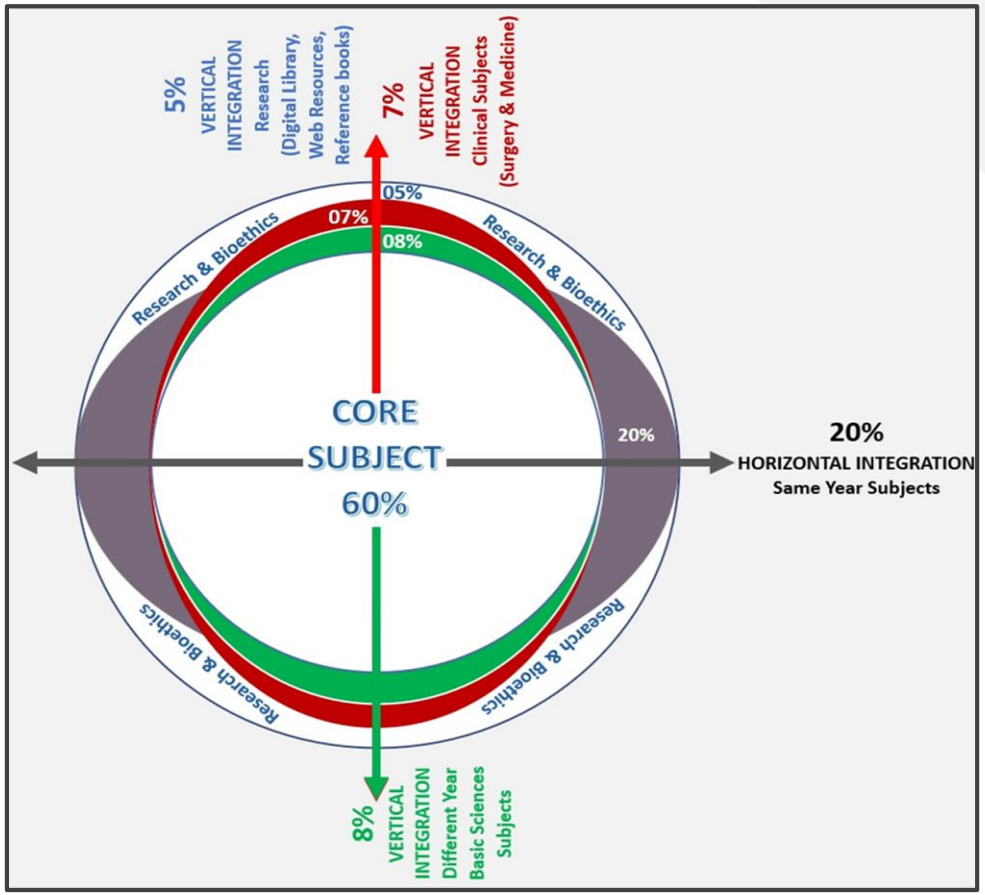
ANTI-VIRAL DRUGS

Dr. Zunera Hakim

UMAR'S MODEL OF INTEGRATION

3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	



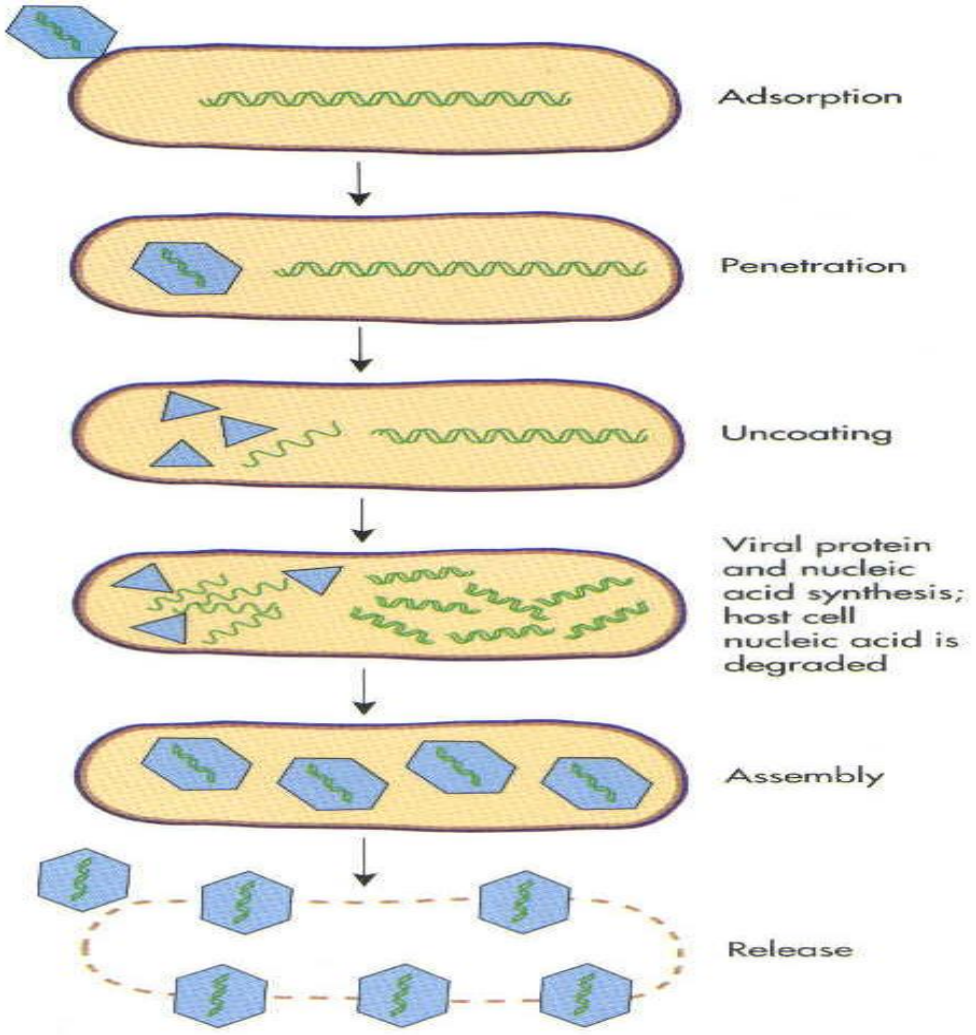
LEARNING OBJECTIVES

