Antiviral Agents
• Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cells.

• Antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell.

• Antiviral agents are most active, when viruses are replicating.

• The earlier that treatment is given, better the result.
Difficulties in treatment

1. Substantial multiplication has already occurred, before symptoms occur.
2. Intracellular – use host metabolic processes
   - Highly selective toxicity is harder to achieve.
3. Resistance to the drug
DNA VIRUSES

• Adenoviruses (URT & eye infection)
• Hepadnaviruses (hepatitis - B)
• Herpesviruses -
  • Herpes Simplex Virus type -1 – causes oral herpes, ocular herpes, viral encephalitis, herpes keratitis
  • Herpes Simplex Virus type-2 – genital herpes
  • Varicella Zoster Virus - chicken pox, zoster or shingles
  • Cytomegalovirus - infectious mononucleosis
  • Epstein Barr virus – inf. mono, B-cell lymphoma
• Papillomavirus – warts
• Poxvirus – small pox
RNA VIRUSES

- **Picornaviruses** – Poliovirus causing polio & hepatovirus causing hepatitis-A
- **Orthomyxovirus** – influenza A,B,C – influenza,H1B1 causes swine flu
- **Paramyxoviruses** – rubella virus causing mumps, RSV causing LRTI,
- **Rhabdoviruses** – causing rabies
- **Arbovirus**, rotavirus, retrovirus, arenavirus, coronavirus
Viral replication

• Viral attachment & entry
• Penetration
• Uncoating
• Early protein synthesis
• Nucleic acid synthesis
• Late protein synthesis & processing
• Packaging & assembly
• Viral release
Viral Replication

• Recognise host surface proteins & get attached
• Virusus penetrates the host cell membrane by endocytosis
• Envelope merges with the host cell membrane
• Capsid along with genome enters the interior of cell
• Capsid removed within the cell, to free the genome containing DNA
• Viral genome enters the cell nucleus & its DNA is transcribed into viral m-RNA by the host cell’s RNA polymerase.
• Host cell’s ribosomes then utilise the viral m-RNA for the synthesis of viral proteins and enzymes.
• During this process, regulatory proteins are synthesised first, which initiate the transcription of early genes responsible for viral DNA replication by viral DNA-polymerase.
- After DNA replication late genes are transcribed & translated to produce **structural proteins** required for assembly of new virions.
- Viral components are then **assembled** to form a mature virus particle.
- **Release** of progeny virus takes place through **budding** of host cell.
C/F OF ANTIVIRAL DRUGS

• DNA POLYMERASE INHIBITORS –
  • PURINE ANALOGUES-
    • ACYCLOVIR        VALACYCLOVIR
    • GANCICLOVIR      VALGANCICLOVIR
    • FAMCICLOVIR      PENCICLOVIR
    • CIDOFOVIR        ADEFOVIR
    • ENTECAVIR         VIDARABINE
  • PYRIMIDINE ANALOGUES –
    • IDOXURIDINE , TRIFLURIDINE, TELBIVUDINE
  • NON-NUCLEOSIDES - FOSCARNET
• m-RNA SYNTHESIS INHIBITORS
  • RIBAVIRIN, FOMIVIRSEN
• INHIBITORS OF VIRAL PENETRATION & UNCOATING
  • AMANTADINE, RIMANTADINE, DOCOSANOL
• NEURAMINIDASE INHIBITORS
  • ZANAMIVIR, OSELTAMIVIR, PERAMIVIR
• IMMUNOMODULATORS
  • INTERFERONS, PALIVIZUMAB, IMIQUIMOD
• ANTI-RETROVIRAL DRUGS
Drugs for Herpes Simplex Virus (HSV) & Varicella-Zoster infection

- Acyclovir
- Valacyclovir
- Famciclovir
  - Acyclovir is only one available for I/V use.
  - Valacyclovir & Famcyclovir - Superior for Herpes zoster
- Not indicated in varicella
Acyclovir

- HSV-1, HSV-2, VZV

**INDICATIONS** –

- **Skin infections** – Initial & recurrent labial & genital herpes (as a cream), most effectively when new lesions are forming. For Skin & m.m. infections - as tablets or oral suspensions.

