

PHARMACOLOGY

Antimicrobial Agents: Antifungal & Antiviral Drugs

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The incidence and spectrum of local as well as systemic fungal infections have increased dramatically over the past two decades. Various factors which predispose patient to invasive fungal infections are advances in medical technology, use of invasive monitoring devices, mechanical ventilation, parenteral nutrition, broad spectrum antimicrobial agents, intensive cancer chemotherapies, corticosteroid and other immunosuppressives.

Classification of Antifungal Drugs

A. Systemic Antifungal Drugs

1. Polyenes antibiotics
 - Amphotericin B
2. Azole derivatives
 - a) Imidazole: Ketoconazole, Miconazole
 - b) Triazole: Fluconazole, Itraconazole, Voriconazole, Posaconazole, Ravuconazole
3. Echinocandin: Caspofungin, Anidulafungin, Micafungin
4. Antimetabolite: Flucytosine (5-FC)
5. Nikkomycin

B. Topical Antifungal drugs

1. Polyene antibiotics: Amphotericin B, Nystatin, Hamycin, Natamycin (Pimaricin), Rimocidin, Hitachimycin, Filipin
2. Azoles–Imidazole: Clotrimazole, Ketoconazole, Miconazole, Econazole, Butaconazole, Oxiconazole, Sulconazole, Fenticonazole, Isoconazole, Bifonazole, Tiaconazol, Terconazole
3. Others: Tolnaftate, Undecyclinic acid, Povidone iodine, Triacetin, Gentian violet, Sodium thiosulphate, Cicloporox olamine, Benzoic acid, Quinidochlor

C. Systemic antifungal drugs for superficial infections

1. Heterocyclic benzofurans: Corticofunvin, Griseofulvin
2. Allylamine: Terbinafine, Butenafine, Naftifine.

Classification of Human Fungal Infections

Fungal infection	Site infected	Example
Superficial	Outermost skin and hair	Malasseziasis
Cutaneous	Deep epidermis and nails	Dermatophytosis
Subcutaneous	Dermis and subcutaneous tissue	Sporotrichosis
Systemic opportunistic		Candidiasis, Aspergillosis, Cryptococcosis, Mucormycosis
Non-opportunistic		Histoplasmosis, Blastomycosis, Coccidioidomycosis

1. Polyene Antibiotics

Its name is derived from highly double bonded structure, amphotericin B (AMB) is prototype.

Amphotericin B: It was derived from *Streptomyces nodosus* in 1956. It is an amphoteric polyene macrolide antibiotic insoluble in water. It has wide spectrum of antifungal activity, which includes *Candida albicans*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Blastomycosis dermatitidis*, *Sporothrix schenckii* and many strains of *Aspergillus*. It is fungicidal at high dose. It is also active on *Leishmania*.

Mechanism of Action: It binds to ergosterol moiety in the membranes of fungi. This causes pores in the cell membrane, eventually causing leakage of low molecular weight cytoplasmic constituents. This effect, coupled with amphotericin ability to stimulate granulocytes, T cells and B cells, ultimately lead to death of fungi.

Pharmacokinetics – It is not absorbed by oral route. Administered IV infusion as colloidal suspension made with deoxycholate (DOC). It is distributed widely in the body but penetration in the CSF is poor. Its $t_{1/2}$ is 15 days. Excretion occurs slowly in urine and bile. It takes more than two months for complete clearance of the drug.

Clinical uses:

1. It is in use for more than 40 years and served as the Gold standard for the treatment of most of systemic fungal infections. Its very effective drug, but its limitations are i.v. administration, toxicities and inability to penetrate CSF.
2. It is a reserve drug for the resistant cases of kala-azar and mucocutaneous leishmaniasis.
3. Topically amphotericin B is used for the treatment of mycotic corneal ulcers, keratitis, fungal arthritis and candidiasis.

Adverse effects:

1. **Toxicity** is high, acute infusion related side effects like aches, fever, chills, and rigors. Usually the intensity of reaction decreases with continued medication. Premedications with acetaminophen (10 mg/kg), diphenhydramine (50 mg), meperidine (25-60 mg) administered one and half hour before or hydrocortisone (25 mg) added to the infusion have been shown to reduce the incidence of fever and chills.

