Anti-viral Drugs
Anti-viral drugs

• Viruses have no cell wall and made up of nucleic acid components
• Viruses containing envelope – antigenic in nature
• Viruses are obligate intracellular parasite
• They do not have a metabolic machinery of their own – uses host enzymes
Anti-viral drugs

- Certain viruses multiply in the cytoplasm but others do in the nucleus
- Most multiplication take place before diagnosis is made
Anti-Viral drugs

- Many antiviral drugs are *Purine* (A & G) or *Pyrimidine* (C & T) 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.
Anti-viral drugs

- Current anti-viral agents do not eliminate non-replicating or latent virus
- Effective host immune response remains essential for the recovery from the viral infection
- Clinical efficacy depends on achieving inhibitory conc. at the site of infection within the infected cells
Anti-viral drugs

Stages of viral replication

• Cell entry – Attachment - Penetration

• Uncoating

• Transcription of viral genome

• Translation

• Assembly of virion components

• Release
Maraviroc
CCR5 receptor antagonist

- Blocked by enfuvirtide (HIV)
- Blocked by amantadine (influenza A)
- Blocked by fomivirsen (CMV)
- Blocked by neuraminidase inhibitors (influenza)
- Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
- Blocked by methisazone (variola); protease inhibitors

Viruses:

1. Viral adsorption
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
Anti-viral drugs

Anti-herpes virus agents
• Acyclovir / Valacyclovir
• Famiclovir / Penciclovir
• Ganciclovir / Cidofovir
• Foscarnet
• Trifluridine / Idoxuridine / Vidarabine
Anti-viral drugs

Acyclovir & related compounds:

- Valacyclovir is a prodrug of Acyclovir with better bioavailability.
- Famciclovir is hydrolyzed to Penciclovir and has greatest bioavailability.
- Penciclovir is used only topically whereas Famciclovir can be administered orally.
Anti-Viral drugs

Pharmacology of acyclovir and related compounds

- Acyclovir, Valacyclovir, Ganciclovir, Famciclovir, Penciclovir all are guanine nucleoside analogs.
Anti-viral drugs

Mechanism of action of Acyclovir and related compounds:

• All drugs are phosphorylated by a viral thymidine-kinase, then metabolized by host cell kinases to nucleotide analogs.
• The analog inhibits viral DNA-polymerase
• Incorporation of acyclovir triphosphate into the growing viral DNA chain
• Only actively replicating viruses are inhibited
Acyclovir (acycloguanosine)

1. Viral kinase:
   - Acycloguanosine monophosphate (acyclo-GMP)

2. Host cell kinase:
   - Acycloguanosine triphosphate (acyclo-GTP)

3. Viral DNA polymerase:
   - Growing strand

Template

Viral DNA
Anti-viral drugs

• Acyclovir is thus selectively activated in cells infected with herpes virus.
• Uninfected cells do not phosphorylate acyclovir.
Anti-Viral drugs

Antiviral spectrum:

- Acyclovir: HSV-1, HSV-2, VZV, Shingles.
- Ganciclovir / Cidofovir: CMV
- Famciclovir: Herpes genitalis and shingles
- Foscarnet: HSV, VZV, CMV, HIV
- Penciclovir: Herpes labialis
- Trifluridine: Herpetic keratoconjunctivitis
Anti-Viral drugs

Pharmacokinetics of Acyclovir:
• Oral bioavailability ~ 20-30%
• Distribution in all body tissues including CNS
• Renal excretion: > 80%
• Half lives: 2-5 hours
• Administration: Topical, Oral, IV
Anti-viral drugs

Adverse effects of Acyclovir / Ganciclovir

• Nausea, vomiting and diarrhea
• Nephrotoxicity - crystalluria, haematuria, renal insufficiency
• Myelosuppression – Neutropenia and thrombocytopenia – Ganciclovir
Anti-viral drugs

Therapeutic uses:

*Acyclovir* is the drug of choice for:
- HSV Genital infections
- HSV encephalitis
- HSV infections in immunocompromised patient

*Ganciclovir* is the drug of choice for:
- CMV retinitis in immunocompromised patient
- Prevention of CMV disease in transplant patients
Anti-viral drugs

Cidofovir:

• It is approved for the treatment of CMV retinitis in immunocompromised patients and Adenovirus infections.
• It is a nucleotide analog of cytosine – no phosphorylation required.
• It inhibits viral DNA synthesis.
• Available for IV, Intravitreal inj, topical.
• Nephrotoxicity is a major disadvantage.
Anti-viral drugs

PHARMACOLOGY OF VIDARABINE

• Vidarabine is a nucleoside analog. (adenosine)

Antiviral spectrum of Vidarabine:

HSV-1, HSV-2 and VZV.

