

# PHARMACOLOGY

## Antimicrobial Agents: Antifungal & Antiviral Drugs

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## Antifungal Drugs

Fungal infections seen in human can be :

- a) **Superficial fungal infections** of skin, hair, nail, mucous membrane. These are due to:
  - i) Dermatomycoses which causes ring worm or tinea infestation. These dermatophytes are Epidermophyton, Microsporum and Trichophyton, and are classified according to their site of infestation e.g.; Tinea Capitis (Scalp infection), Tinea corporis (body infection), Tinea barbae (infection in the beard), Tinea cruris (infection in groin), Tinea pedis (also called athlete's foot), Tinea manum (infection in hands) and Tinea unguium (infection in the hairs).
  - ii) Candidiasis (or often referred to as thrush) or infection caused by Candida spp affects chiefly the skin, oropharynx and vagina. Seen commonly in immune compromised patients e.g., in patients of AIDS, or with HIV infections, following the use of AMA's over prolonged periods, and in patients of diabetes mellitus.
  - iii) Pityrosporum orbiculare causing Ptyriasis versicolor or Tinea versicolor. This is characterized by hyperpigmented macules, which are distinct with fine scaling. Commonly seen on the face, proximal extremities and in the oropharynx.
  - iv) Sporothrix infection of cutaneous region seen as granulomatous lesion. These spread to distant region via the lymphatic system.
- b) **Systemic fungal infection** affecting deeper tissues and organs. These include the respiratory tract infection with candidiasis, cryptococcal meningitis and endocarditis, histoplasmosis infection common in the respiratory tract, coccidiomycosis, paracoccidiomycosis, pneumocystis carinii pneumonia all affecting the respiratory system.

There has been an increase in the incidence of fungal infection during the past few decades. This increase may be attributed to :

- 1) An excessive or irrational use of AMA, which alter the pattern of the commensals in the body, leading to super-infection with the fungal infections, some of which are normally present as commensals.
- 2) A decrease in host defense mechanism as seen in patients of AIDS or patients on cancer chemotherapy, leading to iatrogenic fungal infections.
- 3) An increase in the use of immunosuppressant drugs also causes iatrogenic fungal infections.

**The antifungal agents include :**

1. Antibiotics like a) polyenes, Amphotericin B, Nystatin, Hamycin, Natamycin and  
b) Heterocyclic Benzofurans like Griseofulvin
2. Antimetabolites: flucytosine
3. Azoles: Imidazoles, Clotrimazole, Miconazole, Econazole, Ketoconazole, Triazoles, Fluconazole iatraconazole.
4. Topical agents : Tolnaftate, Benzoic acid, undecylenic acid, Quiniodochlor, Buclosamide, Haloprogin, Cyclopiroxolamine, Sodium thiosulphate.

## Drugs used in Systemic fungal infection

### Amphotericin B

It is obtained from Streptomyces nodosus

**Antifungal activity :** The antifungal activity of amphotericin B includes *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Candida albicans*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Aspergillus*, *Sporothrix*

**Mechanism of action :** It acts as a fungistatic drug in low concentration and as a fungicidal agent in high concentration.

The polyene AMA binds with high affinity to ergosterol present in the fungal membrane. This binding leads to alteration in the cell permeability where micropores are formed through which macromolecule and ions leak out of the cell leading to cellular death.

Mammalian cell membrane has cholesterol (which resembles ergosterol) to which the polyene AMA binds with much less affinity. This accounts for the drug toxicity seen. Similarly bacterial cell wall lacks ergosterol and hence the polyenes AMA do not have activity against the bacteria.

**Resistance:** Resistance to Amphotericin B is associated with alteration in the cell wall ergosterols. However, these alterations lead to a decrease in the virulence of the organism.

**Pharmacokinetics:** Amphotericin B is not absorbed orally. Hence it is indicated for intestinal candidiasis. For systemic fungal infection Amphotericin B is administered intravenously as slow infusion. This is also available as liposomal preparation and as a lipid complex. These preparations selectively transfer the drug to the ergosterol in the fungal cell wall thereby decreasing the toxicity to the mammalian cells. This drug has a long  $t_{1/2}$  of 15 days and is excreted slowly in the bile and urine.

#### **Clinical uses :**

- i) Amphotericin B is used in most systemic infections including histoplasmosis, invasive aspergillosis, blastomycosis and in fungal infection in immune compromised patients or patients with AIDS. However, Ketoconazole is preferred to amphotericin B because of its lower toxicity.
- ii) Polyene antibiotics can also be used topically as creams or as 3% lotion; as ointment to treat cutaneous and oropharyngeal candidiasis. Eye drops are used for mycotic infections of the eye. It is also used topically for vaginal and otomycosis.
- iii) Amphotericin B is used as a reserve drug for mucocutaneous Leishmaniasis and in resistant cases of Kala Azar. (This is not a fungal infection)

**Dose :** 0.5 – 0.6 mg/kg/day as slow I.V. infusion in glucose up to a total dose of 2 gm. For systemic fungal infection 250 mg/kg daily; if tolerated, the dose is increased to 1 mg/kg over 4-6 hrs. It is important to administer a test dose in all patients.

**Adverse effects:** Amphotericin B is a toxic drug causing impairment of both hepatic and renal function. Hepatic function impairment can lead to the development of jaundice and renal toxicity is manifested as tubular necrosis, azotemia and irreversible renal damage. These adverse effects are dose dependent. Liposomal dosage form of amphotericin B has lesser incidence of renal toxicity.

Intravenous administration of amphotericin B can cause chills, fever, vomiting, headache, and thrombophlebitis in the injected vein. Severe reaction may be treated with Paracetamol, an antihistamine and corticosteroids. Topically administered amphotericin B is usually well tolerated except for an occasional yellow discoloration of the skin.

### **Flucytosine**

Flucytosine is also called 5-fluorocytosine or 5-FC. This is a pyrimidine antimetabolite and is structurally similar to the anticancer drug 5-fluorouracil. 5-FC however, does not have any anticancer activity.

**Mechanism of action :** 5-FC is taken up by the fungal cells where it is converted to 5-fluorouracil by the fungal enzyme cytosine deaminase. 5-Fluorouracil is further converted to 5-fluorodeoxyuridine monophosphate. This compound is a competitive inhibitor of thymidylate synthetase. Thus ultimately the synthesis of DNA is inhibited. 5-FC has a greater selectivity of action against the fungal cells, as the mammalian cells are virtually devoid of cytosine deaminase.