- **Ocular keratitis** – as ointment

- **Prophylaxis & Treatment in immunocompromised**- Oral, tab, suspension,

- **Encephalitis, disseminated disease**
Acyclovir

- V-Z viruses
- Chicken-pox
- immunocompromised (i.v.),
- immunocompetent with pneumonitis, hepatitis
- Shingles –
- in immunocompetent, tab/suspension within 48 hrs of appearance of rash
- In immunocompromised – i.v.
- Oral & topical 5 times a day.
• **Mechanism:**
  – Three phosphorylation steps for activation.
    • First converted to the *monophosphate* derivative by the *virus-specified* thymidine kinase; *(selective activation)*
    • Then to the di- and triphosphate compounds by *host’s* cellular enzymes.
  – Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:
    • Inhibition of *viral DNA polymerase*, with binding to the DNA template as an irreversible complex;
    • Incorporation into the viral DNA → chain termination
ADRs

- Gen. well tolerated
- N/D, Headache
- I/V - Extravasation – local inflammation
- Reversible renal dysfunction
- Neurologic toxicity
Valacyclovir

- Prodrug of acyclovir
- Oral bioav. 54 %, given 8 hrly
- Use –
  - genital herpes
  - Oro-labial herpes
- S/Es – N/V, rash, dizziness, liver enzyme elevation, anemia, neutropenia, confusion, hallucinations, seizures.
Cytomegalovirus

- In advanced immunosuppression
- Reactivation of latent infection
- End organ disease – Retinitis, Colitis, esophagitis, CNS ds. & pneumonitis
- AIDS & organ transplantation
- GANCYCLOVIR
- VALGANCYCLOVIR
- FOSCARNET
- CIDOFOVIR
GANCICLOVIR

• SIMILAR TO ACYCLOVIR IN ITS MODE OF ACTION BUT MUCH MORE TOXIC.
• I/V OR ORALLY, ELIMINATED IN URINE, UNCHANGED.
• HALF LIFE – 4 HRS.
• I.V. USE IS LIMITED TO – LIFE OR SIGHT – THREATENING CMV INFECTION IN IMMUNO-COMPROMISED PTS.
GANCICLOVIR

• ORAL – FOR MAINTENANCE OF SUPPRESSIVE TREATMENT OF RETINITIS IN PTS WITH AIDS.
• TO PREVENT CMV DISEASE IN PATIENTS WHO ARE IMMUNO-COMPROMISED & FOLLOWING ORGAN TRANSPLANTATION.
• ADRs – NEUTROPNENIA, THROMBOCYTOPENIA, FEVER, RASH, GI SYMPTOMS, CONFUSION & SEIZURE.
FOSCARNET

- I.V. FOR RETINITIS DUE TO CMV IN PATIENTS WITH HIV INFECTION (WHEN GANC. C/I)
- ACYCLOVIR –RESISTANT HSV INFECTION
- **S/Es** – RENAL TOXICITY, N/V, NEUROLOGICAL REACTIONS, MARROW SUPPRESSION
FOMIVIRSEN

- AN OLIGONUCLEOTIDE
- ANTI-CMV AGENT
- BINDS TO m-RNA –INHIBITS THE SYNTHESIS OF IMMEDIATE EARLY PROTEINS NEEDED FOR VIRAL REPLICATION
- RESISTANCE LEAST COMMON
- SELECTIVE ACCUMULATION IN RETINA & VITREOUS HUMOUR
- INJECTED INTRAVITREALLY FOR CMV RETINITIS IN AIDS PATIENTS
- S/E- Iritis, Vitreitis, Increased Intraocular Pressure
TRIFLURIDINE