Its use is limited to HSV keratitis only.
Anti-viral drugs

Vidarabine

• The drug is converted to its triphosphate analog which inhibits viral DNA-polymerase.
• Oral bioavailability ~ 2%
• Administration: Ophthalmic ointment
• Used in HSV keratoconjunctivitis in immunocompromised patient.
• Anemia and SIADH are adverse effects.
PHARMACOLOGY OF TRIFLURIDINE

• Trifluridine is a Pyrimidine (C, T) nucleoside analogs - inhibits viral DNA synthesis.

Antiviral spectrum  Trifluridine :

• HSV-1, HSV-2 and VZV.
• Use is limited to Topical - Ocular HSV Keratitis
Anti-viral drugs

PHARMACOLOGY OF FOSCARNET

• Foscarnet is an inorganic pyrophosphate analog

• It directly inhibits viral DNA and RNA - polymerase and viral reverse transcriptase (it does not require phosphorylation for antiviral activity)
Anti-viral drugs

Foscarnet

• HSV-1, HSV-2, VZV, CMV and HIV.
• Oral bioavailability ~ 10-20%
• Distribution to all tissues including CNS
• Administration: IV
Anti-viral drugs

Therapeutic uses of Foscarnet

• *It is an alternative drug for*

• HSV infections (acyclovir resistant / immunocompromised patient)

• CMV retinitis (ganciclovir resistant / immunocompromised patient)
Anti-viral drugs

Respiratory viral infections

Influenza –
• Amantadine / Rimantadine
• Oseltamivir / Zanamavir
  *(Neuraminidase inhibitors)*

RSV bronchiolitis –
• Ribavirin
Anti-viral drugs

Amantadine and Rimantadine: Influenza

• Prevention & Treatment of influenza A
• Inhibition of viral uncoating by inhibiting the viral membrane protein M2
• Influenza A virus only
Amantadine and Rimantadine: Mechanism of Action

- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription
Anti-viral drugs

Pharmacokinetics of Amantadine

- Oral bioavailability ~ 50-90%
- Amantadine cross extensively BBB whereas Rimantadine does not cross extensively.
- Administration: Oral
Anti-viral drugs

Neuraminidase inhibitors: Influenza A & B
Oseltamivir / Zanamavir

- **Influenza** contains an enzyme *neuraminidase* which is essential for the replication of the virus.

- **Neuraminidase inhibitors** prevent the release of new virions and their spread from cell to cell.
Anti-viral drugs

Neuraminidase inhibitors: Influenza Oseltamivir / Zanamavir

• These are effective against both types of influenza A and B.
• Do not interfere with immune response to influenza A vaccine.
• Can be used for both prophylaxis and acute treatment.
Anti-viral drugs
Neuraminidase inhibitors : Influenza
Oseltamivir / Zanamavir

• Oseltamivir is orally administered.
• Zanamavir is given intranasal.
• Risk of bronchospasm with zanamavir
Anti-viral drugs

PHARMACOLOGY OF RIBAVIRIN

- **Ribavirin** is a guanosine analog.
- Requires phosphorylation to mono-, di- and triphosphate
- Triphosphate Inhibits RNA polymerase and depletes cellular stores of guanine (inhibit IMDH)
- Decrease synthesis of mRNA 5’ cap (interfere with guanylation and methylation of nucleic acid base)

**Antiviral spectrum** : RNA viruses are susceptible, including influenza, parainfluenza viruses, **RSV**, Lassa virus
Anti-viral drugs

Ribavirin : RSV

- Distribution in all body tissues, except CNS
- Administration : Oral, IV, Inhalational in RSV.
- Anemia and jaundice are adverse effects
- Not advised in pregnancy.
Anti-viral drugs

Therapeutic uses Ribavirin

*Ribavirin is the drug of choice for:*
- RSV bronchiolitis and pneumonia in hospitalized children (given by aerosol)
- Lassa fever

*Ribavirin is an alternative drug for:*
- Influenza, parainfluenza, measles virus infection in immunocompromised patients
Anti-viral drugs