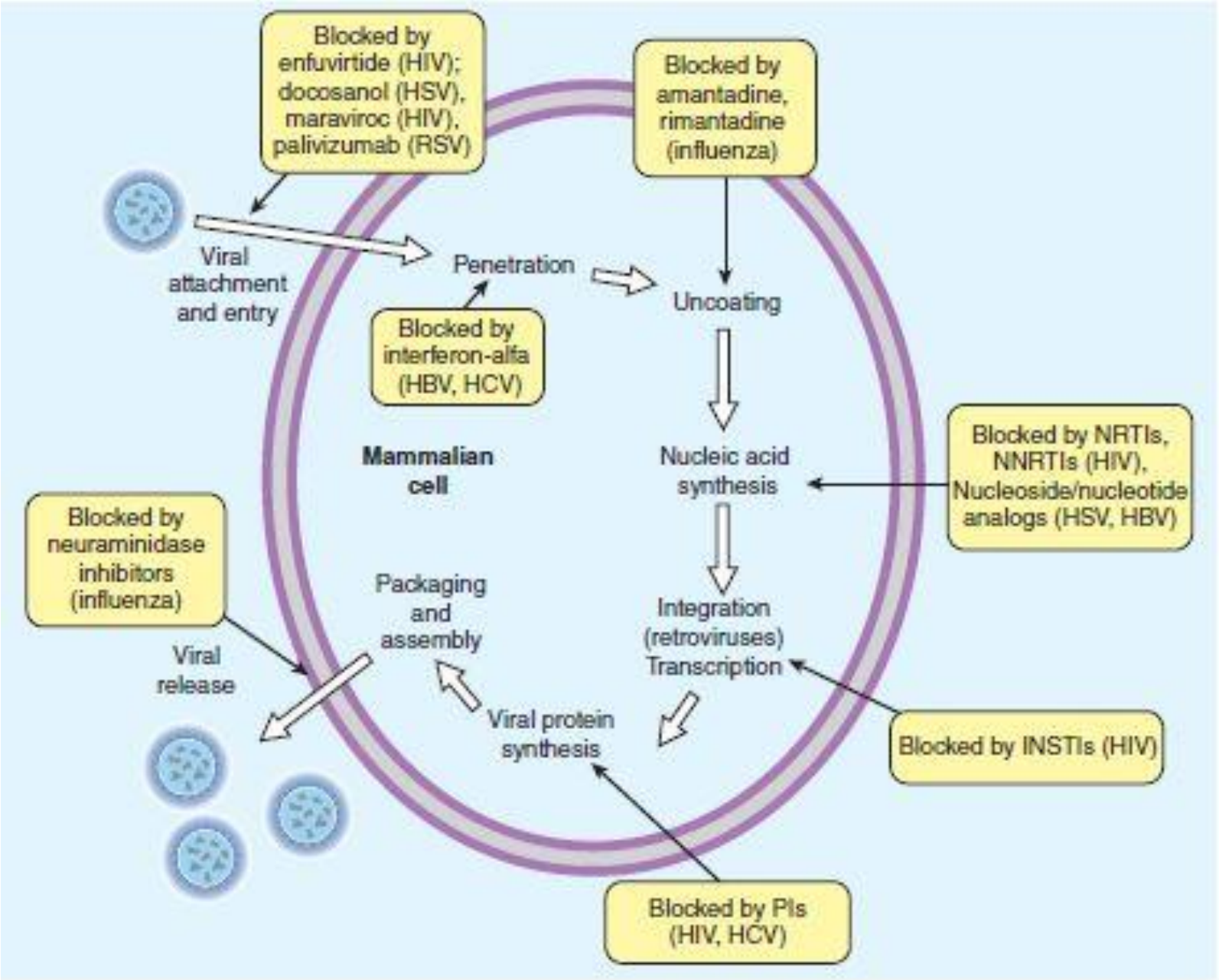
At the end of the lecture, students will be able to:

- Recall life cycle of viruses
- Classify antiviral drugs according to action on virus replication
- Classify antiviral drugs according to viral diseases
- Outline the salient pharmacokinetic & pharmacodynamic features of antiviral drugs used to treat HSV, VZV & CMV and influenza infections
- Define HAART
- Describe the mechanism of action of major drug groups used in AIDS

