenza Virus Anatomy
Blocked by CCR5 receptor antagonists

Binding

Host cell membrane

Chemokine receptors

Fusion and uncoating

CD4

Blocked by fusion inhibitors

Reverse transcription

Blocked by NRTIs, NNRTIs

Integration

Blocked by integrase inhibitors

Transcription

DNA

Translation

RNA

Virion assembly

Budding and maturation

Blocked by protease and maturation inhibitors
CURRENT CLASSES OF ANTIRETROVIRAL DRUGS

Three main enzymatic targets:
- Reverse Transcriptase,
- Protease,
- Integrase

six drug classes
1. **Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**
2. **Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**
3. **Protease inhibitors (PIs)**
4. **Entry inhibitors**
5. **CCR5 receptor antagonists**
6. **Integrase inhibitors**
## Current ARV Medications

### NRTI
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir
- Zidovudine

### NNRTI
- Efavirenz
- Etravirine
- Nevirapine

### PI
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Saquinavir
- Tipranavir

### Fusion Inhibitor
- Enfuvirtide

### CCR5 Antagonist
- Maraviroc

### Integrase Inhibitor
- Raltegravir

### Fixed-dose Combinations
- Zidovudine/lamivudine
- Zidovudine/lamivudine/abacavir
- Abacavir/lamivudine
- Emtricitabine/tenofovir
- Efavirenz/emtricitabine/tenofovir
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

• The first type of drug available to treat HIV infection
• NRTIs interfere with the action of an HIV protein called reverse transcriptase
  • virus needs to make new copies of itself
• Most regimens contain at least two of these drugs
  ○ Act by competitive inhibition of HIV reverse transcriptase
All NRTIs may be associated with

mitochondrial toxicity, lactic acidosis with fatty liver

Zidovudine and Stavudine: dyslipidemia and insulin resistance

Increased risk of myocardial infarction in: Abacavir or

Didanosine
NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

- Bind directly to HIV reverse transcriptase, prevents viral RNA from conversion to the viral DNA that infects healthy cells, by causing conformational changes in the enzyme.
- Binding site of NNRTIS is near to but distinct from that of NRTIS.
- **Do not** require phosphorylation to be active.
PROTEASE INHIBITORS

• Prevent the processing of viral proteins into functional conformations, resulting in the production of immature, noninfectious viral particles

• Do not need intracellular activation

• A/E:
  • Metabolic Disorders
    • Hepatotoxicity
    • Hyperglycemia, insulin resistance
    • Lipid abnormalities (increases in triglyceride and LDL levels)
    • Fat redistribution
  • Bone Disorders, GI Intolerance
ENTRY INHIBITORS

Binds to the viral envelope glycoprotein, preventing the conformational changes required for the fusion of the viral and cellular membranes

Enfuvirtide

By subcutaneous injection

- Toxicity
  - Injection site reactions
  - Nausea, diarrhea, fatigue, hypersensitivity
CCR5 receptor antagonists

- Inhibitors of the human CCR5 receptor
- Thought to alter the conformational state of the CCR5 receptor

**Maraviroc**

- A/E: Abdominal pain, Upper respiratory tract infections, Cough, Hepatotoxicity, Musculoskeletal symptoms, Rash
INTEGRASE INHIBITORS

Bind integrase, a viral enzyme essential to the replication of HIV, **Inhibits strand transfer**, the final step of the provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.

**Raltegravir**

A/E: Nausea, Headache, Diarrhea
HIV Drug Regimens

- Always combine multiple agents
- Usually 2 NRTIs along with:
  - A PI enhanced with a low dose of a second PI,
  - An NNRTI
  - An integrase inhibitor
  - An enter inhibitor

HAART

- Taking 3 or more antiretroviral drugs at the same time vastly reduces the rate at which resistance develops, the approach is known as highly active antiretroviral therapy, or HAART
HIV Drug Toxicity

- HIV drugs have side effects that are either drug or drug class specific (but distinguishing them from effects of prolonged infection are challenging)
- Severe, life-threatening, and essentially irreversible

HIV Drug Resistance

- HIV mutates readily
ANTI-INFLUENZA AGENTS
Classes of Influenza Antiviral Drugs

M2 ion channel inhibitors
  - Amantadine
  - Rimantadine

Neuraminidase inhibitors
  - Oseltamivir
  - Zanamivir
Influenza A

- Is the only strain that causes pandemics.
- Is classified into 16 H (hemagglutinin) and 9 N (neuraminidase) known subtypes based on surface proteins.
- Can infect a variety of animal hosts.
- Avian influenza subtypes are highly species-specific, but they can also on rare occasions crossed the species barrier to infect humans and cats.
Viruses of the H5 and H7 subtypes (eg, H5N1, H7N7, and H7N3) may:

- Rapidly mutate within poultry
- Have recently expanded their host range to cause both avian and human disease.

**H5N1 virus**

- First caused human infection (including severe disease and death) in 1997 and has become endemic in some areas since 2003. It is feared that the virus will become transmissible from person to person rather than solely from poultry to human.
Amantadine & Rimantadine

- Block the M2 ion channel of the virus particle and inhibit Uncoating of the viral RNA within infected host cells, thus preventing its replication.
- Activity: influenza A only.
- Rimantadine is 4 to 10 times more active than amantadine in vitro.
- A/E
  - GI disturbance, nervousness, insomnia.
Oseltamivir & Zanamivir

- Neuraminidase inhibitors, 1999
- Chemically related, but have different routes of administration
- Interfere with release of influenza virus from infected to new host cells.
- Competitively and reversibly interact with the active enzyme site to inhibit neuraminidase activity and destroy the receptors found on normal host cells recognized by viral hemagglutinin.
• Activity: both influenza A and influenza B viruses.

• Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.

• Oseltamivir is FDA-approved for patients 1 year and older, whereas zanamivir is approved in patients 7 years or older.