**Pharmacokinetics :** Flucytosine is well absorbed orally and is widely distributed in the body tissue including the CSF. It has a plasma  $t_{1/2}$  of 3-6 hrs. It is excreted unchanged in the urine and hence to avoid accumulation of the drug in the tissues, the dose of 5-FC needs to be adjusted in patients with renal impairment.

**Clinical use :** It has been observed that when 5-FC is used alone, resistance develops rapidly. Hence it is advisable to give 5-FC along with amphotericin B. It is useful in disseminated candidiasis, aspergillosis, cryptococcosis when it is used in combination with amphotericin B. As this is synergistic effect, amphotericin B may be given in lower dose (see above for dose of amphotericin B).

### **Adverse effects :**

- 5-FC is relatively a non-toxic drug.
- Nausea, vomiting, epigastric distress and skin rash may be seen. In addition, rarely 5-FC may cause bone marrow suppression leading to thrombocytopenia and leucopenia. Hence, 5-FC should be avoided in patients with terminal HIV infection.
- In addition, as 5-FC is administered along with amphotericin B, a nephrotoxic drug, close monitoring of patient with renal impairment is imperative. 5-FC has a narrow therapeutic window and hence it is important to keep the dose on the lower side, as higher doses of 5-FC may lead to a greater incidence of toxicity.

### **Griseofulvin**

Griseofulvin is the first orally effective antifungal agent to be identified. The source of griseofulvin is *Penicillium griseofulvum*.

**Mechanism of action :** Griseofulvin interferes with the mitosis of the actively multiplying fungi. By combining with the microtubules of the actively dividing fungal cells, the drug disrupts the mitotic spindle and arrests the fungal mitosis in the metaphase. In addition, griseofulvin binds to the newly synthesized keratin, especially around the tinea-infected cells. This keratin now

becomes resistant to fungal invasion. Therefore, the treatment of infection will depend on the site of infection, the cellular turnover and thickness of the keratin.

**Pharmacokinetics :** The absorption of griseofulvin from the GIT is irregular. Griseofulvin is ineffective when applied locally. Presence of fatty food in the GIT increases its absorption. The plasma  $t_{1/2}$  is 24 hrs. However, as it gets bound to the Keratin, it is retained for weeks in the skin.

**Clinical use :** It is administered systemically to treat dermatophytes including Microsporum, Trichophyton and Epidermophyton. As mentioned above, duration of treatment depends on the site of fungal infection e.g.; for the treatment of Tinea corporis treatment should be for 2-4 weeks; for Tinea capitis (scalp) it is 4-6 weeks; infections of the nail, the treatment is for 3-6 months. It is important to continue the antifungal treatment till both the visual and microscopic evidence is negative.

**Dose :** 125 – 250 mg 4 times a day orally.

**Adverse effects :** Generally the incidence of toxicity with griseofulvin is low. Apart from GI upset, griseofulvin can cause headache, photophobia, peripheral neuritis and rashes.

### Azoles

Azoles are synthetic and semi-synthetic compounds. They have a broad spectrum of activity. Azoles can be classified as :

1. Imidazole group : these can be
  - a. Topical agents: Clotrimazole, Econazole miconazole, butaconazole,
  - b. Systemic agent : Ketoconazole
2. Triazole group:
  - a) Topical agent: teraconazole, itraconazole,
  - b) Systemic agents: fluconazole, itraconazole, voriconazole

Triazoles show a greater selectivity to the fungi; these are distributed into the CSF and have fewer side effects.

**Spectrum of Activity :** Azoles are effective against dermatophytes, candida, anaerobic bacteria and gram +ve bacteria like S. aureus, S. Fecalis and Bacillus fragilis .

**Mechanism of action :** Azoles inhibit the ergosterol synthesis in the fungi. This they do by inhibiting the fungal cytochrome p450 dependent 14  $\alpha$  demethylase enzyme. This enzyme is required for the conversion of lanosterol to ergosterol. This results in damage to the fungal cell membrane.

**Clotrimazole, Econazole :** They are used locally.

**Spectrum of activity :** Tinea infection, athlete's foot, otomycosis, candidiasis (oral cutaneous and vaginal) skin infection caused by cornyobacteria. It is well tolerated. Local irritation is observed in few patients. As the drug is not absorbed there is no systemic toxicity following its local application.

**Miconazole :** Topical antifungal drug.

**Spectrum of activity:** Tinea pityriasis versicolor, otomycosis candidiasis (cutaneous and vulvovaginal) and Onchomycosis. Systemic use is restricted for the treatment of *Petridillidum boydii* resistant to amphotericin B.

**Adverse effects :** Topical application of Miconazole may result in mild irritation. There is a greater incidence of vaginal irritation which may result in lower abdominal cramps. Systemic administration may result in phlebitis, anemia, chills, fever, nausea, itching and rashes.

**Ketoconazole:** Ketoconazole is the first orally effective azole derivative. High incidence of adverse effects and relapse of fungal infection limits its use

**Pharmacokinetics :** Ketoconazole is well absorbed orally. It has a greater bioavailability in an acidic pH. Hence in patients taking concomitantly antacids, H<sub>2</sub> receptors blockers, or proton pump inhibitors, and patients of achlorohydria, there will be decrease in the bioavailability of ketoconazole. The drug is distributed into all peripheral body compartments; however, it has poor penetration into the CNS. Ketoconazole has a  $t_{1/2}$  is about 8 hrs.

**Clinical Uses :** The use of Ketoconazole is restricted because of its toxicity and has now been replaced by newer triazoles anti fungal agents.

- i) Oropharyngeal candidiasis in patients of AIDS. Ketoconazole is administered orally.
- ii) Histoplasmosis, Sporotrichosis and paracoccidioidomycosis Ketoconazole serves as an alternative to itraconazole  
Dose : 200 – 400 mg once daily  
Children > 2 years the dose is 3.3 – 6.6 mg/kg/day OD
- iii) Patient of advanced prostatic cancer, with metastasis and bone pain Ketoconazole acts by inhibiting testosterone
- iv) Hyperadrenal corticism ketoconazole acts by inhibiting cortisol synthesis.

