Chapter III
ANTIVIRAL AND ANTIFUNGAL DRUGS

“AN OUNCE OF PREVENTION WORTH POUND OF CURE”

Year III Pharm.D
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Viruses are small (20-30 nm) infective agents that are incapable of reproduction outside their host cells.
(1) Binding

(2) Entry

CXCR4 Ck receptor → CD4

(3) Uncoating

Reverse transcriptase inhibitors

(4) Reverse transcriptase makes a double-stranded DNA copy of viral RNA

(5) DNA copy (+integrase: O) enters nucleus and integrates with host DNA, forming provirus

(6) Transcription of provirus

(7) Translation by host ribosomes

Polypeptides → mRNA

(8) Protease action

(9) Assembly and budding

NUCLEUS

mRNA

Genomic RNA

PLASMA MEMBRANE

Reverse transcriptase inhibitors

Protease inhibitors

Inhibitors viral translation

Inhibitors viral uncoating

Inhibitors viral entry
DIFFERENT HOST DEFENCES:

- Skin
- T-lymphocytes
- NK cells
- Gene silencing

VIRAL PLOY:

- Subversion of immune response
- Interference with surface protein markers
- Interference with apoptotic pathway
- Adopting ‘baby turkey’ ploy
Mechanism of action:

Phosphorylation to 5’-triphosphate residues

Competes with host triphosphate for proviral DNA synthesis

Incorporation into growing viral DNA and chain termination
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ANALOGUE</th>
<th>HALF-LIFE</th>
<th>R.O.A</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIDOVUDINE (AZT)</td>
<td>THYMIDINE</td>
<td>1-3 HR</td>
<td>ORAL</td>
<td>ANEMIA, MYOPATHY</td>
</tr>
<tr>
<td>DIDANOSINE (ddI)</td>
<td>ADENOSINE</td>
<td>1-1.5 HR</td>
<td>ORAL</td>
<td>PERIPHERAL NEUROPATHY</td>
</tr>
<tr>
<td>STAVUDINE (d4T)</td>
<td>THYMIDINE</td>
<td>1.5 HR</td>
<td>ORAL</td>
<td>LIPODYSTROPHY</td>
</tr>
<tr>
<td>LAMIVUDINE (3TC)</td>
<td>CYTOSINE</td>
<td>6-8 HR</td>
<td>ORAL</td>
<td>ANOREXIA</td>
</tr>
<tr>
<td>ABACAVIR (ABC)</td>
<td>GUANOSINE</td>
<td>1-1.5, 12 HR</td>
<td>ORAL</td>
<td>HYPERSENSITIVITY AND FLU LIKE SYMPTOMS</td>
</tr>
</tbody>
</table>
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE UNHIBITORS

NEVIRAPINE
- Orally well absorbed
- Bioavailability-90%
- T1/2-30 hours
- Prevent mother to baby transmission
- Hepatotoxic

EFAVIRENZ:
- Bioavailability-50%
- T1/2-48 hours
- 99% albumin bound
- Insomnia, dizziness
PROTEASE INHIBITORS

Saquinavir, nelfinavir, indinavir, ritonavir, amprenavir

Given orally

Increase CD4 count in AIDS patients

Tablet load is high

Lipodystrophy, numbness, rhabdomyolysis are adverse effects
DNA POLYMERASE INHIBITORS

Mechanism of action:

Converted to monophosphate by thymidine kinase of virus

Host cell convert monophosphate to triphosphate

Inhibits DNA polymerase and terminate nucleotide chain
<table>
<thead>
<tr>
<th>DRUG</th>
<th>ANALOGUE</th>
<th>DRUG OF CHOICE FOR</th>
<th>R.O.A</th>
<th>HALF LIFE</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACICLOVIR</td>
<td>GUANIDINE</td>
<td>HERPES, VARICELLA</td>
<td>I.V, TOPICAL</td>
<td>2-3 HR</td>
<td>TREMORS, MALAISE, RENAL DYSFUNCTION</td>
</tr>
<tr>
<td>GANCICLOVIR</td>
<td>GUANIDINE</td>
<td>CYTOMEGALY</td>
<td>I.V</td>
<td>2-4 HR</td>
<td>CARCINONECITY, BONE MARROW DEPRESSION</td>
</tr>
<tr>
<td>RIBAVIRIN</td>
<td>GUANIDINE</td>
<td>SYNCYTIAL VIRUS</td>
<td>I.V</td>
<td>2-3 HR</td>
<td>INSOMNIA, MYALGIA</td>
</tr>
<tr>
<td>FOSCARNET</td>
<td>NON NUCLEOSIDE</td>
<td>CYTOMEGALY</td>
<td>ORAL</td>
<td>4-8 HR</td>
<td>ANEAMIA, CONVULSION</td>
</tr>
</tbody>
</table>
INHIBITORS OF VIRAL FUSION:

**ENFURVIRTIDE:**
Given subcutaneously
Flu like symptoms

NEURAMINIDASE AND VIRAL COAT ASSEMBLY INHIBITORS:

**ZANAMIVIR AND OSELTAMIVIR-**
Inhalation and oral preparation
G.I upset

**AMANTIDINE AND RIMANTIDINE-**
Block M2 ion channel
Effective only against influenza A virus
Dizziness, insomnia, slurred speech
**BIOLOGICS AND IMMUNOMODULATORS**

**Immunoglobulin**: Pooled antibodies against virus envelope are used

Hyperimmune globulin against hepatitis B, rabies, varicella are used

**Palivisumab**: Monoclonal antibody directed against glycoprotein on surface of syncytial virus

**Inosine pranobex**: Interfere with viral nucleic acid synthesis and has immunopotentiating action on host
INTERFERONS:

- Bind to specific ganglioside receptors on host cell
- Induce enzymes that inhibit viral mRNA translation
- Broad spectrum
- Half life of 2-4 hours
- Do not cross blood brain barrier
- Interferon-α-2a—treatment of hepatitis B and kaposi sarcoma
- Interferon-α-2b—treatment of hepatitis C
- Myalgia, bone marrow depression, alopecia
ANTIFUNGAL AGENTS

- Fungi are eukaryotic, complex and more evolved organisms.
- Most fungal infections are opportunistic in nature.

<table>
<thead>
<tr>
<th>ORGANISM</th>
<th>PRINCIPAL DISEASE</th>
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<tbody>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>Meningitis</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Systemic candidiasis</td>
</tr>
<tr>
<td>Trichophyton spp.</td>
<td>Skin and nail infections</td>
</tr>
<tr>
<td>Microsporum spp.</td>
<td>Skin and nail infections</td>
</tr>
<tr>
<td>Epidermophyton</td>
<td>Skin and nail infections</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>Pulmonary aspergillosis</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>coccidiomycosis</td>
</tr>
</tbody>
</table>
ANTIBIOTICS

POLYENES:

**Amphotericin B**: Obtained from *streptomyces nodosus*
- Has high affinity to ergosterol
- Several polyene molecules orient to form a ‘micropore’
- Hydrophilic side towards interior through which ions move out
- Broad spectrum antibiotic
- Fungicidal at high and static at low concentrations
- Given orally and I.V as a suspension
- Nephrotoxicity, hypersensitivity, thrombocytopenia
- Used topically for oral, vaginal and cutaneous candidiasis, leishmaniasis
HETEROXYCLIC BENZOFURAN:

- Antibiotic extracted from penicillium griesofulvum
- Not active against candida and deep mycosis infections
- Fungistatic by interfering with microtubules and arresting cell division
- Given orally along with fatty meal
- Plasma half life is 24 hours
- Photosensitivity and allergy are common

ECHINOCANDINS

- Found naturally in A.nidulans
- Inhibit synthesis of 1,3-β-glucan, glucose polymer for cell wall synthesis
IMIDAZOLES AND TRIAZOLES

- Group of synthetic fungistatic agents with broad spectrum of activity
- Imidazoles-clotrimazole, econazole, ketoconazole, miconazole, tioconazole
- Triazole-itraconazole, voriconazole, fluconazole
- Act by inhibiting lanosine-14α-demethylase responsible for converting lanosterol to ergosterol
- Alters fluidity of membrane and inhibit replication
- Inhibit transformation of candidial yeast cells to hyphae, the invasive form
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<tbody>
<tr>
<td>KETOCONAZOLE</td>
<td>ORAL</td>
<td>1.5-6 HOURS</td>
<td>DERMATOPHYTOSIS, KALA AZAR</td>
<td>GYNACOMASTIA, ALOPECIA</td>
</tr>
<tr>
<td>KETOCONAZOLE</td>
<td>ORAL, I.V</td>
<td>25-60 HOURS</td>
<td>CANDIDIASIS, COCCIDIOIDAL</td>
<td>ABDOMINAL PAIN</td>
</tr>
<tr>
<td>ITRACONAZOLE</td>
<td>ORAL</td>
<td>30-64 HOURS</td>
<td>ASPERGILLOSIS, MYCOsis</td>
<td>PRURITIS, IMPOTENCE, L.V DYSFUNCTION</td>
</tr>
</tbody>
</table>
**FLUCYTOSINE:**

- Orally active narrow spectrum drug
- Converted to antimetabolite and inhibits thymidilate synthetase
- Given by I.V infusion, orally
- Half life is 3-5 hours
- Thrombocytopenia and alopecia

**TERBINAFINE:**

- Lipophilic, broad spectrum fungicidal compound
- Inhibit squalene epoxidase
- Accumulation of squalene is toxic
- Orally given to treat worm infections
- Joint and muscle pains