CHEMOTHERAPY OF VIRAL DISEASES-II

ANTI-RETRO VIRUSES, HIV

R.M. SRSV

Human Immunodeficiency virus

- **HIV is a RNA (RETROVIRUS-lentivirus) virus:** HIV-I is more common worldwide. HIV-II is restricted to West Africa. The virus has an enzyme reverse transcriptase which transcribes the RNA genome to double stranded DNA and is incorporated into host cell. • The target for HIV is the CD-4+ Helper T-Cells, which are the backbone of the immune system.
- **How HIV affects our body:** Virus enters the immune cells (CD4 cells) => Gets integrated to the cells nucleus => Replicates inside the cells => Ultimately destroys the immune cells => Immunodeficiency => Multiple infections.
- **Is HIV curable?** No, HIV is treatable but not curable. Anti retroviral (ARV) drugs suppress the virus and improve immune status. However, the patient remains HIV positive for life and can transmit the disease to others.

Human Immunodeficiency virus

- **What is ART?** Anti-retroviral therapy (ART) is a combination of least three drugs from different groups. It works to control HIV replication in the body and prevent the destruction of CD_4 Cells. Hence it delays disease progression, prevents opportunistic infections (OIs), reduces hospitalization, reduces transmission of HIV.
- ART increases survival & quality of life. It is a life long therapy, requires high adherence, similar to treatment taken for high BP and diabetes. They have certain side-effects should be prescribed by specialized physicians .