**Adverse effects:** Nausea, vomiting anorexia caused following the administration of ketoconazole can be minimized by administering the along with food. Pruritis, giddiness, headache rash, photophobia, paraesthesia are some of its other adverse effects.

Ketoconazole impairs the synthesis of testosterone and estradiol. This may lead to gynecomastia, loss of hair and libido in males and menstrual irregularities in females. It also cause a decrease in serum hydrocortisone Ketoconazole is also known to alter the hepatic enzymes albeit transiently.

**Fluconazole :** Fluconazole is more water soluble than Ketoconazole. It is administered orally or I.V. Fluconazole is distributed in various body fluids like CSF, vaginal tissue, ocular fluid, saliva and nails. It has a  $t_{1/2}$  of 24 – 35 hrs.

**Clinical Uses :** Fluconazole is used in the treatment of :

- i) Candidiasis seen in the Oral cavity, and in Pharyngeal vaginal, mucocutaneous and systemic candidiasis
- ii) Urinary Tract Infection due to candida, Fluconazole is administered for 3 days

iii) In meningeal cryptococcus infections, meningeal coccidiomycosis fluconazole is administered

**Dose :** 400 mg on first day followed by a maintenance dose of 200 – 400 mg once daily

**For Prophylaxis** the dose of fluconazole is 5 -100 mg O.D.

In children > 1 year fluconazole is given in a dose of 3-6 mg/kg/day

**Iatroconazole:** Iatroconazole is orally effective anti fungal agent. It is metabolized in the liver and has a  $t_{1/2}$  of 30-35 hrs

**Mechanism of action:** This azole derivative has a greater specificity of action on the fungal  $14\alpha$  demethylase, an enzyme required for the conversion of lanosterol to ergosterol. This results in damage to the fungal cell membrane.

**Clinical uses:**

- i) Chronic pulmonary or disseminated histoplasmosis in patients of AIDS
- ii) Non meningeal blastomycosis
- iii) Invasive aspergillosis
- iv) Candidiasis, oropharyngeal and cutaneous
- v) Tinea infection : Capitis or Corporis, unguium

**Dose** of itraconazole is 200 – 400 mg O.D.

**Adverse Effects:** Itraconazole is generally **well** tolerated. Some of adverse effects that may be seen in patients treated with itraconazole include headache, nausea, epigastric distress, dose dependent hypokalemia, hypertension and edema. Hepatic transaminases may be transiently elevated

**Nystatin**

Nystatin is chemically similar to amphotericin B.

**Mechanism of action :** The action of Nystatin is similar to amphotericin B. It inhibits the ergosterol synthesis in the fungal cell wall.

**Pharmacokinetics :** Nystatin is not absorbed from GIT, skin or mucous membrane. It is very toxic for systemic use and hence is primarily used topically.

**Clinical Uses :**

- i) Candida infections. To suppress superficial candida infection
- ii) Monilial diarrhea. Nystatin is the drug of choice.

**Adverse effects :** Bitter and foul taste when used orally.

A number of anti fungal agents are used only for topical infections. These are given in the following table:

| S.N. | Name                                                       | Use                                                                                                                                                                                                                                                                  | Organism                  | Remarks                                                                                           |
|------|------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|---------------------------------------------------------------------------------------------------|
| 1.   | Natamycin                                                  | Ocular keratitis<br>1.Oral,and vaginal candidiasis<br>2.Trichomonas vaginitis                                                                                                                                                                                        | Fusarium<br>Cephalosporin |                                                                                                   |
| 2.   | Hamycin                                                    | 1.Oral and Cutaneous, Candidiasis<br>2.Trichomonas vaginitis<br>3.Otomycosis                                                                                                                                                                                         | Candida<br>aspergillus    |                                                                                                   |
| 3.   | Tolnaftate                                                 | 1. Dermatophytosis<br>2. Tinea                                                                                                                                                                                                                                       |                           | Does not penetrate hyperkeratinised lesion. Relapses common. Important to treat for long duration |
|      | Benzoic acid (fungistatic)                                 | Topical fungal infection like Tineases                                                                                                                                                                                                                               |                           | Used in combinations with salicylic acid on hyper keratinised lesions                             |
|      | Undecylenic acid (weak fungistatic)                        | Tinea pedis<br>nappy rash<br>Tinea cruris                                                                                                                                                                                                                            |                           | Used with Zinc salts                                                                              |
|      | Quinidochlor (weak antifungal and antibacterial activity ) | <ul style="list-style-type: none"> <li>• Dermatophytosis</li> <li>• Mycosis barbae</li> <li>• Seborrhoeic dermatitis</li> <li>• Furunculosis</li> <li>• Pityriasis versicolor</li> <li>• Monilial and trichomonas vaginitis</li> <li>• Luminol amoebicide</li> </ul> |                           |                                                                                                   |

Other topical antifungal agents are elioquinol, Quinidochlor, Sodium thiosulfate, Cyclopirox olamine, Haloprogin.

### Antiviral Drugs

Viruses are obligate parasites, entirely dependent on the host for their growth and reproduction. For this, the virus uses the mechanism involved in protein synthesis of the host cells whereby the host RNA and DNA are modified towards the propagation of the viruses. Hence, it is difficult to have chemical agents directed specifically targeted at the virus.

The basic structure of a virus consists of the core RNA or DNA which constitutes the genome which in turn is surrounded by a protein shell called the capsid. This may be surrounded by a

lipoprotein envelope. The last mentioned envelope is not present in all the viruses. Hence, these viruses are either a DNA virus or a RNA virus. The whole infective particle is called a virion.