VIRAL REPLICATION & DRUG TARGETS

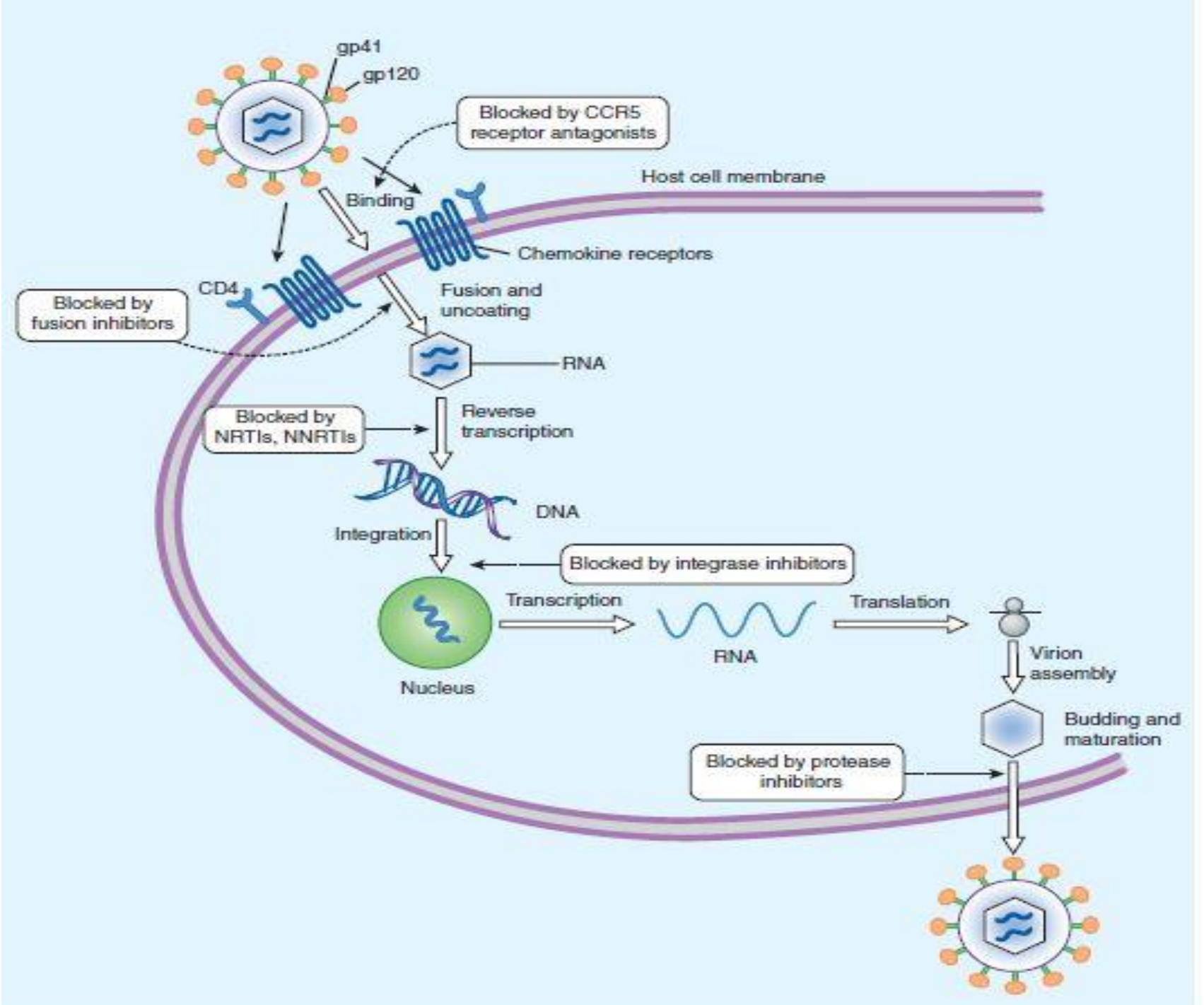
- Cell entry
  - Attachment
  - Penetration
- Uncoating/dismantling
- Viral nucleic acid and protein synthesis
- Post-translational modifications
- Assembly of virion components
- Release of virions




Blocked by enfuvirtide (HIV); docosanol (HSV), maraviroc (HIV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs, NNRTIs (HIV), Nucleoside/nucleotide analogs (HSV, HBV)
Blocked by neuraminidase inhibitors (influenza)
Packaging and assembly
Integration (retroviruses) Transcription
Viral release
Viral protein synthesis
Blocked by INSTIs (HIV)
Blocked by PIs (HIV, HCV)

“There is no one in the world who, once infected, has been able to clear the virus from their body with no external treatment”

Professor Lucy Dorrell


gp41
gp120
Blocked by CCR5 receptor antagonists
Host cell membrane
Binding
Chemokine receptors
CD4
Blocked by fusion inhibitors
Fusion and uncoating
RNA
Blocked by NRTIs, NNRTIs
Reverse transcription
DNA
Integration
Blocked by integrase inhibitors
Transcription
Translation
RNA
Nucleus
Virion assembly
Budding and maturation
Blocked by protease inhibitors