- PYRIMIDINE NUCLEOSIDE AGAINST HSV-1, HSV-2, VACCINIA, AND SOME ADENOVIRUSES.
- INCORPORATION OF TRIFLURIDINE TRIPHOSPHATE INTO BOTH VIRAL AND CELLULAR DNA PREVENTS ITS SYSTEMIC USE.
- THERAPY FOR KERATO-CONJUNCTIVITIS AND FOR RECURRENT EPITHELIAL KERATITIS DUE TO HSV-1 AND HSV-2.
- TOPICAL APPLICATION, ALONE OR IN COMBINATION WITH INTERFON ALFA, HAS BEEN USED SUCCESSFULLY IN TREATMENT OF ACYCLOVIR-RESISTANT HSV INFECTIONS.
IDOXURIDINE

• INHIBITION OF VIRAL DNA POLYMERASE → BLOCKS DNA SYNTHESIS.
• NO EFFECT ON RNA VIRUS.
• ONLY TOPICAL APPLICATION BECAUSE OF ITS GREATER SIDE EFFECTS IN SYSTEMIC APPLICATION.
• TREATMENT OF OCULAR OR DERMAL INFECTIONS DUE TO HERPES VIRUS, ESPECIALLY ACUTE EPITHELIAL KERATITIS DUE TO HERPES VIRUS.
VIDARABINE

• ADENINE NUCLEOSIDE ANALOGUE
• AGAINST HSV, VZV, CMV, HBV AND SOME RNA VIRUSES.
• PHOSPORYLATED INTRACELLULAR BY HOST ENZYMES TO FORM VIDARABINE TRIPHOSPHATE & INHIBITS VIRAL DNA POLYMERASE
• ACTS AS DNA CHAIN TERMINATOR
• BUT INCORPORATED INTO BOTH VIRAL AND CELLULAR DNA → EXCESSIVE TOXICITY
VIDARABINE

• RAPIDLY METABOLIZED TO HYPOXANTHINE ARABINOSIDE.

• INSTABILITY AND TOXICITY LIMITED ITS CLINICAL UTILITY.

• **ONLY TOPICAL USE** - IN HSV KERATO- CONJUCTIVITIS, SUPERFICIAL KERATITIS IN PTS NOT RESPONSIVE TO IDOXURIDINE.

• **S/E**- LACRIMATION, IRRITATION, PHOTOPHOBIA
RIBAVIRIN

• GUANOSINE ANALOG.
• PHOSPHORYLATED INTRACELLULARLY BY HOST CELL ENZYMES.
• MECHANISM: TO INHIBIT THE VIRAL RNA-DEPENDENT RNA POLYMERASE OF CERTAIN VIRUSES
• RIBAVIRIN TRIPHOSPHATE INHIBITS THE REPLICATION OF A WIDE RANGE OF DNA AND RNA VIRUSES, INCLUDING INFLUENZA A AND B, PARAINFLUENZA, RESPIRATORY SYNCYTIAL VIRUS, PARAMYXOVIRUSES, HCV, AND HIV-1.
RIBAVIRIN

• Oral absorption is rapid, first pass extensive, yet oral bioav. 65%
• Also given as aerosol to treat influenza & infections due to respiratory syncytial virus
• i.v. to reduce mortality in lassa fever (arena)
• Highly effective ag. Influenza –A & B viruses.
• Oral ribavirin & s.c. interferon-alpha -2b is synergistically effective ag. Hepatitis –C.
ANTI-HEPATITIS AGENTS

• INTERFERONES –
• RELEASED BY HOST CYTOKINES
• COMPLEX ANTI-VIRAL, IMMUNOMODULATORY
• ANTI-PROLIFERATIVE ACTIVITIES
• $\alpha, \beta, \gamma$ according to antigenic & physical properties.
• **INF-α** – synthesised primarily by human leukocytes

• **INF –β** - from fibroblasts

• **INF –γ** - which is a lymphokine, is produced by T-lymphocytes as a part of the immune response to viral and non-viral antigens.

• Commercial synthesis of IFNs is done by recombinant DNA tech.in bacterial cultures.