**Table 1 List of some common pathogenic virus**

| S.N.                  | Name                     | Clinical conditions                                         |
|-----------------------|--------------------------|-------------------------------------------------------------|
| <b>I. DNA Virus :</b> |                          |                                                             |
| 1                     | Adenovirus               | Upper respiratory tract infections and eye infections       |
| 2.                    | Herpes Simplex Type 1    | Oral, genital, Herpes, viral encephalitis, herpes keratitis |
| 3.                    | Herpes simplex Type 2    | Genital herpes                                              |
| 4.                    | Varicella Zoster         | Chicken pox, herpes zoster (shingles)                       |
| 5.                    | Pox virus                | Small pox                                                   |
| 5.                    | Papilloma virus          | Warts                                                       |
| 6.                    | Cytomegalo virus (CMV)   | Infectious mono nucleosis                                   |
| 7.                    | Epstein Barr virus (EBV) | Infectious mono nucleosis, cancer                           |
| <b>II. RNA Virus</b>  |                          |                                                             |
|                       | Orthomyxo virus          | Influenza                                                   |
|                       | Paramyxo viruses         | Measles, mumps                                              |
|                       | Picornavirus             | Polio meningitis, upper respiratory tract infections        |
|                       | Cornavirus               | Upper respiratory tract infections                          |
|                       | Rabdo viruses            | Rabies                                                      |
|                       | Retroviruses             | AIDS, Leukemia                                              |
|                       | Toga virus               | Rubella, German measles                                     |

**Viral replication :** The Virus attaches itself to the host cell and penetrates the cell membrane by pinocytotic mechanism whereby the virus first uncoats and subsequently transfers the viral DNA in to the host cell.

In DNA virus the nucleic acid gets incorporated into the host nucleus. The host cell protein synthesis translates the viral DNA into mRNA and subsequently to viral specific proteins. The virion thus formed is released by a process of budding or by the lysis of the host cell.

In the case of RNA virus, the nucleic acid synthesizes its own mRNA or the virus itself acts as an mRNA. The host cell then replicates the mRNA with the help of a reverse transcriptase enzyme present in the virus which helps in the synthesis of the complementary DNA. This newly formed DNA is incorporated into the host cell. Virions formed are released by a process of budding. Neuraminidase an enzyme present in the virus plays an important role in the release of progeny virus. It is only the polio virus that lyses the cell while being released from the host cells thus damaging the host cells completely.

Vaccines can be used to control some of the non retroviral infections. These vaccines act by stimulating the host defense mechanism and are useful for the prevention of measles, small pox

(now totally eradicated) rubella, mumps, poliomyelitis, hepatitis B. Vaccine provides active immunity to the patient.

Human immunoglobulins may be used to provide passive immunity.

**Classification:** Antiviral drugs may be classified according to their therapeutic use as: Antiretroviral agent, Antiherpes agent, immuno-modulators and antiretroviral agents.

1. Antiherpes virus agents are primarily those drugs that are DNA polymerase inhibitors and may be further classified as :
  - Purine analogs like acyclovir, valacyclovir, ganciclovir, famciclovir, penciclovir, vidarabine
  - Pyrimidine analogs : Idoxuridine, Trifluridine
  - Non nucleosides analog : Foscarnet
2. Other antiviral agents :
  - mRNA synthesis Inhibitors: Ribavirin,
  - Inhibitors of viral penetration and uncoding: Amantadine, Rimantadine
3. Immunomodulators: Immunoglobulin, Interferons
4. Antiretroviral agents

### 1. Antiherpese virus agents

#### a. DNA Polymerase inhibitors: Acyclovir, Valacyclovir :

Acyclovir is a synthetic guanosine (purine) analog. Valacyclovir is rapidly and almost completely converted to acyclovir after oral administration.

**Mechanism of action :** The viral thymidine kinase converts acyclovir to its monophosphate. This monophosphate is converted to diphosphate and finally to the active form of acyclovir triphosphate by the host cell enzyme guanidylate kinase. The acyclovir triphosphate inhibits viral DNA polymerase and prevents the elongation of the viral DNA chain, thus preventing the viral replication.

The acyclovir triphosphate has 10-30 times greater selectivity for the DNA polymerase of the virus. Also the non infected host cells are unable to convert the acyclovir to its active triphosphate metabolism. Thus acyclovir has greater selectivity of action against the invading viruses.

**Resistance :** Resistance to acyclovir includes decrease activity of thymidine kinase activity in the viral cells, alteration in the substrate specificity of viral thymidine kinase or DNA developing resistance to acyclovir binding.

**Pharmacokinetics:** Oral bioavailability of acyclovir is only 15-30%. The  $t_{1/2}$  in normal adult patients is 2.5 hours, where as in neonates the  $t_{1/2}$  is 4 hours. The  $t_{1/2}$  may be increased in patients with renal dysfunction.

**Clinical Uses :** Acyclovir and valacyclovir may be used in the following conditions:

- i) Herpes Simplex Virus 1 (HSV-1) which are responsible for herpes labialis (cold sores), herpes oesophagitis, herpes keratitis, herpes encephalitis.
- ii) Herpes Simplex virus – 2 (HSV-2) responsible for genital herpes.
- iii) Varicella Zoster virus which cause chicken pox and shingles.
- iv) Epstein Barr virus (EBV), acyclovir has weak effect against infectious mononucleosis.
- v) Cytomegalovirus (CMV) responsible for causing pneumonia, gastroenteritis, and encephalitis in immune compromised patients.

Acyclovir ointment for local applications is available for treatment of early genital herpes and for herpes kerato conjunctivitis.

**Adverse effects :** There are no serious effects with either oral or topical use of acyclovir. Frequent side effects following chronic use include, nausea vomiting vertigo, headache. Intravenous use may lead to local reaction at the site of injection and may cause pain, inflammation and phlebitis.

Rarely mild hypotension, increased blood levels of urea and creatinine may be observed, which may progress to renal dysfunction and acute renal failure. Adequate hydration and slow infusion of the drug could minimize the renal toxicity.

Caution must be used while using other drugs known to produce renal dysfunction as this may lead to an increase in the risk for development of renal toxicity.

**b. Ganciclovir :** Ganciclovir is an analogue of acyclovir. As seen for acyclovir ganciclovir is converted intracellularly to ganciclovir triphosphate. This is more active than the corresponding acyclovir.

**Pharmacokinetics:** Ganciclovir has poor oral bioavailability and hence has to be administered I.V. It has a  $t_{1/2}$  of 3-4 hours.

**Clinical Use :**

- i. CMV retinitis especially in immuno-compromised patients.  
Dose : 5 mg / kg 12 hourly for 10-21 days.
- ii. Acyclovir resistant HSV
- iii. CMV in organ transplant patients and immuno-compromised patients.  
Dose 5 mg / kg for 100 -120 post transplant days. Dose adjustment is required in patients with renal dysfunction.

**Adverse effects:** Most serious adverse effect is bone marrow suppression which may reverse on stopping in drug. Other adverse effects include anemia, rash fever, hepatic abnormalities, phlebitis, headache, behavioral changes, psychosis convulsions and coma. Animal studies have shown ganciclovir to be teratogenic and carcinogenic. Studies have also shown that ganciclovir decrease the sperm production.