ANTI-RETROVIRAL AGENTS

CLASSIFICATION

A. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Zidovudine
- Didanosine
- Lamivudine
- Stavudine
- Zalcitabine
- Abacavir
- Emtricitabine
- Tenofovir (nucleotide)

ANTI-RETOVIRAL AGENTS

CLASSIFICATION

B. Non-Nucleoside Reverse Transcriptase inhibitors (NNRTIs)

- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine
- Rilpivirine

C. Protease Inhibitors (PI)

- Atazanavir
- Saquinavir
- Ritonavir
- Tipranavir
- Indinavir
- Nelfinavir

Darunavir
Lopinavir
Fosamprenavir

ANTI-RETROVIRAL AGENTS

CLASSIFICATION

D. Integrase Strand Transfer Inhibitors

- Raltegravir
- Elvitegravir
- Dolutegravir

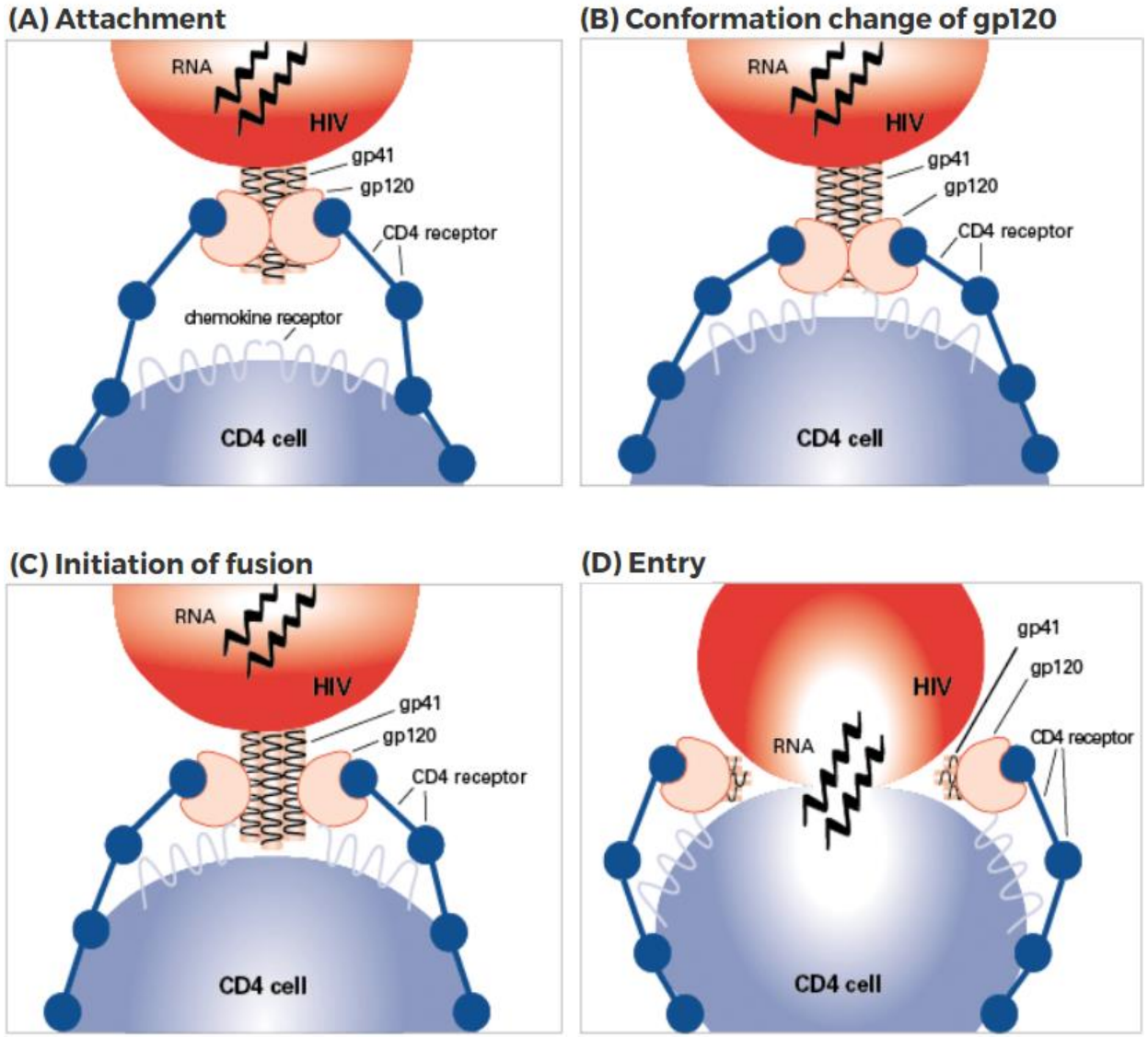