• **INF –α & β** exert potent antiviral effects

• **IFN –γ** has antiviral & immunomodulatory effects.
BINDING TO SPECIFIC CELL MEMBRANE RECEPTORS & AFFECT VIRAL REPLICATION AT MULTIPLE STEPS -

• INHIBITION OF VIRAL PENETRATION, UNCOATING
• INHIBITION OF TRANSLATION –
• INHIBITION OF TRANSCRIPTION, PROTEIN PROCESSING, MATURATION & RELEASE
• INCREASED EXPRESSION OF MHC-antigen
• ACTIVATION OF MACROPHAGES & NATURAL KILLER CELLS ALONG WITH MODULTION OF CELL SURFACE PROTEINS TO FASCILITATE IMMUNE RECOGNITION
• ALL DNA & RNA VIRUSES ARE SENSITIVE TO IFNs
• ENDOGENOUS IFNs ARE RESPONSIBLE FOR MAKING MOST VIRAL INFECTIONS SELF-LIMITING.
• IFNS CAN BE ADMINISTERED S.C., I.M., I.V., OR INTRA-LESIONALLY
• DO NOT CROSS BBB
• ELIMINATED THROUGH PHAGOCYTOSIS OR BY KIDNEY/LIVER.
CLINICAL USES

• **IFN –α -2a** – chronic hepatitis –B infection, AIDS related Kaposi’s sarcoma, chronic hepatitis –C, hairy cell leukemia & chronic myelogenous leukemia

• **IFN –α -2b** (s.c., i.m.) – Hepatitis –C, malignant melanoma, condyloma acuminata, chronic hepatitis –B, chronic hepatitis –C and non-hodgkin’s lymphoma

• As an adjunt in treatment of viral infections including AIDS.
• **S/Es** – flu –like syndrome – Headache, fever, chills, myalgias, malaise, transient hepatic enzyme elevation.

• Chronic therapy – neurotoxicities, myelosuppression, profound fatigue, wt.loss, rash, cough, myalgia, alopecia, tinnitus, hepatic and thyroid dysfunction.
Lamivudine

• Cytosine analogue
• Inhibits HBV DNA polymerase
• Inhibits HIV reverse transcriptase by competing with deoxycytidine triphosphate for incorporation into viral DNA
• Resulting in chain termination.
• Against HIV-1, synergistic with a variety of antiretroviral nucleoside analogs, including zidovudine and stavudine.
• Treatment of chronic hepatitis B infection.
• oral bioavailability > 80%
• Not food dependent
• The majority of lamivudine is eliminated unchanged in the urine.
• Excellent safety profile
• Headache, nausea, dizziness,
• Co-infection with HIV – risk of pancreatitis.
Anti-influenza agents

• Amantadine & Rimantadine
• Zanamivir & Oseltamivir
Amantadine

- Inhibits uncoating of viral RNA within infected host cells
- Inhibits replication of Influenza A
- A proton ion channel M2 of the viral membrane is the target.
- Inhibition of M2 protein – prevention of H+ mediated dissociation of ribonucleoprotein core segment (a prerequisite for viral replication)
- Well absorbed orally
- Excreted unchanged in urine over 2-3 days
- Half life 16 hours
Rimantadine

- 4-10 times more active than amantidine
- Better tolerated, longer acting, more potent.
- Dose reduction required for both in – elderly & in patients with renal insufficiency.
- For rimantadine – in patients with marked hepatic insufficiency also.
• **S/Es** – generally well tolerated
• Nausea, Anorexia, insomnia, dizziness, nightmares, lack of mental conc., hallucinations, postural hypotension, ankle edema.

• **Uses** – prophylaxis of Influenza A2
• Treatment of influenza A2
• Parkinsonism
• C/I – Epilepsy & other CNS ds, gastric ulcer, pregnancy
Zanamivir & Oseltamivir

• Neuraminidase inhibitors
• Interfere with the release of progeny influenza virus from infected – new host cells
• (Neuraminidase enzyme required for release)
• Preventing the spread of infection in respiratory tract
• Activity ag. Both Infl.A & Infl. B
• Zanamivir is given through inhalation
• 5-15 % of total dose is absorbed & excreted in the urine.
• S/Es - Cough, brochospasm, reversible decrease in pulmonary function & transient nasal & throat discomfort.
Oseltamivir