**c. Valganciclovir :** Rapidly and completely converted to acyclovir after oral administration. Valganciclovir is a pro drug of ganciclovir

**d. Famciclovir :** is a pro drug of Penciclovir

**e. Penciclovir:** It is a guanine nucleoside analogue, structurally similar to acyclovir. Penciclovir is competitive inhibitor of viral DNA polymerase. It is less efficacious than acyclovir and does not cause the termination of DNA chain elongation. Penciclovir persists inside infected cell for long period of time. It has a  $t_{1/2}$  of 8-20 hrs.

**Clinical Uses :**

i) HSV -1 and HSV -2 infections. Acute case of less than 3 days duration especially in immune compromised patients.

**Dose :** 500 mg three times a day for 7 days.

ii) Herpes labialis – Topical penciclovir is used.

**Adverse effects :** Penciclovir is generally well tolerated. It can cause GIT disturbances, fatigue, and headache.

**f. Vidarabine :**

It is adenine nucleoside analogue.

**Mechanism of action :** It is phosphorylated in the cell and inhibits the viral DNA synthesis in a manner similar to acyclovir. Vidarabine has higher affinity for the DNA polymerase enzyme. It also inhibits the DNA chain prolongation of the virus.

**Resistance:** Resistance to vidarabine develops as a result of mutation of the viral DNA polymerase enzyme.

**Pharmacokinetics :** Poorly absorbed from GIT and hence it should be used either parentally or topically. The  $t_{1/2}$  of vidarabine is 3.5 hours.

**Clinical Uses :**

i) HSV kerato-conjunctivitis as a 3% topical ointment (concomitant use of steroids should be avoided).

ii) Herpes simplex encephalitis. 15 mg / kg/ day. Large volume of the solution is required as it is only slightly soluble in water.

iii) Neonatal Herpes Zoster or Varicella in immuno-compromised patients.

**g. Idoxuridine :**Idoxuridine is structurally similar to thymidine, a pyrimidine base

**Mechanism of action:** Like acyclovir it is phosphorylated and incorporated into the DNA of the host cell and virus. This causes a faulty transcription and thereby inhibits the DNA synthesis. Idoxuridine also causes breakage of the viral chromosome and altered synthesis of viral proteins. The incorporation into host cell DNA leads to toxicity with this drugs and hence Idoxuridine is primarily used only topically.

**Clinical Use :**

- i) HSV keratitis 0.5% ophthalmic ointment and 0.1% solution administered every hourly during the day and 2 hourly at night.

**Adverse effects:** Common adverse effects seen with idoxuridine are pain, purities, corneal clouding, inflammation or edema of eye or eyelids, photophobia and lacrimation. Teratogenic effects have been observed in laboratory animals.

**Trifluridine :** is a derivative of idoxuridine and hence has similar mechanism of action.

**Clinical Uses:** HSV 1 and HSV 2 infections causing kerato-conjunctivitis. It is also used in patients with recurrent keratitis unresponsive to idoxuridine or vidarabine.

**Dose** 1% ophthalmic solution, hourly during waking hours. Dosage is reduced when the cornea starts to heal.

**Adverse effects :** Irritation, palpebral edema, hyperemia, burning and an increase in intraocular pressure are some of the adverse effects seen with trifluridine.

**h. Foscarnet :** Foscarnet is an inorganic pyrophosphate analogue of tri-sodium phosphonoformate.

**Mechanism of action:** Foscarnet binds non-competitively to pyrophosphate binding site of the herpes virus DNA polymerase enzyme and the HIV reverse transcription enzyme. It is 100 times more selective to the DNA polymerase of the herpes virus than for the mammalian enzyme.

**Resistance :** Resistance to Foscarnet occurs as a result of mutation of viral DNA polymerase.

**Pharmacokinetics :** Because of its poor bioavailability Foscarnet is administered I.V. It accumulates in the aqueous humor, bones and is eliminated unchanged in the urine.

**Clinical Uses :**

- i) CMV retinitis in patients of AIDS.
- ii) Acyclovir resistant HSV-2 infection associated with AIDS. In this case combination of Foscarnet with Zidovudine is beneficial.

**Adverse effects :** Major adverse effect with Foscarnet is nephrotoxicity manifested as raised serum creatinine, electrolyte disturbance, hypocalcaemia, hypomagnesaemia, and hypokalaemia. Saline loading may reduce the risk of nephrotoxicity. CNS toxicity includes headache, tremors, seizures, hallucinations. Sometimes fever nausea and vomiting may also occur.

**2. Other Antiviral Drugs**

**a. Ribavirin:** Ribavirin an mRNA synthesis inhibitors is a synthetic analogue of the purine base guanosine.

**Spectrum of activity:** It is active against both RNA and DNA virus and hence may be called a broad spectrum antiviral drug. Activity includes myxoviruses, paramyxoviruses, adenoviruses, arenavirus.

**Mechanism of action :** Ribavirin is converted by the host cell to its monophosphate, diphosphate and triphosphate derivatives. The monophosphate inhibits inosine monophosphate dehydrogenase thereby inhibiting the syntheses of guanine nucleotide synthesis. Ribavirin triphosphate inhibits viral mRNA transcriptase activity to block viral RNA polymerase. It also competes with GTP and ATP for substrate site. Hence Ribavirin has activity at multiple sites and thereby inhibits viral replication.

**Resistance:** Resistance to ribavirin is uncommon as it also delays the mutation rate of RNA virus.

**Pharmacokinetics :** Oral absorption is rapid and the bioavailability is 45-65%. It can be administered parenterally and also as an aerosol. It shows a biphasic elimination kinetics. The initial half life is 1-2 hours but the second half life is 20 – 36 hrs. The drug accumulates in the RBC with a half life of 40 days.

**Clinical Uses :**

- i) Respiratory syncytial virus which causes pneumonia and bronchiolitis. Ribavirin is administered as an aerosol.
- ii) Lassa fever (arena virus infection)
- iii) Influenza A and Influenza B virus
- iv) Hepatitis C viral infection : Ribavirin is given along with interferon.

Ribavirin antagonizes the actions of Zidovudine when administered concomitantly in patients with HIV infection.