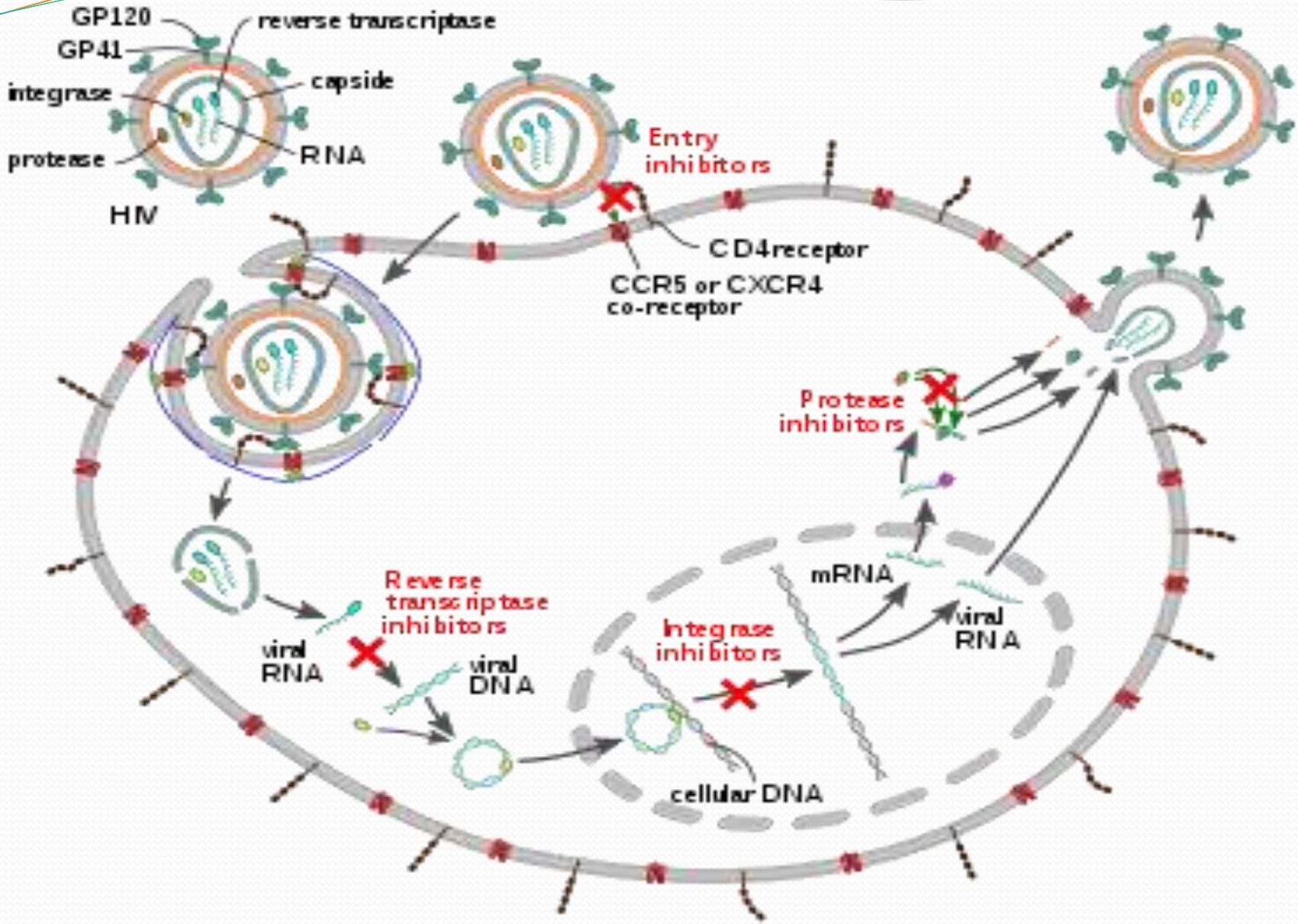
Human Immunodeficiency virus

- **Diagnosis:** ELISA (Enzyme Linked Immuno-Sorbent Assay) -to detect HIV antibodies.
- positive ELISA must be confirmed by Western blot or immunofluorescence assay (IFA) to detect specific HIV proteins. • HIV core protein p24 is the most abundant protein produced by HIV.
- Anti-p24 is the first reliably detected antibody but declines as viral titres rise in late infection.
- Other HIV proteins such as p55, p40, gp120 and gp41 may also be analysed.
- Measurement of CD4+ lymphocyte levels and viral load are often useful indexes of the disease progression as well as the effectiveness of antiretroviral therapy.

ANTI-HIV DRUGS

- **Classification:**
- Nucleoside reverse transcriptase inhibitors (NRTIs)- Zidovudine, Stavudine, Lamivudine, Abacavir, Zalcitabine, Emtricitabine, Didanosine.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) – Nevirapine, Efavirenz, Dilavirdine, Etravirine.
- Nucleotide reverse transcriptase inhibitors (NtRTI)- Tenofovir
- Protease Inhibitors(PI)- Saquinavir, Indinavir, Ritonavir, Lopinavir, Darunavir, Fosamprenavir.
- Entry/Fusion Inhibitors(EI/FI)- Enfuvirtide
  - CCR5 receptor inhibitor- Maraviroc
- Integrase inhibitor- Raltegravir
- Newer Anti-Retroviral Drugs- Elvitegravir, Bevirimat, Elvucitabine, Vicriviroc

ANTI-HIV DRUGS



Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Mechanism of Action:** Drugs are first converted to their active triphosphate metabolites by host cell kinase enzymes.
- The triphosphate form of these drugs then competes with viral nucleoside triphosphates and competitively inhibits the viral reverse transcriptase enzyme and hinders its action to produce complementary DNA from RNA and terminate chain elongation.
- **Drug Name:** **Zidovudine**
- **Focus:** thymidine analogue, 1st line triple regimen. Post exposure prophylaxis. Prevention of mother to child transmission
- **Doses:** 200mgTDS or 300mg BD