E. Fusion Inhibitors

- Enfuviritide

F. Entry Inhibitors

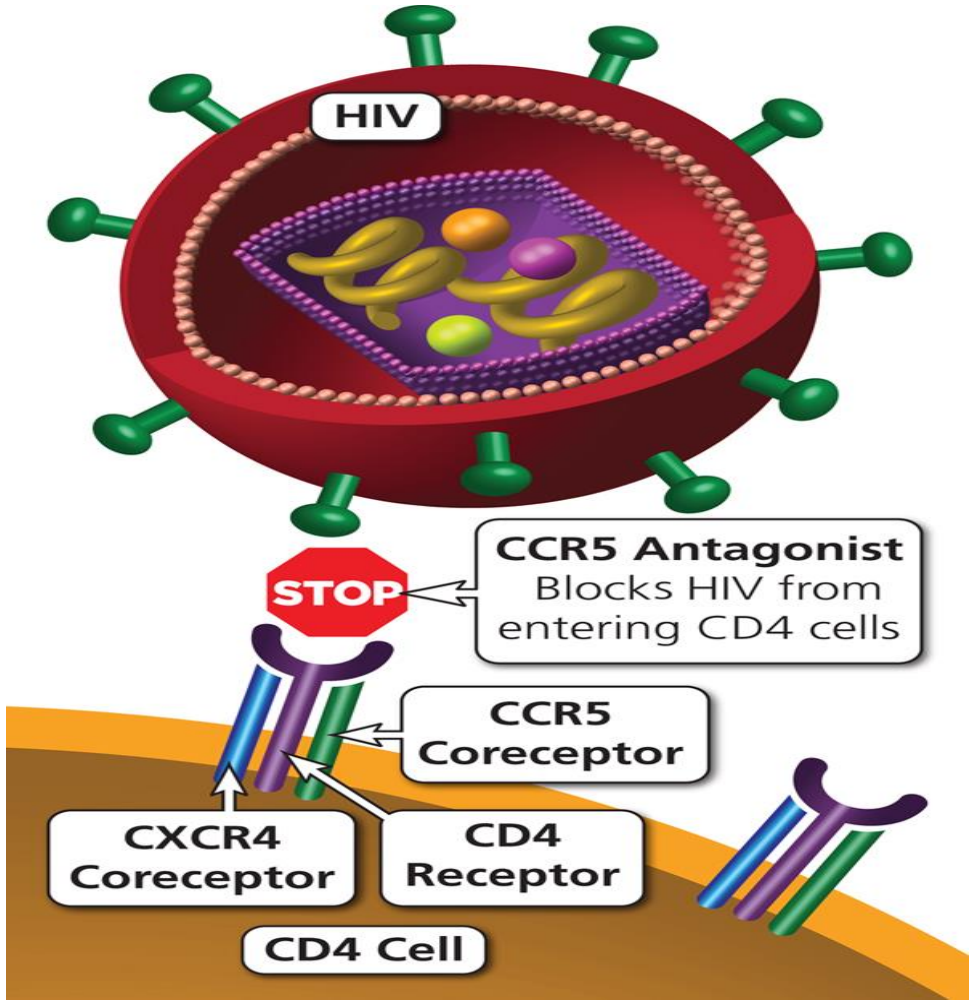
- Maraviroc

ENTRY AND FUSION OF HIV



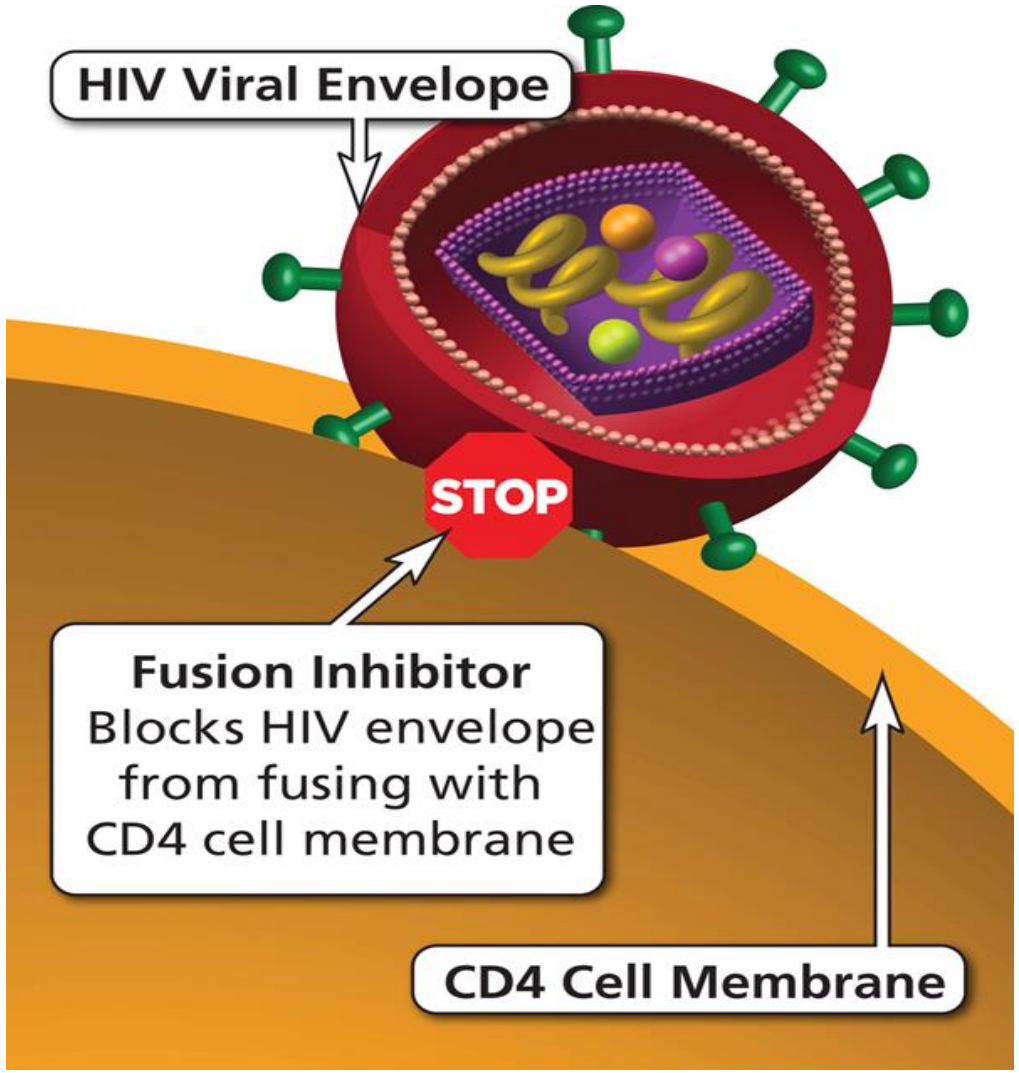
- **Attachment inhibitor**: Fostemsavir
- **Post-attachment inhibitor:** Ibalizumab
- **CCR5 antagonist**: Maraviroc
- **Fusion inhibitor:** Enfuvirtide