**Adverse effects :** Ribavirin causes anemia which may be due to extra-vascular hemolysis and bone marrow suppression; Uric acid and bilirubin levels may increase. Ribavirin may cause hypotension and deterioration of cardiac functions. Long term use may cause CNS and GIT symptoms. In experimental animals it has been found to have teratogenic mutagenic and carcinogenic effects.

**b. Inhibitors of viral un-coating and viral penetration :**

**Amantadine and Rimantadine :** Amantadine is a synthetic tricyclic amine and is not related to any other antiviral drugs.

Rimantadine is an analogue of amantadine and has similar mechanism of action and other characteristics like amantadine.

**Mechanism of action :** Amantadine acts by interfering with the action of M<sub>2</sub> protein. This M<sub>2</sub> protein acts as an ion channel in the influenza A virus. As a consequence of this acid mediated dissociation of ribonucleoprotein, the core segment is inhibited; thereby inhibiting an early stage of viral replication.

In addition M<sub>2</sub> protein inhibition alters the conformation of haemagglutinin during its intracellular transport leading to a block in the viral assembly. Influenza B virus contains a protein different than the M<sub>2</sub> protein seen in Influenza A virus.

**Resistance:** Resistance to amantadine is seen when there is a point mutation in the M<sub>2</sub> protein.

**Pharmacokinetics :** Both amantadine and rimantadine is absorbed from the GIT; where as amantadine is excreted unchanged in the urine, Rimantadine is extensively metabolized and only a small part is excreted unchanged. The t<sub>1/2</sub> of amantadine is 16 hours in young adults and 30 hours in the elderly. The t<sub>1/2</sub> of rimantadine is 30 hours in young adults and 35 hours in the elderly.

**Clinical Uses :**

i) . Influenza A virus infection. Amantadine is used both for the prevention and treatment of this infection.

**Dose :** 100 mg BD or 200 mg daily as a single dose.

ii) Parkinson's disease: this use of amantadine is unrelated to its antiviral activity.

**Adverse effects :** Adverse effects are chiefly related to GIT and CNS. Loss of appetite, nausea, insomnia, difficulty in concentration is often observed. Patients suffering from psychiatric disorder or epilepsy and treated with amantadine or its analogue should be monitored closely. Amantadine should not be given to pregnant and nursing women.

### **3. Immunomodulators**

Immunomodulators are drug which modulates the immune response against the invading virus or activates the immune mechanism to target the virus.

#### **a. Interferons (IFN)**

Interferons are produced endogenously as a protective response to the invading virus, bacteria, endotoxins and other intracellular organism. These interferons are glycoproteins and act as immunomodulators, antiviral and as anti-proliferative agents. Interferons do not cure viral infection. They are present at the site of infection even before antibody production starts. The amount of interferon present correlates with the virus. They primarily act as host defense mechanism and have a role in preventing viral infection. They are however unable to cure viral infections.

There are 3 major types of interferons present in the body.

- IFN  $\alpha$  is synthesized primarily by human leucocytes and has antiviral effect.
- IFN  $\beta$  is synthesized primarily by human fibroblasts and also has antiviral effect
- IFN  $\gamma$  are produced by T lymphocytes. These are also called lymphokines. The stimulus for their production includes viral and non viral antigens. These have both antiviral and immunomodulatory effects.

**Mechanism of action :** Antiviral activity of the immunomodulators varies with the nature of the virus and the cell type that is infected. Interferons bind to specific cell surface receptors and inhibit viral penetration, viral translation of proteins and viral release.

Viral protein synthesis inhibition occurs when the IFN induce the production of enzymes in the host cell ribosomes, which inhibits the translation of viral m-RNA into viral proteins. This will thus stop viral replication. In addition, IFN can activate macrophages and natural killer cells along with modulation of the cell surface proteins. These will help immune recognition. Both DNA and RNA virus are sensitive to IFN to varying degrees.

**Resistance:** Virus produces proteins that can overcome the effects of interferons and thus are able to develop resistance to interferons.

**Pharmacokinetics:** IFN can be administered subcutaneously, intramuscularly, intravenously or intra lesionally. They have an initial  $t_{1/2}$  of 40 minutes and a terminal  $t_{1/2}$  of 5 hours. The activity of interferons however, remains for 6 days even after the plasma levels decline.

#### **Clinical Uses:**

- i) IFN  $\alpha$  2a is used to treat Hepatitis B, AIDS related Kaposi sarcoma, chronic hepatitis C, hairy cell leukemia and chronic myelogenous leukemia.
- ii) IFN  $\alpha$  2b is useful in Hepatitis C, malignant melanoma, chronic hepatitis B and C (in combination with ribavirin) and non Hodgkin lymphoma, condylomata acuminata (anogenital warts caused by human papilloma virus)
- iii) IFN  $\alpha$  2b is useful in Condylomata acuminata
- iv) IFN  $\beta$  -1a and IFN  $\beta$ -1b is used in Multiple sclerosis
- v) IFN  $\gamma$ -1b in Chronic granulomatous disease

IFNs are also used as an adjunct with other antiretroviral drugs in the treatment of AIDS. Immuno suppressed transplant patients should not receive IFN. Decrease in viral activity may be seen due to development of antibodies against interferons.

**Adverse effects :** Influenza like illness which includes fever, weakness, nausea, vomiting, myalgia, headache, and diarrhea may be observed. Antipyretic pretreatment reduces these reactions. Bone marrow suppression, rashes, alopecia, cardiovascular, hepatic and thyroid dysfunction is rarely seen. Insomnia, somnolence, confusion, behavioral changes is also seen sometimes.

#### **4. Antiretroviral Drugs**

There are primarily two viruses associated with Auto Immune Deficiency Syndrome (AIDS) . These are the Human Immuno deficiency viruses (HIV) namely:

1. HIV -1 which is the Causative organ for most HIV infection globally
2. HIV – 2 associated with infection seen chiefly in India and Western Africa

#### **Human Immune deficiency virus (HIV):**

Infection with HIV leads to the development of Acquired Immunodeficiency syndrome (AIDS). It was first identified in the USA in 1981. HIV is a RNA retro virus. The surface of this virus has two major glycosylatic proteins viz. gp41 and gp 120. The virus has specific affinity to the helper T cells of the host i.e.; the human being. In the humans the helper T cells are the important

component of the cellular immune responses. The virus binds to the CD-4 receptors on the T cells with the help of surface glycoprotein gp120. Once the virus is internalized the reverse transcriptase utilizes the viral RNA for reverse transcription and synthesis of viral DNA. New virion formation thus takes place within the helper T cell. These virions are pinched off the cell membrane and are released which then subsequently attach themselves to other healthy cells, thus completing the viral life cycle.