- is orally given
- A prodrug
- Activated by hepatic esterases
- Widely distributed throughout the body
- Headache, fatigue & diarrhea.
- AVIAN INFLUENZA
PERAMIVIR

• FOR EMERGENCY TREATMENT OF HOSPITALISED PATIENTS WITH H1N1 INFLUENZA
• ORAL BIOAV. POOR
• USED FOR PATIENTS SHOWING RESISTANCE TO OSELTAMIVIR OR TO ZANAMIVIR INHALATION
• USED AS THE ONLY I/V OPTION FOR TREATING SWINE FLU
• CLEARED PHASE III
Anti-Retroviral (Anti-HIV) Agents
Viral RNA → reverse transcriptase → double helix DNA → HIV integrase → Incorporated into host genome

Polyproteins → HIV protease → Final structural proteins

Drugs: NRTIs, NNRTIs, PIs
• Surface proteins gP120, linked to a transmembrane stalk (gP41)
• Antigenic & facilitate viral attachment to CD4 cells of T lymphocytes
• Core genome contains RNA along with 3 genes: gag, pol, env
• Gag & pol code for formation of reverse transcriptase, integrase & protease enzymes
• Env genes code for the formation of envelope proteins gP120 & gP41.
• Integrated into host genome by **viral enzyme integrase**
• Provirus DNA transcribed into new genomic RNA & m-RNA
• m-RNA translated into viral proteins by host ribosomes
• Assembly of virion
• Maturation in which **viral protease** enzyme cleaves the polypeptide into functional structural proteins & viral enzymes.
• Budding & Release to infect other cells
• Prime target – Helper T-lymphocytes, which have CD4 expressed on their surface.
• gP120 binds to CD4 & to Chemokine co-receptors (CXCR4), (CCR5 for macrophages)
• Gp 41 causes **fusion** of viral envelope with plasma membrane of T-cells.
• After fusion, virus **enters** the target cells.
• Uncoating
• Viral **reverse transcriptase** synthesises DNA from viral RNA.
C/F OF ANTI-HIV DRUGS

• Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
  • Zidovudine
  • Stavudine
  • Lamivudine
  • Abacavir
  • Zalcitabine
  • Emtricitabine
  • Didanosine
• Non-nucleoside Reverse transcriptase inhibitors (NNRTIs) –
• Efavirenz
• Nevirapine
• Delavirdine
• Etravirine
• Nucleotide Reverse transcriptase inhibitors –
• Tenofovir
• Protease Inhibitors (PIs) –
  • Saquinavir
  • Indinavir
  • Nelfinavir
  • Amprenavir
  • Fosamprenavir
  • Ritonavir
  • Lopinavir
• Entry/fusion Inhibitors
  • Enfuvirtide

• CCR5 Inhibitors
  • Maraviroc

• Integrase Inhibitors
  • Raltegravir
Nucleoside Reverse Transcriptase Inhibitors
Mechanism of Action

① **Competitive inhibition** of HIV-1 reverse transcriptase;

② **Incorporated into** the growing viral DNA chain \(\rightarrow\) cause termination

- Drugs requires intracytoplasmic activation---**phosphorylation** \(\rightarrow\) triphosphate form
- Most have activity against HIV-2 as well as HIV-1.
Zidovudine

- Azidothymidine (AZT)
- Deoxythymidine analog
- Anti-HIV-1 and HIV-2
- Well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid.
- Eliminated primarily by renal excretion following glucuronidation in the liver.
• Decreases the rate of clinical disease progression and prolongs survival.
• Reduces the rate of **vertical** (mother-to-newborn) transmission of HIV.
• Begin b/w 14-34 weeks
• In neonate, birth to 6 weeks of age.
• Also used for post-exposure prophylaxis for healthcare workers.
• **Adverse effect:** myelosuppression → anemia or neutropenia; gastrointestinal intolerance, headache, insomnia, myopathy
• Less frequent – thrombocytopenia, hyperpigmentation of nails

• Interactions – increased serum levels of – Probenecid, Phenytoin, Fluconazole, valproic acid, lamivudine.
Zalcitabine (ddC)