2. Long Term Toxicity:

- a. **Nephrotoxicity** – It is most important toxicity. It manifests as hypokalemia, renal tubular acidosis and inability to concentrate urine. Nephrotoxicity can be minimized by mannitol administration, sodium loading and alternate day administration. However, caution may be taken while liberalizing salt intake in patients with CHF, renal failure or cirrhosis with ascites. The lipid based amphotericin B product (e.g. Abelcet, Amphotec, Ambisome) have all shown a lower incidence of nephrotoxicity. In addition, none of the lipid based products demonstrate superior efficacy when compared with amphotericin B against invasive candidiasis and cryptococcal meningitis.
- b. **Thrombophlebitis** can be minimized by using dilute solutions (<0.1 mg/ml) and addition of heparin 500 – 1000 U per liter of solutions.
- c. **Anaemia**
- d. **CNS toxicity:** On intrathecal injection it results in headache and vomiting.

New Amphotericin B formulations: To circumvent toxicities of amphotericin B, three lipid formulated products have been developed and approved for use (Table 1).

Table 1: Different Formulations of Amphotericin B

Product	Form	Percent Am B by weight	Size	Dose
AMB Lipid Complex (ABLC) (Abelcet)	Non liposomal	33%	1600-11000	5 mg/kg/d
AMB Colloidal dispersion (ABCD) (Amphocil)	Non liposomal	50%	120 – 140	1-5 mg/kg/d
LAMB (Ambisome)	Liposomal spherical unilamellar vesicle	10%	80	1-5 mg/kg/d
ABLE	Spherical vesicle	Variable	300-500	1 mg/kg
AMB fungizone IV	N/A	100%	N/A	0.5-1 mg/kg/d

Abbreviations: AM B amphotericin B; N/A not applicable

They have shown lower incidence of nephrotoxicity, but none of the preparations have shown superior efficacy.

Dose: An initial 1 mg test dose is recommended. However, recent clinical experience suggests that this practice may not be necessary and may delay therapy in an acutely ill patient. Dose for conventional formulation is 3.0 – 5.0 mg/kg.

Drug Interactions:

1. Amphotericin B has synergistic effect with flucytosine in the treatment of systemic candidiasis and cryptococcosis.
2. Amphotericin B and ketoconazole are antagonistic.
3. Additive toxicity with other nephrotoxic drugs.

Other polyenes like nystatin, natamycin, hamycin etc are not given systemically as they are too toxic. Therefore, they are only used topically for candidial infections such as oropharyngeal thrush, vaginal and intertrigonal candidial infections. However, nystatin is given orally for the treatment of monilial diarrhoea.

2. Azoles

The azoles were introduced in the 1980s and have some distinct advantages over amphotericin B e.g. they are fairly nontoxic and can be given orally. They have broad spectrum antifungal activity covering dermatophytes, deep mycoses, nocardia and few bacteria also.

Mechanism of Action – It inhibits the enzyme Cytochrome P450 14 α -demethylase. This enzyme converts lanosterol to ergosterol which is required for fungal cell membrane synthesis. These drugs also block steroid synthesis in humans.

Uses: Systemic antifungal azoles (Table 2)

Table 2: Summary of Azole Antifungal Drugs

Drug	Route	Advantages	Comments
Ketoconazole	po	Oral treatment of Histoplasmosis, Coccidioidomycosis, mucocutaneous, candidiasis, cheaper than triazoles	Oral absorption erratic, absorbed at low pH, CSF conc. poor, not used for serious systemic infections
Fluconazole	i.v., po	Good oral absorption, excellent CNS penetration	Used as supp. therapy of cryptococcal meningitis in HIV infected patients. Drug Interactions are rare DOC in oropharyngeal and mucocutaneous candidiasis
Itraconazole	po	Only imidazole acting against, Aspergillosis	Poor CNS penetration
Voriconazole	i.v., po	Good oral absorption, good activity against candida (including fluconazole resistant species) and aspergillosis	Can produce reversible visual abnormality

3. Echinocandins

Capsosfungin is the first approved drug in this new class of antifungal agents. It acts uniquely by inhibiting the synthesis of β -(1,3)-D-glucan, a vital component of cell wall. Capsosfungin acetate is an antifungal drug approved for the treatment of invasive aspergillosis in immunosuppressed adults who do not tolerate or do not respond to amphotericin B or itraconazole. Unlike azoles, it does not inhibit or induce CYP enzyme. It is metabolized by hydrolysis and N-acetylation.