The initial sign and symptoms with HIV infection may be similar to any other viral infection, with symptoms of fever, headache, myalgia, rash and enlarged lymph node. However, there may be a symptom free latent period of upto 10 years before the full blown picture of AIDS is manifested. These symptoms are in the form of opportunistic infections, as these patients are immuno compromised. Neurological symptoms, bone marrow suppression, chronic gastrointestinal infections and loss of weight are some of the sign and symptoms observed in patients of AIDS .

Majority of viral infection are self limiting as the host immune system helps in the removal of the infecting viruses. However, in patient of AIDS, the HIV causes the collapse of the cell mediated immune system and a decline in the CD4 T lymphocyte cells. This leads to a massive invasion of opportunistic infecting agents and also to the development of non infective conditions like malignancies (AIDS related complex). Monitoring of AIDS patient is based on the plasma assay of HIV – RNA and on the CD4 lymphocyte count.

Anti HIV drugs also known as the anti retroviral (ARV) agents are classified as :

1. Nucleoside reverse transcriptase Inhibitors (NRTIs), Zidovudine, Stavudine, Lamivudine, Abacavir, Zalcitabine, Didanosine
2. Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Efavirenz, Nevirapine
3. Nucleotide Reverse Transcriptase Inhibitor Tenofovir
4. Protease Inhibitor, Saquinavir, Indinavir, Nelfinavir, Ritonavir
5. Entry / fusion Inhibitors **Enfuvirtide**

**a. Nucleoside Reverse Transcriptase Inhibitors :** The first anti-retrovirus drug developed in 1987 was Zidovudine.

**Mechanism of action :** The NRTIs when taken up by the host cells are converted to their respective triphosphate derivative by the host cell kinase enzyme. These then compete with the viral nucleoside triphosphate and there by get incorporated into the DNA, producing complementary DNA from the altered RNA. This results in termination of viral growth and multiplication. Hence the virus is now unable to infect new host cells.

**Resistance:** When used alone as in the past, more than 50% of AIDS patients became non responsive due to development of resistance. This resistance occurs by point mutation.

**Pharmacokinetics :**

| Name              | t <sub>1/2</sub> (hrs) | Metabolism.                | Remarks                                                                                                                                                                                                  |
|-------------------|------------------------|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zidovudine (AZT)  | 1-3                    | Liver                      | Food decrease the bioavailability as it undergoes extensive first pass metabolism. This drug should not be combined with Stavudine or ribavirin                                                          |
| Stavudine(d4T)    | 1.5                    | Renal                      | Peripheral neuropathy is its chief toxicity.                                                                                                                                                             |
| Lamivudine (3TC)  | 6-9                    | Largely excreted unchanged | Also used for chronic hepatitis B infections                                                                                                                                                             |
| Abacavir (ABC)    | 61.5                   | Liver                      | Generalized hypersensitivity reaction seen in the form of rash with in 6 weeks of administration Avoid re-challenge.<br>It inactivates Zalcitabine.                                                      |
| Zalcitabine (ddc) | 2.0                    | Excreted largely unchanged | Food decreases its bioavailability<br>Peripheral neuropathy is major adverse effect. It is contraindicated in pancreatitis, hepatitis and alcohol abuse. Should not be used with didanosine, lamivudine. |
| Didanosine (ddl)  | 1.5                    | Purine metabolic pathway   | Major adverse effect is diarrhoea and peripheral neuropathy. Contraindicated in patient of Gout, Pancreatitis, Peripheral neuropathy, visual problem.                                                    |
| Tenofovir (TFV)   | 17                     | Excreted unchanged         | Not given in patient with renal insufficiency. It increases the plasma levels of didanosine and hence increase its toxicity                                                                              |

**Adverse effects:** Anemia, neutropenia are most important adverse effects and are dose related. Treatment of this condition should include transfusion, erythropoietin/ G-CSF/ GM-CSF. Nausea, anorexia, abdominal pain, insomnia, myalgia, are other adverse effects. Myopathy, fatal lactic acidosis, severe hepatomegaly, convulsions, encephalopathy are some of the important side effects with this class of agents. It has been observed that alcoholics and obese females are more prone to some of these toxic effects. In the event of these effects it is important to withdraw the offending immediately.

#### **b. Nonnucleoside Reverse Transcriptase or Nnrtis:** Efavirenz, Nevirapine

**Mechanism of action :** The NNRTIs inactivate the viral reverse transcriptase by binding to the catalytic site of the enzyme. They thus cause the inactivation and inhibition of complementary DNA synthesis.

**Resistance:** Resistance develops by point mutation and cross resistance has been reported between NNRTIs.

|                  | Metabolism                        | t <sub>1/2</sub><br>(hrs) | Remarks                                                                                                  |
|------------------|-----------------------------------|---------------------------|----------------------------------------------------------------------------------------------------------|
| Nevirapine (NVP) | Hepatic Induce Cy p450            | 25-30                     | Well absorbed orally. Enhance their own metabolism                                                       |
| Efavirenz (EFV)  | Hepatic, Induce microsomal enzyme | 40 -50                    | Fatty meal increase the bioavailability. Teratogenic effects in experimental animals Avoid in pregnancy. |

**Adverse Effects:** Skin Rashes, headache Stevens Johnson Syndrome, elevation of liver enzymes diarrhea, dizziness are seen commonly with NNRTIs

**Drug Interactions:** Since NNRTIs induce the cytochrome enzyme system in the liver, these drugs are known to induce their own metabolism. Nevirapine decreases the levels of Protease Inhibitors like lopinavir, saquinavir and indinavir, where as Efavirenz increases the plasma concentration of nelfinavir and ritonavir. Nevirapine levels may increase with the use of other microsomal enzyme inhibitors like erythromycin. Nevirapine may also decrease the effectiveness of oral contraceptives.