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Adverse Effects:** Nausea, Vomiting, Headache, Asthenia, Anaemia, Granulocytopenia, Myopathy, lactic acidosis, hepatomegaly with steatosis nail pigmentation, lipid abnormalities, Lipoatrophy, hyperglycaemia.
- **Interactions:** Probenecid, fluconazole, atovaquone, and valproic acid may increase plasma concentrations of zidovudine, probably through inhibition of glucuronosyl transferase. Zidovudine can cause bone marrow suppression and should be used cautiously in patients with pre-existing anaemia or granulocytopenia and in those taking other marrow-suppressive drugs. Nelvinafir decreases plasma levels. Paracetamol increases AZT toxicity by competing for glucoronidation.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Drug Name:** Stavudine
- **Focus:** Thymidine nucleoside analogue
- **Dose:** 30-150mg BD
- **Adverse effects:** Peripheral neuropathy Pancreatitis lactic acidosis Lipoatrophy hyperlipidaemia.
- **Interactions:** Combining stavudine with didanosine leads to increased risk and severity of peripheral neuropathy and potentially fatal pancreatitis.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Drug Name:** Lamivudine
- **Focus:** [3TC] is a cytidine analogue for HIV
- **Dose:** 100mg orally/day, for Hepatitis-B 40mg BD.
- **Adverse effects:** Lamivudine is one of the least toxic antiretroviral drugs and has few significant adverse effects. Neutropenia Headache nausea .
- **Interactions:**
  Lamivudine+zidovudine=Enhance CD4 counts, Lamivudine+zalcitabine inactivate each other by inhibiting each others phosphorylation.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Drug Name:** Abcavir
- **Focus:** guanosine analogue, Used in HIV-1 therapy in adults and in children. Used post exposure prophylaxis
- **Dose:** 300mg BD.
- **Adverse effects:** Hypersensitivity reaction (may include fever, rash, nausea, vomiting, diarrhoea, malaise, shortness of breath, cough, pharyngitis); patients positive for HLA-B*5701 are at highest risk for hypersensitivity.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- **Drug Name:** Emtricitabine
- **Focus:** cytidine analogue
- **Dose:** 200mg OD
- **Adverse effects:** Minimal toxicity, hyperpigmentation Used in combination with protease inhibitor and/or NNRTI
- **Drug Name:** Didanosine
- **Focus:** adenosine nucleoside, active against HIV-1, HIV-2, and other retroviruses including HTLV-1
- **Dose:** 250mg BD, 30mins before or 2 hrs after meal
- **Adverse effects:** Peripheral neuropathy, pancreatitis, nausea, lactic acidosis, hyperuricemia, optical neuritis.

Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

- **Drug Name:** Tenofovir disoproxil
- **Focus:** derivative of adenosine 5'-monophosphate lacking a complete ribose ring. Tenofovir disoproxil is hydrolyzed rapidly to tenofovir and then is phosphorylated by cellular kinases to its active metabolite, tenofovir diphosphate. Tenofovir diphosphate is a competitive inhibitor of viral reverse transcriptases and is incorporated into HIV DNA to cause chain termination because it has an incomplete ribose ring.
- **Dose: 300mg orally/ day**
- **Adverse effects:** Nausea, Vomiting, Diarrhea, Headache, Asthenia, renal insufficiency, osteomalacia.
- **Interactions:** Tenofovir increase plasma levels of didanosine leading to toxicity (pancreatitis, hepatotoxicity, lactic acidosis), It decreases serum concentration of atazanavir.

Non-Nucleoside Reverse Transcriptase Inhibitors(NNRTIs)

- NNRTIs have potent activity against HIV-1 and are part of preferred initial regimens. Nevirapine is introduced first, Efavirenz confers most significant inhibition of viral infectivity, All exhibit same mechanism of action.
- **Mechanism of action:** • HIV reverse transcriptase is a heterodimer composed of 2 subunits (p66 and p51). NNRTIs bind p66 subunit at a hydrophobic pocket distant from active site of enzyme (allosteric site). This non-competitive binding induces a conformational change and inhibits reverse transcriptase enzymes.

Non-Nucleoside Reverse Transcriptase Inhibitors(NNRTIs)

- **Drug Name:** Nevirapine
- **Focus:** It is enzyme inducer- causes auto-induction of its own metabolism.
- **Dose:** Initially it is started at low dose and then is gradually increased in 2 weeks as level decreases by auto-induction. To reduce the skin rash only 200mg orally /day immediate release tablets are administered.
- **Adverse effects:** Nevirapine can cause severe life threating side effects, these include severe liver problems, skin rash and skin reactions.
- **Interactions:** nevirapine may reduce the blood levels and effect of ergotamine. It also may decrease the effect of methadone.

Protease Inhibitors

- First introduced in 1995 • Are an integral part of treatment • Exhibit activity against clinical isolates of both HIV-1 and HIV-2.
- **Mechanism of Action:** HIV protease is a 99 amino acid protein responsible for cleaving large proteins and enzymes leading to maturation of virus particles. PI's are competitive inhibitors which bind to HIV protease and prevent subsequent cleavage of polypeptides preventing the maturation of new virus particles further leading to production of immature non infectious viral progeny, which prevents further infection. • Acts at late step of virus cycle. • Effective in both acute and chronic infection.