Adverse effects: It includes fever, headache, abdominal pain, nausea, vomiting, diarrhoea, rash, itching, redness and pain around injection site may occur. Altered liver enzyme level and blood abnormalities may also occur.

Drug Interaction: Current evidence suggest that capsosfungin does not interfere with anti-HIV agents, however, level of capsosfungin may be lowered in patients taking efavirenz, nevirapine, rifampicin, dexamethasone, phenytoin or carbamazepine. Other agents are Anidulafungin and Micafungin.

4. Antimetabolite

Flucytosine (5-FC): It is a fluorinated cytosine analog, acts by inhibiting nucleic acid synthesis. It is actively transferred into susceptible cells by the enzyme cytosine permease. It is converted into active form, 5-fluorouracil, which acts as an antimetabolite and inhibit thymidylate synthetase and DNA synthesis.

Spectrum: It has narrow spectrum of activity. It is active against cryptococcus, torula, chromoblastomyces and few strains of candida. It is fungistatic in action.

Uses: It is not used as sole therapy except in chromoblastomycosis. Its role in therapy is primarily for use in combination with amphotericin B for treating cryptococcal meningitis.

Adverse effects: Bone marrow depression, loss of hair.

5. Nikkomycins

It is a new class of antifungal agents, act by inhibiting enzyme required for cell wall synthesis. They are currently undergoing clinical trials.

6. Topical Azoles

Several azoles are available for topical use. Commonly use drugs are clotrimazole and miconazole. Both are used for athlete's foot, otomycosis, oral, cutaneous and vaginal candidiasis, pityriasis versicolor and dermatophytic infections including tinea corporis, tinea pedis and tinea cruris.

Topical ketoconazole in the form of shampoo is useful in the treatment of seborrheic dermatitis and pityriasis versicolor.

Adverse effects: Ketoconazole is much less toxic than amphotericin B. It is less effective and more toxic than newer azoles.

1. Ketoconazole interferes with biosynthesis of adrenal and gonadal steroid hormones producing significant endocrine effects, such as gynaecomastia, infertility and menstrual irregularities. This effect is less with fluconazole, itraconazole and voriconazole.
2. Gastric upset is seen with all orally used azoles.
3. Hepatic impairment occurs with ketoconazole. There is asymptomatic increase in serum transaminases.

Drug Interactions:

1. H₂ antagonists, proton pump inhibitor and antacids decrease oral absorption of ketoconazole by reducing gastric acidity.
2. Hepatic enzyme inducers like rifampicin, phenobarbitone, carbamazepine and phenytoin induce ketoconazole metabolism and reduce its efficacy.
3. Ketoconazole inhibits cytochrome P450A4 and raises blood level of several drugs including warfarin, cyclosporine, sulfonylureas, phenytoin, diazepam, nifedipine and indinavir.
4. Dangerous interaction with terfenadine, astemizole and cisapride in the form of torsades de pointes has been noted.
5. Azoles and flucytosine have some additive effects.
6. Azoles and amphotericin combination is antagonistic as azoles decrease ergosterol biosynthesis.

Posaconazole and ravuconazole are under investigation.

7. Heterocyclic Benzofurans

Griseofulvin: It is an antibiotic derived from penicillium griseofulvum.

Mechanism of Action: Griseofulvin inhibits growth by inhibiting fungal cell mitosis caused by polymerization of cell microtubules, thereby disrupting mitotic spindle formation.

Pharmacokinetics: It is given orally. Microfined or ultrafined griseofulvin particles are absorbed much faster. Fat in the food improves absorption. Drug is particularly concentrated in the infected skin where it binds to keratin, protecting the skin from new infection.