- Cytosine analogue
- Anti-HIV-1
- Zalcitabine + Zidovudine + one protease inhibitor
- Suitable for patients intolerant to or resistant to zidovudine.
- Long intracellular half-life of 10 hrs.
- Dose-dependent peripheral neuropathy. Contraindication to use with other drugs that may cause neuropathy.
- Stomatitis & esophageal ulceration
Stavudine(d4T)

- Thymidine analog (d4T), not used with AZT because AZT may reduce the phosphorylation of d4T.
- Anti-HIV-1 and HIV-2
- High oral bioavailability (86%) that is not food-dependent.
- Plasma protein binding is negligible, mean cerebrospinal fluid concentrations are 55% of those of plasma.
- Excretion is by active tubular secretion and glomerular filtration.
• USED FOR THE THERAPY OF HIV INFECTIONS AS A PART OF MULTIDRUG REGIMEN & ALSO FOR POST EXPOSURE PROPHYLAXIS

• ADVERSE EFFECTS:
  – DOSE-LIMITING TOXICITY IS A DOSE-RELATED PERIPHERAL SENSORY NEUROPATHY.
  – PANCREATITIS, ARTHRALGIA S, ELEVATION IN SERUM AMINO-TRANSFERASES.
Didanosine (ddl)

- Synthetic analog of deoxy-adenosine
- Plasma protein binding is low (<5%), cerebrospinal fluid concentrations are 20% of serum concentrations.
- Eliminated by glomerular filtration and tubular secretion.
- Administered in combination due to resistance.
- Should be taken on an empty stomach.
- FQs and tetracyclins should be given at least 2 hrs before or after ddl to avoid decreased antibiotic conc. due to chelation.
• ADVERSE EFFECTS:
  – DOSE-DEPENDENT PANCREATITIS
  – PAINFUL PERIPHERAL DISTAL NEUROPATHY
  – DIARRHOEA
  – HEPATITIS
  – ESOPHAGEAL ULCERATION
  – CARDIO-MYOPATHY
  – CENTRAL NERVOUS SYSTEM TOXICITY (HEADACHE, IRRITABILITY, INSOMNIA)
Non-nucleoside reverse transcriptase inhibitors

• Including delavirdine, nevirapine, efavirenz.
• Bind directly to a site on the viral reverse transcriptase that is near to but distinct from the binding site of the NRTIs.
• Neither compete with nucleoside triphosphates nor require phosphorylation to be active.
• The binding to the enzyme’s active site results in blockade of RNA- and DNA-dependent DNA polymerase activities.
• Specific activity against HIV-1.
• Cross-resistance among this class of agents.
• The rapid emergence of resistance prohibits mono-therapy with any of the NNRTIs.
• No cross-resistance between the NNRTIs and the NRTIs or the protease inhibitors.
• Oral bioavailability is high.
• Metabolized by the CYP3AP 450 isoform, excreted in the urine.
• Adverse effects: skin rash, elevation in liver enzymes
NEVIRAPINE

• As a combination of multidrug anti-retroviral therapy.
• 200 mg/day oral is effective in preventing vertical transmission (given at the time of labour); single dose of 2mg/kg oral dose to be given to the neonate within 3 days after birth.
• Half life 25-30 hrs.
EFAVIRENZ

• Used as post-operative prophylaxis.
• 600mg orally OD.
• S/Es involve CNS: dizziness, nightmares, insomnia, headache & euphoria
• Other S/Es – skin rash, nausea, vomiting, elevated liver enzymes and serum cholesterol levels.
• teratogenic
**DELAVIRDINE**

- Used for treatment of HIV-1 infection as a part of combination therapy.
- Dose 400 mg TDS
- If didanosine or antacids are to be used, its dosing to be withheld by 1 hr as they decrease its oral bioavailability.
- Metabolised by and inhibits CYP3A4 & thus increases the plasma conc. of several protease inhibitors such as amprenavir, indinavir, lopinavir, ritonavir, saquinavir.
- Dose reduction of these required.
NtRTIs

