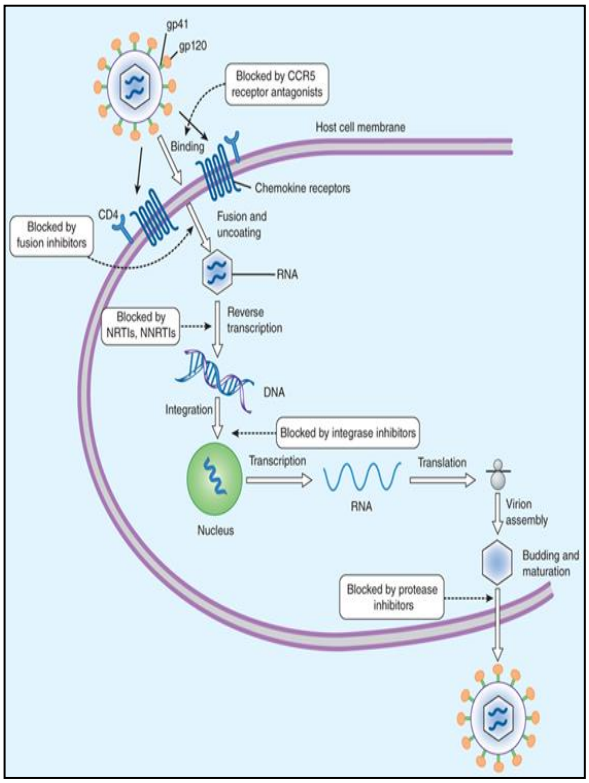
Problem 8 – Unit 6 – Pharmacology: Antiretroviral drugs

- **Summary of the replicative cycle of HIV virus:**
  - The gp120 which is present on the envelope of HIV virus will attach to CD4 receptors present on the host cell.
  - Then, gp120 will interact with chemokine receptors (CCR5 or CXCR4).
  - Gp41 which is embedded in the envelope of the virus will mediate the fusion of the virus with the host cell.
  - After fusion occurs, the virus will release nucleocaspid, RNA genome & reverse transcriptase, integrase and protease in the cytoplasm of the host cell.
  - The enzyme reverse transcriptase will use the RNA genome of the virus to synthesize a DNA copy from it and an RNA-DNA complex will be formed.
  - Then, reverse transcriptase will have a ribonuclease H activity and it will remove the RNA strand from the RNA-DNA complex so double-stranded DNA genome can be synthesized.
  - The double-stranded DNA will move to the nucleus of the host cell to be integrated with the host cell DNA and this will be mediated by integrase.
  - Replication will occur and RNA will be released from the nucleus to the cytoplasm. Protease will cleave polyproteins to polypeptides and assembly them in the new viral particles.
  - Viral particles will be released from the host cell.



- **Classes of antiretroviral drugs:**
  - **Entry inhibitors: they are divided into:**
    - ✓ CCR5 co-receptor antagonist (maraviroc).
    - ✓ Fusion inhibitor (enfuvirtide).
  - **Reverse transcriptase inhibitors: they are divided to:**
    - ✓ *NRTIs*: including zidovudine, stavudine, abacavir & tenofovir.
    - ✓ *NNRTIs*: including efavirenz
  - **Integrase inhibitors:**
    - ✓ Including raltegravir.
  - **Protease inhibitors:**
    - ✓ Including: indinavir, ritonavir, saquinavir & amprenavir.
- **Classes of HIV:**
  - **HIV-1**: it is more common worldwide.
  - **HIV-2**: common in west Africa and only 40% identical with proteins of HIV-1. When we will talk about drugs, we will not consider this type of the virus because:
    - ✓ Patterns of susceptibility to antiretroviral drugs vary.
    - ✓ Innate resistance to NNRTIs.
    - ✓ Some resistance to NRTIs and PIs.
    - ✓ Data regarding maraviroc are inconclusive.

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ENTRY INHIBITORS

- **Mechanism of action:**
  - **Maraviroc**: binds to CCR5 preventing gp120 binding, fusion and entry.
  - **Enfuvirtide**: targeting gp41 preventing fusion of the virus with the host cell.