It is only used for dermatophytosis caused by Epidermophyton, Trichophyton and Microsporum. It is given in dose of 125-250 mg QID with mCals for 3 weeks to 12 weeks. Griseofulvin binds to polymerized microtubules and inhibits fungal mitosis.

Adverse effects:

1. Hypersensitivity reactions: Urticaria, angioedema
2. Photosensitivity dermatitis
3. GI disorders: nausea, vomiting
4. Neurologic complications: headache, paraesthesia, altered sensorium.

8. Allylamine

It is a new class of antifungal agent. It includes terbinafine, naftifine, butenafine, amorolfine. It is fungicidal and relapse rate is low.

Mechanism of Action: It prevents ergosterol synthesis of fungal cell by inhibiting the fungal enzyme squalene epoxidase.

Uses:

1. Dermatophytosis of skin & nail.
2. Non-fumigatous aspergillous

It has synergistic potential with azoles against azole resistant candida species.

9. Other Topical Antifungal Agents

These are fungistatic and used for dermatophytosis. Benzoic acid is used in combination with salicylic acid (Whitfield ointment). Sodium thiosulfate is active against malassezia furfur, quinodochlor has weak antifungal and antibacterial activity and is also used for mycosis barbae, seborrhoeic dermatitis, infected eczema, furunculosis and pityriasis versicolor.

Most topical antifungal drugs require 4 weeks of treatment. Infections in some areas, particularly the spaces between toes, and nails may take up to 6 months for cure.

Adverse Reactions: Most topical antifungal are well tolerated. The most common adverse effects are localized irritation, redness, itching and burning sensations.

Antiviral Drugs

Viruses are the ultimate expression of parasitism. They are obligate intracellular parasites and can replicate only in living cells. Viruses consist of nucleic acid surrounded by protein. There are three closely related terms like virusoids, virioids and prion which need a special mention.

Virusoids are nucleic acid that needs helper viruses for their activation in living cell.

Virioids are naked nucleic acid that do not have protein envelope. They are mostly cyclical ds RNA parasites of plant viruses.

Prions are infectious proteinaceous particles that can integrate with the host cell and change their normal regulatory function e.g. Creutzfeldt Jakob disease, Gerstmann Straussler disease, Kuru

Viruses consist of a nucleic acid surrounded by a protein envelope. They are obligate intracellular parasites and thus depend upon host cell for their replication. Several steps are involved in the viral replication like:

- a) adsorption
- b) Penetration
- c) Uncoating
- d) Synthesis of regulatory proteins
- e) Assembly of viral particles and
- f) Finally release

Thus antiviral drugs can target any of these steps. The development of antiviral drugs poses several challenges, as the virus requires host cell enzymes, organelles for the synthesis of viral particles. Therefore, antiviral drugs must discriminate between normal cell function and viral function. In other words it must have a high degree of specificity.

Classification of Antiviral Drugs

I Anti Herpes Group:

Idoxuridine, Acyclovir, Famciclovir, Ganciclovir, Valacyclovir, Foscarnet, Fomivirsen

II. Antiretroviral drugs

- a) Nucleoside reverse transcriptase inhibitors (NRTIs), Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir
- b) Nucleotide inhibitors – Tenofovir
- c) Non-nucleoside reverse transcriptase inhibitors (NNRTIs) – Delaviridine, Nevirapine, Efavirenz
- d) Protease inhibitors – saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir
- e) Fusion inhibitors – Enfuvirtide

III. Antiinfluenzal

Amantadine, Rimantidine, Zanamivir, Oseltamivir

IV. Antihepatitis

Lamivudine, Adefovir, Ribavirin, Interferon

V. Other drugs

Plecoranil, Palivizumab, Imiquimod

I. Anti Herpes Group

1. Idoxuridine

Mechanism of Action: It is a thymidine analogue, so it competes with the thymidine and gets incorporated in DNA and faulty DNA is formed. The faulty DNA so formed produces ineffective viral particles.