Protease Inhibitors

- Pharmacokinetics • Significant first-pass metabolism by cytochrome P450 (CYP) 3A4 and 3A5.
- **Drug Name:** Ritonavir
- **Focus:** potent enzyme inhibitor, sufficient to inhibit CYP3A4 and increase the concentrations of most concurrently administered CYP3A4 substrates. Boosted PI regimen-decreases the frequency and toxicity of the co-administered drugs.
- **Dose:** 100 or 200 mg once or twice daily
- **Adverse effects:** asthenia, diarrhoea, hypertriglyceridemia, increased γ-glutamyl tranferase, nausea, vomiting and unpleasant taste.
- **Interactions:** ritonavir may increase the blood level of buprenorphine which may increase drowsiness, dizziness etc. cetirizine effect may increase by ritonavir.

Entry/Fusion Inhibitors

- **Mechanism of Action:** Binding of gp120 HIV surface protein to CD4 receptor induces a structural change that reveals V3 loop of the protein. V3 loop then binds with a chemokine co-receptor (principally either CCR5 or CXCR4), allowing gp41 to insert itself into the host cell membrane and folds to form six helical bundle. The latter is the driving force that bring the opposing membranes in close proximity resulting in the formation of fusion pore.
- **Drug Name:** Maraviroc
- **Focus:** selectively and reversibly binds CCR5 co-receptor, blocking V3 loop interaction and inhibiting fusion of cellular membranes.

Entry/Fusion Inhibitors

- **Pharmacokinetics:** 75% protein-bound, primarily to albumin and alpha1 acid glycoprotein. Terminal half-life is 15-30 hours. Metabolized through CYP3A4 and is a substrate for efflux pump p-glycoprotein.
- **Dose:** Dosage adjustment is required when administered in combination with potent inhibitors or inducers of CYP3A4. 300 mg PO bid, 150 mg PO bid (CYP3A4 inhibitors), 600 mg PO bid (CYP3A4 inducers), 300mg BD when given in combination with other ARD.
- **Adverse effects:** Hepatotoxicity, Constipation, Dizziness, Cough, Pyrexia, Upper respiratory tract infections, Rash, Musculoskeletal symptoms - Abdominal pain, nasopharyngitis.

Entry/Fusion Inhibitors

- Fusion Inhibitors • Act extracellularly to prevent fusion of HIV to CD4 or other target cell. • Blocks second step in fusion pathway by binding to gp41. • Thus preventing the formation of 6 helical bundles of gp41 required to complete the final step in the fusion process. • Not active against HIV-2.
- **Drug Name:** Enfuvirtide
- **Dose:** 90 mg SC bid • Dose adjustments are not required in patients with renal insufficiency or mild-to-moderate hepatic insufficiency.
- **Adverse effects:** Injection-site reactions (eg, pain, erythema, induration, nodules), diarrhea, nausea, fatigue, hypersensitivity reactions, increased rate of bacterial pneumonia.

Integrase Inhibitors

- HIV integrase -Responsible for transport and attachment of pro-viral DNA to host-cell chromosomes, allowing transcription of viral proteins and subsequent assembly of virus particles.
- Integrase inhibitors competitively inhibit integrase activity and thus preventing the integration of viral DNA into host chromosomes.
- Raltegravir & Elvitegravir ,
- Dolutegravir is Newest integrase inhibitor, appears to work against virus that is resistant to raltegravir and/or elvitegravir.
- once-a-day medication, doesn't require a booster.

Integrase Inhibitors

- Raltegravir:
- **Pharmacokinetics:** Rapid absorption, taken with or without food. half-life of 10-12 hours • 83% bound to plasma proteins • Metabolized by uridine diphosphate glucuronyl transferase •
- **Interaction:** Antacids may decrease absorption by divalent cation binding.
- Elvitegravir:
- **Dose:** Administered with low-dose ritonavir (100 mg) to reduce its first- pass metabolism and systemic clearance.
- **Interaction:** Coadministration results in a 20-fold increase in systemic exposure and a terminal half-life of 10-13 hours. • Antacids may decrease absorption.

VIRAL VIRUS