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REVERSE TRANSCRIPTASE INHBITORS

- **NRTIs**:
  - They are the backbone of antiretroviral therapy: the regimen of antiretroviral therapy is using a combination of 3 drugs (two of them must be from different classes: more effective and minimizing resistance). Therefore, 2 drugs are chosen from this class and the other drug will be chosen from other classes such as PIs. This combination of drugs will be given in a (fixed-dose combination) which means that they will be combined in one tablet instead of taking each one of them separately (better for compliance)
  - **Certain NRTIs combination should be avoided because:**
    - ✓ There might be drug-drug interactions.
    - ✓ Similar resistance.
    - ✓ Overlapping toxicities.
  - **Mechanism of action:**
    - ✓ Competitive inhibition of reverse transcriptase enzyme.
    - ✓ There is incorporation into the growing viral DNA chain and this will lead to premature termination and thus no active viral particles will be produced.
    - ✓ These drugs must be activated via phosphorylation (being in the triphosphate form).
  - **Toxicity:**
    - ✓ Mitochondrial toxicity.
    - ✓ Lactic acidosis + hepatic steatosis (which can be fatal and patient must stop taking the drug when this condition occurs).
    - ✓ Zidovudine & stavudine: they cause dyslipidemia and insulin resistance.
    - ✓ Abacavir: causes increased risk of MI.
- **NNRTIs:**
  - **Mechanism of action:**
    - ✓ Non-competitive inhibition of reverse transcriptase enzyme.
    - ✓ Binding directly to allosteric sites and thus mediating the inhibition of the enzyme.
    - ✓ They don't need to be activated via phosphorylation.
  - **Toxicity:**
    - ✓ GI intolerance.
    - ✓ Skin rash, which can be serious (Steven-Johnson syndrome).
    - ✓ Potential drug-drug interactions (due to the metabolism of NNRTIs by CYP450 system).

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INTEGRASE INHBITIORS

- **Mechanism of action:**
  - They bind to the enzyme integrase and thus inhibiting the transfer of viral genome from the cytosol to the nucleus of the host cell. The viral genome cannot integrate with the host cell DNA.
- **Toxicity:**
  - Headache & GI intolerance.
  - Neuropsychiatric effects.
  - Some effects on lipid metabolism.
  - Rare but severe: systemic hypersensitivity & rhabdomyolysis (destruction of striated muscle cells).

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PROTEASE INHIBITORS

- **Mechanism of action:**
  - Preventing the processing of viral proteins into functional conformations and this will produce immature non-active viral particles.
  - They do not need to be activated.
- **Toxicity:**
  - Mild-moderate nausea, diarrhea and dyslipidemia.

- There is increased risk of: cardiovascular disease, drug-induced hepatotoxicity & intracranial hemorrhage with spontaneous bleeding.
- These drugs are extensively metabolized by CYP3A4 and thus they have enormous potential for drug-drug interactions. Ritonavir acts as both inhibitor and inducer of the cytochrome system and because it can inhibit the cytochrome system it has a boosting effect:
    - ✓ Which mean that it is given to patients with HIV to inhibit the cytochrome system and therefore the metabolism of other drugs will be reduced. This will prolong their half life and allow reduction in frequency.

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TUBERCULOSIS

- **Challenges of treating HIV + Tb:**
    - Polypharmacy: using multiple drugs to treat both conditions.
    - Toxicity.
    - Interactions between drugs will be increased.
    - Compliance.
- Rifabutin is the safest to be given although it is not given in normal situations (patient suffering only from Tb) because it is more expensive.

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PREGNANCY

- **During pregnancy**: antiretroviral drugs are given to the mother to reduce the viral load.
- **Mode of delivery**: caesarian is preferred although if the viral load is reduced normal vaginal delivery can be considered.
- **After delivery**:
    - **Mother**: will continue taking antiretroviral therapy.
    - **Newborn**: will be given drugs at least for 6 months.
    - **Breast feeding**: prevented.