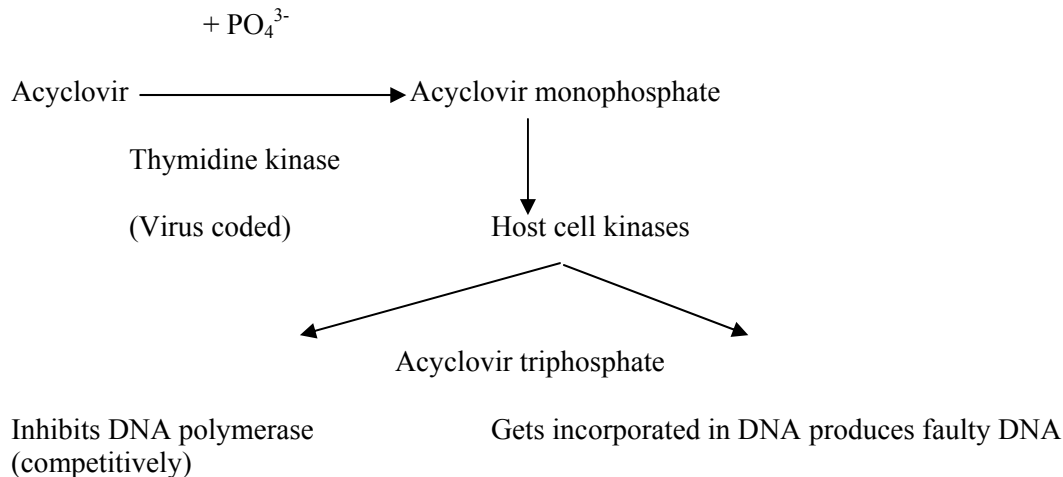
Uses: Today the only indication of Idoxuidine is H. simplex keratoconjunctivitis.

Side effects: Photophobia, irritation, edema of lids

Ridinox: 0.1% eye drops, 0.5% eye ointment.

2. Acyclovir

Mechanism of Action: it is a deoxyguanosine analogue and its active metabolite inhibits DNA synthesis



Resistance: Primarily due to mutations which reduces or modifies thymidine kinase activity.

Pharmacokinetics: Oral bioavailability is around 20%. It has wide volume of distribution including the CSF and is little protein bound. Plasma $t_{1/2}$ is 3 hr in patients with normal renal functions, prolonged in renal impairment. Acyclovir is excreted by kidneys mainly by glomerular filtration and Tubular secretion.

Uses:

- 1) Genital Herpes
- 2) Recurrent Herpes
- 3) Mucocutaneous H. Simplex
- 4) H.simplex encephalitis
- 5) Varicella Zoster
- 6) Neonatal HSV infections

Preparations:

Zoviran 200 mg tab. 250 mg/vial for IV inj.

Herpex 200 mg tab. 3% eye ointment

Occuvir 200, 400, 800 mg tab 3% eye ointment

Adverse effects: It is well tolerated orally. Nausea, vomiting, headache are infrequent. The M/c complication after i.v. infection is renal impairment, may need dose reduction, tremors, lethargy in few patients. It causes chromosomal breakage at high doses but none the less it can be administered in pregnant women.

3. Valacyclovir: Valacyclovir, the L-valyl ester of acyclovir and is converted to acyclovir. It has 3-5 times greater bioavailability than acyclovir. Adverse effects are same as acyclovir

except for Hemolytic uraemic syndrome, Thrombotic Thrombocytopenia in immunocompromised patients.

Uses:

- 1) Genital Herpes
- 2) Recurrent genital Herpes
- 3) Varicella Zoster

4. Fanciclovir: It is the diacetyl 6-deoxyester of guanosine analogue penciclovir. After oral administration it is converted to penciclovir. Penciclovir mechanism of action and spectrum is quite similar to acyclovir.

Mechanism of action: It is same as acyclovir except that it does not cause chain termination.

Mode of Resistance: Mutants having deficient thymidine kinase and is resistant to acyclovir.

Adverse effects: Well tolerated orally, nausea, vomiting, headache may occur. Testicular toxicity and mammary adenocarcinoma in experimental models.