Tenofovir

• Available as tenofovir disoproxil fumarate
• Prodrug, first hydrolysed in liver to tenofovir
• Which is subsequently phosphorylated to an active tenofovir diphosphate (that is the active form)
• inhibits HIV reverse transcriptase enzyme
• Causes termination of chain elongation after getting incorporated into viral DNA
• Analogue of adenosine 5 monophosphate
• Used along with other anti-HIV drugs in the treatment of HIV in a dose of 300 mg once daily after meals.
• Oral bioavailability with meals 40 %
• Usually well tolerated
• Nausea, Vomiting, diarrhoea and osteomalacia
• Hepatomegaly, pancreatitis, lactic acidosis
• Increases the plasma levels of didanosine leading to toxicity.
Protease inhibitors

ritonavir, nelfinavir, saquinavir, indinavir and amprenavir

Gag and Gag-Pol gene translate Polyproteins, Immature budding particles protease Final structural proteins, Mature virion core
• Protease is responsible for cleaving precursor molecules to produce final structural proteins of mature virion core.

• By preventing cleavage, PIs result in the production of immature, noninfectious viral particles.
• Combination therapy with PIs and other antiretroviral drugs significantly improves the efficacy by blocking HIV replication at different stages in intracellular life cycle.

• Cross resistance between indinavir and ritonavir can occur.
**S/Es**

- A syndrome of redistribution & accumulation of body fat that results in central obesity, dorso-cervical fat enlargement & a cushingoid appearance is seen with PIs.
- Increase in triglyceride, LDL levels along with glucose intolerance & insulin resistance
- Increase in spontaneous bleeding in patients with hemophilia A & B.
- Drug interactions due to enzyme induction & inhibition.
Drug interactions

• Competitive inhibitors of drugs metabolised by CYP3A4 family
• Life threatening toxicities with-
  • Cisapride (arrythmias),
  • ergot alkaloids (vasospasm)
  • Statins (rhabdomyolysis)
  • Midazolam (resp.depression)
• Enzyme inducers may decrease plasma levels of PIs.
Fusion Inhibitors

**ENFUVERTIDE**

- Blocks entry into cell
- Binds to gp41 subunit of viral envelope glycoprotein
- Prevents conformational changes required for fusion of viral & cellular membranes.
- Metabolism by hydrolysis
- Without involvement of CYP450
- Elimination half life 3-8 hrs
S/Es

- Most common s/e is – local injection site reactions
- H/S
- Eosinophilia & pneumonia like manifestations.
Chemokine receptor -5 antagonists

**Maraviroc**

- Binds to CCR5 receptors on CD4 cell membrane & prevents the entry of the virus into the host cell
- Used along with other antiretrovirals, in highly resistant adult patients
- Main s/e hepatotoxicity
- Others — cough, rash, fever, muscular pain, GIT distress
Integrase inhibitors (Raltegravir)

- Inhibits the viral enzyme integrase, thereby preventing the insertion of HIV genetic material into chromosomes of host cells & halting the viral replication process
- Not metabolised by Cytochrome P-450 system
- Drug interactions are not clinically significant
- Rifampicin decreases raltegravir levels
- Antacids and iron bind to integrase, hence dosing should be separated by 2hrs.
- Usual oral dose 200 mg BD orally
- S/Es- nausea, diarrhea, fever, headache, myopathy.
HAART

- Highly Active Antiretroviral Therapy
- Combination of NRTIs & Protease inhibitors, working with different mechanisms, combined drugs produce a sequential blockade of viral reproduction at two different steps. HIV can not develop mutants simultaneously to different drugs working by two different mechanisms.
- Popular combination choices-
  - 2 NRTIs + 1 NNRTI or One/two protease inhibitors i.e.
  - NRTIs (2) + PI (1) or
  - NRTIs (2) + NNRTI (1) or
  - NRTIs(2) + PI (1) + Ritonavir(PI)
• Preffered drug regimens are-
  • Zidovudine + Lamivudine + efavirenz
  • Zidovudine + Lamivudine + Lopinavir/ritonavir
• Alternatives –
  • NRTI (1)+ NNRTI (1) + PI (1) OR
  • NRTI(1) + NNRTI (1)+ PI(2)