Hepatic Viral infections:

- Interferons
- Lamivudine – cytosine analog – HBV
- Entecavir – guanosine analog – HBV – lamivudine resistance strains
- Ribavirin – Hepatitis C (with interferons)
Fig. 39-2. Human immunodeficiency virus (HIV). Within the core capsid, the diploid, single-stranded, positive-sense RNA is complexed to nucleoprotein.
Antiretroviral Drugs

HAART - Highly active antiretroviral therapy

• Includes at least three medications
  – “cocktails”

• These medications work in different ways to reduce the viral load
Antiretroviral Drugs

- **Reverse transcriptase inhibitors (RTIs)**
  - Block activity of the enzyme reverse transcriptase, preventing production of new viral DNA

- **Reverse transcriptase inhibitors (RTIs)**
  - Nucleoside RTIs (NRTIs): Azidothymidine (AZT), Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)
  - Nonnucleoside RTIs (NNRTIs): Nevirapine, delavirdine, efavirenz
  - Nucleotide RTIs (NTRTIs): Tenofovir, Adefovir
Nucleoside RTIs (NRTIs):
Azidothymidine (AZT), Didanosine (ddI), Stavudine (D4T), Lamivudine (3TC)

• Requires phosphorylation by host cellular enzymes (kinases) to their active triphosphate form
• Selective therapeutical effect: HIV RT is more sensitive to AZT than is host cell DNA polymerase
3TC (lamivudine/Epivir)

- **Toxicity**
  - Few
  - Hepatitis B exacerbation
- **Side Effects**
  - Few; class effect
- **Dosing**
  - 150mg bid or
  - 300mg qd
  - Renal dosing available
- **Special Considerations**
  - Hepatitis B
- **Combination with AZT**
D4T (stavudine/Zerit)

- **Toxicity**
  - Lipoatrophy
  - Peripheral neuropathy
  - Pancreatitis
  - Lactic acidosis

- **Side Effects**
  - Gen well-tolerated
  - H/N/V

- **Dosing**
  - 40mg bid (if >60kg)
  - 30mg bid (if <60kg)

- **Combination only**
AZT (zidovudine/Retrovir)

- **Toxicity**
  - Anemia
  - Neutropenia
  - Thrombocytopenia
  - Myopathy

- **Side Effects**
  - Nausea/vomiting
  - Headache
  - Dizziness

- **Dosing**
  - 300mg bid

- **Combination only**
DDI (didanosine/Videx)

- **Toxicity**
  - Lactic acidosis
  - Peripheral neuropathy
  - Pancreatitis
  - Lipodystrophy

- **Side Effects**
  - GI

- **Dosing**
  - If EC, 400mg QD (<60kg: 250mg qd)
  - If reg tabs, 200mg bid (<60kg: 125 bid/250qd)
  - Empty stomach

- **Combination only**
Nonnucleoside RTIs (NNRTIs):
Nevirapine, delavirdine, efavirenz

- Active against HIV-1
- Do not require cellular enzymes to be phosphorylated
- Do not inhibit human DNA polymerase
- Relatively safe: noncytotoxic
- Highly prone to drug resistance
- Used in combination with other drugs active against HIV
Antiretroviral Drugs

- **Protease inhibitors (PIs)**
  - Inhibit the protease retroviral enzyme, preventing viral replication
  - Inhibition of this enzyme blocks viral assembly and release
  - **Examples:**
    - amprenavir (Agenerase)
    - indinavir (Crixivan)
    - nelfinavir (Viracept)
    - ritonavir (Norvir)
    - saquinavir (Invirase)
  - Hepatotoxic
  - Used in combination with other drugs active against HIV
Antiretroviral Drugs

- **Fusion inhibitors**
  - Inhibit viral fusion, preventing viral replication
  - Newest class of antiretroviral drugs
  - Example: enfuvirtide (Fuzeon)

- Used in combination with other drugs active against HIV
- Side effects:
  - peripheral neuropathy, insomnia, depression, cough, dyspnoea, anorexia, arthralgia
Antiretroviral Drugs

• Entry inhibitor
  – Inhibit viral entry into macrophages a T-cells
  – CCR5 receptor antagonist
  – FDA approved in 2007
  – Maraviroc (Selzentry, or Celsentri outside the U.S)
  – Used in combination with other drugs active against HIV
  – HIV can also use other coreceptors, such as CXCR4, an HIV tropism test such as a trofile assay must be performed to determine if the drug will be effective
  – Safety issues regarding blocking CCR5, a receptor whose function in the healthy individual is not fully understood
Antiretroviral Drugs

• Combinations of multiple antiretroviral medications are common

• Adverse effects vary with each drug and may be severe—monitor for dose-limiting toxicities

• Monitor for signs of opportunistic diseases
Anti-viral drugs

Interferons

Interferons (IFNs) are natural proteins produced by the cells of the immune systems in response to challenges by foreign agents such as viruses, bacteria, parasites and tumor cells.