5. Penciclovir: It is the active product of famciclovir. Rest of the profile is similar.

6. Ganciclovir: It is an analogue of acyclovir and is active against a wide variety of Herpes viruses particularly against CMV.

Mechanism of action: Same as acyclovir. Initial phosphorylation is done by UL97 in CMV infected cells. The most common mechanism for resistance are mutation in UL97 and less frequently UL54.

Pharmacokinetics: It can be administered by oral, i.v. and intraocular route. The bioavailability of the oral drug is poor (5-10%). It is eliminated mainly by the kidney.

Uses: CMV retinitis, CMV Prophylaxis

Adverse effects: M/c is myelosuppression, it may be additive with other myelosuppressive drugs, other is rash, fever, headache and seizures. Vitreous hemorrhage and retinal detachment may occur after intravitreal use.

7. Valganciclovir: It is a monoethyl ester prodrug this is hydrolysed to ganciclovir by intestinal and hepatic esterases. Oral bioavailability of the drug is 60%. Uses, side effects and other interactions are same as ganciclovir.

8. Cidofovir: It is a cytosine nucleotide analog that is active against wide variety of viruses. It is active against Herpes virus and other DNA viruses like papilloma, polyoma, adenovirus and poxviridae.

Mechanism of action: It does not require Phosphorylation by virus induced kinases, it is phosphorylated by host cell enzymes to cidofovir diphosphate. It inhibits DNA polymerase and causes premature termination of the DNA chain.

Pharmacokinetics: Cidofovir half life is 2.6 hr, Cidofovir diphosphate half life is 17-65 hr, another metabolite Cidofovir phosphocholine half life is 81 hrs. Elimination is by active renal tubular secretion.

Uses: CMV retinitis

Adverse effects: The M/c side effect is nephrotoxicity other side effects are uveitis, decreased IOP, neutropenia, metabolic acidosis, carcinogenic in rats (Mammary carcinoma).

9. Foscarnet: Foscarnet (phosphonoformic acid) is a pyrophosphate that act against herpes group of viruses.

Mechanism of action: It does not require phosphorylation like acyclovir but inhibits DNA polymerase at the pyrophosphate binding site. It also inhibits reverse transcriptase of HIV.

Pharmacokinetics: Its $t_{1/2}$ is 4.55 to 7 hrs, only available in IV form. Up to 30 % of the drug may be deposited in the bone for many months. Clearance of the drug is by kidney.

Uses: CMV retinitis

Side effects: Side effect is renal impairment. It binds divalent metal ions like Ca^{2+} , Mg^{2+} , K^+ , PO_4^{3-} . Saline hydration and slow infusion can protect against nephrotoxicity and electrolyte disturbance.

10. Fomivirsen: It is the first antisense oligonucleotide to be used in humans. This phosphorothiorate oligonucleotide inhibits CMV messenger RNA. It inhibits viral adsorption.

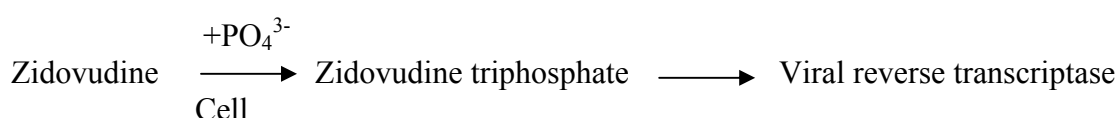
Uses: CMV retinitis

Side effects: Vitritis, iritis but it responds to glucocorticoids.

II Antiretroviral Drugs

a. Nucleoside Reverse transcriptase inhibitors (NRTI's)

1. Zidovudine (AZT): It is a thymidine analog which after phosphorylation in the cell inhibits viral reverse transcriptase.



Pharmacokinetics: Well absorbed orally. Oral bioavailability is 65%, plasma protein binding is 30% and CSF levels are 65% of that of plasma. The drug is cleared by hepatic conjugation, 15 – 20% of the drug is excreted unchanged in urine.

Adverse effects: Major complaints are anemia, neutropenia, GI disturbances, sleep disturbance, others are myopathy, lactic acidosis, hepatomegaly, convulsions and encephalopathy.