**c. Protease Inhibitors:** Saquinavir, Indinavir, Nelfinavir, Ritonavir

**Mechanism of action:** The HIV protease inhibitors act at a late stage in the virus replication. The growing virion synthesizes a large polyprotease which is cleaved by a protease enzyme into various components which go into the formation of the viral core protein and the viral enzyme including the reverse transcriptase enzyme. This protease enzyme can be inhibited by drugs thereby preventing the cleavage of viral polyproteins. As a consequence, immature non infective viruses are produced. As PI's are acting at this step in the viral replication and growth, these drugs are effective in both newly and chronically infected cells.

#### Characteristics of individual PI

| Name             | Metabolism                      | t <sub>1/2</sub> (hours) | Remarks                                                                                                                                           |
|------------------|---------------------------------|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Saquinavir (SQ)  | Hepatic (First pass metabolism) | 8-11                     | Fatty meal enhances bioavailability. Ritonavir increases the plasma levels of Saquinavir                                                          |
| Ritonavir (RTV)  | Hepatic (First pass metabolism) | 3-5                      | It can alter the taste sensation. It is a potent inhibitor of cyp3A4, Hence, is involved in a number of drug interactions                         |
| Lopinavir (LPV)  | Hepatic (First pass metabolism) | 5-6                      | Administered with ritonavir This acts synergistically and has fewer adverse effects                                                               |
| Nelfinavir (NFV) | Hepatic (First pass metabolism) | 4-5                      | Food increases the bioavailability<br>Relatively low toxicity profile                                                                             |
| Indinavir (IDV)  | Hepatic (First pass metabolism) | 1.8                      | Requires dose adjustment in hepatic dysfunction. Can cause nephrolithiasis urolithiasis, renal insufficiency Large intake of water is recommended |

NACO in their guidelines suggest that the PI's should be reserved for second-line therapy because their use in an initial treatment regimen essentially rules out second-line options in the setting of resource-limitations.

PIs as initial therapy with a standard dual NRTI backbone are an option for:

1. treatment of viral types with intrinsic resistance to NNRTIs (e.g. HIV-2)
2. Women with CD4 counts of 250–350 cells/mm<sup>3</sup>
3. Individuals for whom NNRTI drugs are severely toxic and triple NRTI therapy is not available or deemed inappropriate.

**Adverse Effects:** Diarrhea, nausea, abdominal discomfort are some of the common adverse effects seen with the PI's. PI's are also liable to produce hyperglycemia, fat redistribution and hyper-lipidemia. There is an increased risk of bleeding episodes especially in hemophilic patients

#### **d. Fusion entry inhibitors**

**Enfuvirtide:** This drug prevents the entry of HIV – 1 into the CD4 cells by interfering with the fusion of virus to the cell membrane. Enfuvirtide has a  $t_{1/2}$  of 3-4 hours.

**Clinical Uses:** Patients with advanced HIV who cannot be managed adequately with conventional Anti Retro Viral (ARV) therapy

**Adverse Effects:** Local nodule at the site of injection, skin rash, eosinophilia pneumonia like manifestations are commonly seen. It does not have any drug- drug interactions with other ARV agents

#### **HIV Treatment guidelines**

Treatment of HIV infection is prolonged, and complex, and requires experts to treat these patients. On the other side the patient needs to be committed and be adequately motivated to accept this prolonged therapy. In addition the treatment can be expensive Efforts are being made to manufacture the generic drugs so as to reduce the treatment costs.

In order to prevent the development of multi drug resistance to the standard ARV agents it is important that treatment regimens are advocated and guide lines laid down by authorities like the WHO and the National AIDS Control Organization (NACO) .

The **Highly Active Antiretroviral Therapy (HAART)** recommends synergistic combination of 3 or more drugs of NRTIs and NNRTIs with PI. The objective of the combination is

- i) To produce a sequential blockade with different mechanism of action
- ii) To decrease development of resistant strains by the HIV

The commonly employed combinations include:

- |                           |                   |                       |
|---------------------------|-------------------|-----------------------|
| i) 2NRTI + 1 PI           | ii) 2NRTI +1NNRTI | iii) 2NRTI +Abacavir  |
| iv) 2 NRTI +PI +Ritonavir | v) 3NRTI          | vi) 1NRTI+1NNRTI +1PI |
| vii) 1NRTI+1NNRTI+2PI     |                   |                       |

### Indication for treatment

**International AIDS Society** recommends ART for adults when

- CD4 count is <200/ul because at this stage there is a high risk of opportunistic infections
- All symptomatic patients with HIV disease
- Asymptomatic patients with CD4 counts  $\leq$  200/ul
- Asymptomatic patients with a CD4 count  $\geq$  200/ul when
  - i) the rate of decline is >100CD4 cells /ul /annum
  - ii) HIV RNA level >50.000 copies
  - iii) Patient interest and potential to adhere to therapy
  - iv) Individual risk of drug toxicity and interactions

Commonly used drug combinations In India include:

Zidovudine + Lamivudine + Indinavir

Zidovudine + Didanosine + Nelfinavir

Zidovudine + Zalcitabine + Saquinavir

Stavudine + Lamivudine + Lopinavir + Ritonavir

Stavudine + Didanosine + Indinavir + Ritonavir

### Dose and dosage regimens of some of the commonly used ART

| Name of drug | Dosage form                            | Dose                                                                                                                                |
|--------------|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Zidovudine   | Cap 100mg, Tab 300mg<br>Syrup 50mg/5ml | Adults 500mg/day in 2-4 divided doses<br>Children 180mg/m <sup>2</sup> 6-8 hrly Max 200mg<br>Advice patient to take plenty of water |
| Stavudine    | Cap 30 mg and 40mg                     | 40 mg BD (>60 Kg body weight)<br>30mg BD (<60 Kg body weight)                                                                       |
| Lamivudine   | Tab 150mg ;<br>Syrup 50mg/5ml          | Hepatitis B 100mg BD<br>HIV 150mg BD (along with other ART)                                                                         |
| Nevirapine   | Tab 200mg                              | 200mg/day increase to 400mg/day                                                                                                     |
| Efavirenz    | Tab 400mg                              | 600mg OD                                                                                                                            |
| Indinavir    | Cap 400mg                              | 800mg TDS                                                                                                                           |
| Nelfinavir   | Tab 250mg                              | 750mg TDS                                                                                                                           |
| Ritonavir    | Tab 250 mg                             | 600mg BD                                                                                                                            |