• Antiviral, immune modulating and anti-proliferative actions

• Three classes of interferons – \( \alpha \), \( \beta \), \( \gamma \)
Anti-viral drugs

Interferons

- **α and β interferons** are produced by all the cells in response to viral infections
- **γ interferons** are produced only by T lymphocyte and NK cells in response to cytokines – immune regulating effects
- γ has less anti-viral activity compared to α and β interferons
Anti-viral drugs

Mechanism of action of Interferons:

- **Induction** of the following enzymes:
  1) a *protein kinase* which inhibits protein synthesis
  2) an *oligo-adenylate synthase* which leads to degradation of viral mRNA
  3) a *phosphodiesterase* which inhibit t-RNA

The action of these enzymes leads to an inhibition of translation
Anti-viral drugs

Antiviral spectrum: Interferon α

- Includes HBV, HCV (Pegylated interferon) and HPV.
- addition of polyethylene glycol to the interferon, through a process known as pegylation, enhances the half-life of the interferon when compared to its native form.
- Anti-proliferative actions may inhibit the growth of certain cancers - like Kaposi sarcoma and hairy cell leukemia.
Anti-viral drugs

Pharmacokinetics: Interferons

• Oral bioavailability: < 1%
• Administered Intraleisonally, S.C, and I.V
• Distribution in all body tissues, except CNS and eye.
• Half lives: 1-4 hours
Anti-viral drugs

Adverse effects of Interferons

• Acute flu-like syndrome (fever, headache)
• Bone marrow suppression (granulocytopenia, thrombocytopenia)
• Neurotoxicity (confusion, seizures)
• Cardiotoxicity - arrhythmia
• Impairment of fertility
Anti-viral drugs

**Therapeutic uses Interferons**

- Chronic hepatitis B and C (complete disappearance is seen in 30%).
- HZV infection in cancer patients (to prevent the dissemination of the infection)
- CMV infections in renal transplant patients
- Condylomata acuminata (given by intralesional injection). Complete clearance is seen ~ 50%.
- Hairy cell leukemia (in combination with zidovudine)
- AIDS related Kaposi’s sarcoma
<table>
<thead>
<tr>
<th>Virus</th>
<th>Diseases</th>
<th>Drug(s) of choice</th>
<th>Alternative drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLU A</td>
<td>Influenza</td>
<td>Amantadine</td>
<td>Rimantadine</td>
</tr>
<tr>
<td>RSV</td>
<td>Pneumonia, bronchiolitis</td>
<td>Ribavirin (aerosol)</td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>Genital herpes</td>
<td>Acyclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td></td>
<td>Keratitis</td>
<td>Trifluridine</td>
<td>Idoxuridine</td>
</tr>
<tr>
<td></td>
<td>Conjunctivitis</td>
<td></td>
<td>Vidarabine</td>
</tr>
<tr>
<td></td>
<td>Encephalitis</td>
<td>Acyclovir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neonatal HSV infection</td>
<td>Acyclovir</td>
<td>Vidarabine</td>
</tr>
<tr>
<td></td>
<td>Herpes infections in immunocompromised host</td>
<td>Acyclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td></td>
<td>In normal host</td>
<td>No therapy</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td>---</td>
</tr>
<tr>
<td>VZV</td>
<td>In immunocompromised host, or during pregnancy</td>
<td>Acyclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis</td>
<td>Ganciclovir</td>
<td>Foscarnet</td>
</tr>
<tr>
<td>HIV</td>
<td>AIDS</td>
<td>Zidovudine ± protease inhibitors</td>
<td>Didanosine, Stavudine</td>
</tr>
<tr>
<td></td>
<td>HIV antibody positive with CD4 count &lt; 500/mm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBV HCV</td>
<td>Hepatitis B, C</td>
<td>Interferons</td>
<td></td>
</tr>
</tbody>
</table>