Interactions (1) Paracetamol increases AZT toxicity (2) Azoles inhibits its metabolism.

2. Didanosine: It is a synthetic analog of deoxyadenosine. Its mechanism of action is similar to AZT. At acidic pH it is inactivated because of the glycoside bond b/w sugar and basic moieties is cleaved. CSF concentration is 20% of the serum, plasma protein binding is 5%. It is eliminated mainly from the kidney.

Adverse effects: Pancreatitis, peripheral neuropathy, nausea, vomiting, headache, diarrhoea, hyperurecemia, retinal damage, optic neuritis.

3. Lamivudine: It is a cytosine analog and has the same mechanism of action as other (NRTI's).

Pharmacokinetics: High oral bioavailability 80%, plasma protein binding 36%, half life of elimination is 2.5 hrs and inside the cell is around 15 hrs. Excreted unchanged in urine.

Side effects: Headache, insomnia, fatigue, pancreatitis and neuropathy.

Uses: Chronic hepatitis B, AIDS

4. Stavudine: It is a thymidine analog and has very high bioavailability of 86%, plasma half life is 1.22 hrs and intracellular half life is 3.5 hrs. It is excreted by the kidney both by glomerular filtration and tubular secretion.

Side effects: M/c is sensory neuropathy which is reversible on discontinuation of therapy, others are pancreatitis, arthralgia and rise in serum aminotransferases.

5. Abcavir: It is a synthetic carbocyclic analogue of guanosine. It has high oral bioavailability 85%, PPB 50%. The drug is metabolised by alcohol dehydrogenase and glucuronosyl transferase. The metabolites are eliminated chiefly by the kidney.

Resistance occurs through 2 to 3 mutations in M184V L 74V.

Side effects: Hypersensitivity reactions have been reported in 4% of patients such as fever, rash, GI disturbance. These reactions are more commonly encountered in person with HLA-B-57.

b. Nucleotide inhibitors

Tenofovir: Tenofovir disoproxilfumarate that is converted to tenofovir. It inhibits viral reverse transcriptase causes premature chain termination.

Pharmacokinetics: Oral bioavailability is 25% and it is increased if it is taken with food. Maximum serum concentration is achieved after 1 hr. Elimination occurs partly by the kidney and liver.

Adverse effects: GI disturbances are the most common, others are osteomalacia, lactic acidosis, hepatomegaly.

c. Non Nucleoside Reverse transcriptase inhibitors (NNRTIs)

These class of drugs also blocks viral replication. They inhibit RNA dependent DNA polymerase. As with (NRTIs) phosphorylation is not required. There is no cross resistance between NNRTIs, NRTIs and protease inhibitors. Serious drug hypersensitivity has been seen in patients on NNRTIs.

1. Nevirapine: It has high oral bioavailability, 60% of the drug is protein bound and the drug is metabolized by CYP3A.

Adverse effect: Serious hypersensitivity reactions are seen in 15% of patients like Steven Johnson syndrome and toxic epidermal necrolysis (TEN), others are nausea, vomiting, headache, hepatitis.

2. Delaviridine: Its bioavailability is 85%, PPB is 98%. It is metabolized by CYP3A CYP2D6.

Side effects are same as nevirapine.

3. Efavirenz: Oral bioavailability is 45% to 65% and is increased when taken with food. It has long half life of 40-55 hrs, metabolized by CYP3A4 and CYP2B6.

Side effects: M/C are CNS effects like dizziness, drowsiness, insomnia, headache, confusion, amnesia, other are skin reactions like the other NNRTIS.

d. Protease inhibitors

This class of drugs inhibits the proteases/enzymes involved in the cleavage of poly protein. Because they act at a late step in viral replication, they are effective in both old and newly infected cells. Oral bioavailability of PI are variable. All are extensively metabolized by CYP3A4. The most frequently used are saquinavir, ritonavir, indinavir, nelfinavir, indinavir.

Adverse effects: Redistribution of body fat including central obesity and buffalo hump, breast enlargement, cushingoid appearance, increases triglycerides, LDL, insulin resistance, spontaneous bleeding in patients with hemophilia A or B.

e. Fusion inhibitor: Enfuvirtide.

It is also called T-20 that blocks entry into cell. It block the fusion of viral and cellular membrane. Resistance can occur but cross resistance is unusual. The drug is given by SC route. Eliminated $t_{1/2}$ is 3.8 hrs.

Adverse effects: M/c is local tissue damage, others are hypersensitivity reactions and eosinophilia.

III. Antiinfluenzal Drugs

1. Amantadine/Rimantidine: Amantadine and Rimantidine are primary amines which are active against influenza A virus. These drugs are used both in the prevention and treatment of Influenza A infection.

Mechanism of action: They inhibit with the uncoating of the virus after entrance into the cell. They inhibit M_2 ion channel which helps in uncoating.

Pharmacokinetics: Rimantidine is more active than amantadine, $t_{1/2}$ of amantadine is 12-18 hr whereas of rimantidine is 24/36 hrs. Amantadine is excreted unchanged in urine, rimantidine undergoes extensive metabolism by hydroxylation.

Adverse effects: The M/c are gastrointestinal like nausea, vomiting, other are CNS like dizziness, anxiety, difficulty in concentration. Amantadine is nephrotoxic and both are teratogenic.

2. Zanamivir / Oseltamivir: The neuraminidase inhibition have been recently approved for the treatment of influenza infection, unlike the earlier antiinfluenzal, they have actively against both A and B strains of influenza.

Mechanism of action: The enzyme neuraminidase cleaves terminal sialic acid residues thus destroying the receptors.

Pharmacokinetics: Oseltamivir is a pro-drug. It has oral bioavailability of 60%. Zanamivir has low oral bioavailability and is given by intranasal route.

Adverse effect: No serious adverse effects are seen except for mild GI disturbances by oseltamivir.

Uses:

- 1) Zanamivir for ≥ 7 years old treatment
- 2) Oseltamivir for ≥ 1 year old treatment
- 3) Oseltamivir for prophylaxis ≥ 13 year old

IV. Antihepatitis Drugs

1. Lamivudine: has been discussed earlier.

2. Adefovir: Adefovir is a nucleotide analogue of adenosine monophosphate. It has activity against HBV, HIV, HSV, CMV.

Mechanism of action: Adefovir is phosphorylated by cellular kinases to triphosphate which competitively inhibits HBV, DNA polymerase.

Pharmacokinetics: Its $t_{1/2}$ is 7.5 hr, oral bioavailability is 59% PPB is 7.5%. It is excreted mainly by the kidney both by glomerular filtration and tubular secretion.

Adverse effects: Nephrotoxicity is the only significant side effect. Others are lactic acidosis, hepatomegaly and steatosis. It should be cautiously administered with ibuprofen as the oral bioavailability is significantly increased.

3. Ribavarin: It is a synthetic nucleoside analogue which after phosphorylation to Ribavarin monophosphate inhibits the synthesis of guanine nucleotides. It can be given orally for chronic hepatitis C as an aerosol for influenzal and parainfluenzal and IV for lassa fever and Argentinian hemorrhagic fever.

Adverse effects: Reversible hematopoietic toxicity, bronchospasm, rash, conjunctival irritation.

4. Interferon: Interferon are proteins that exhibit wide variety of antiviral, immuno modulating and antiproliferative properties. There are 3 types of Interferon. These are produced by specific cell like : by all leucocytes, by fibroblast and by T cells. They can be given by IM, IV or SC route but not by oral route.

Pegylated IFN- in which the IFN is covalently linked with monomethoxy polyethylene glycol is currently being used for chronic hepatitis C infection. Currently synthetic interferon like IFN-2a (Refaferon) is used.

V. Other drugs

- 1. Pleconaril:** It is an investigational drug for picornavirus. It is presently under clinical trial.
- 2. Palivizumab:** It has been recently approved for the prevention of RSV infection. It is a humanised monoclonal antibody against F glycoprotein of RSV. Common side effect is liver toxicity.
- 3. Imiquimod:** It is used for the treatment of genital warts. Skin rashes are common side effect.