ENTRY INHIBITOR



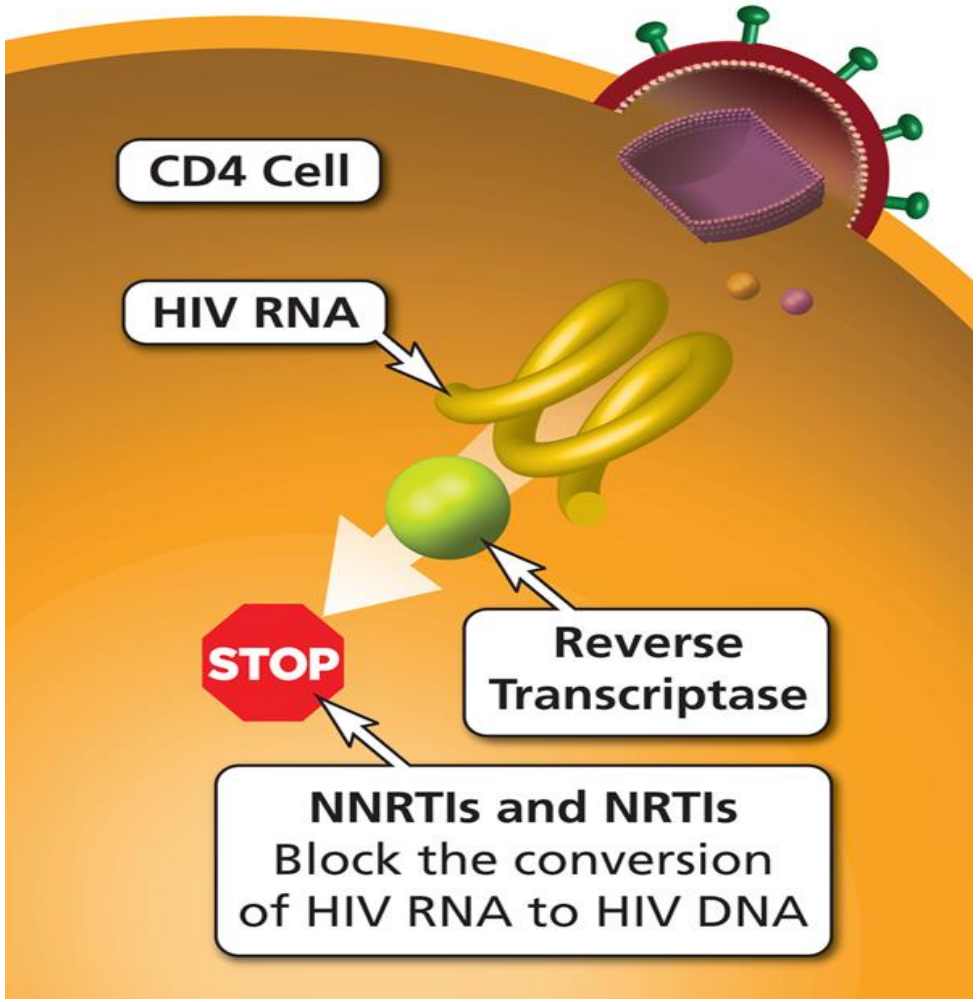
- **Maraviroc** binds specifically and selectively to the host protein CCR5, necessary for entrance of HIV into CD4+ cells
- Only effective against CCR5 tropic viruses(tropism assay required before therapy)
- Orally absorbed, metabolized by CYP3A4 and excreted in **feces** and urine
- GIT upset, headache ,**hepatotoxicity**, URTI and skin rash

FUSION INHIBITOR



- Enfuvirtide is a linear 36 amino acid synthetic peptide
- It binds to glycoprotein 41 on viral envelop, preventing conformational changes, required for fusion of virus with cellular membranes
- Subcutaneous administration ,non CYP metabolism
- Local site reactions, hypersensitivity events

REVERSE TRANSCRIPTASE INHIBITORS



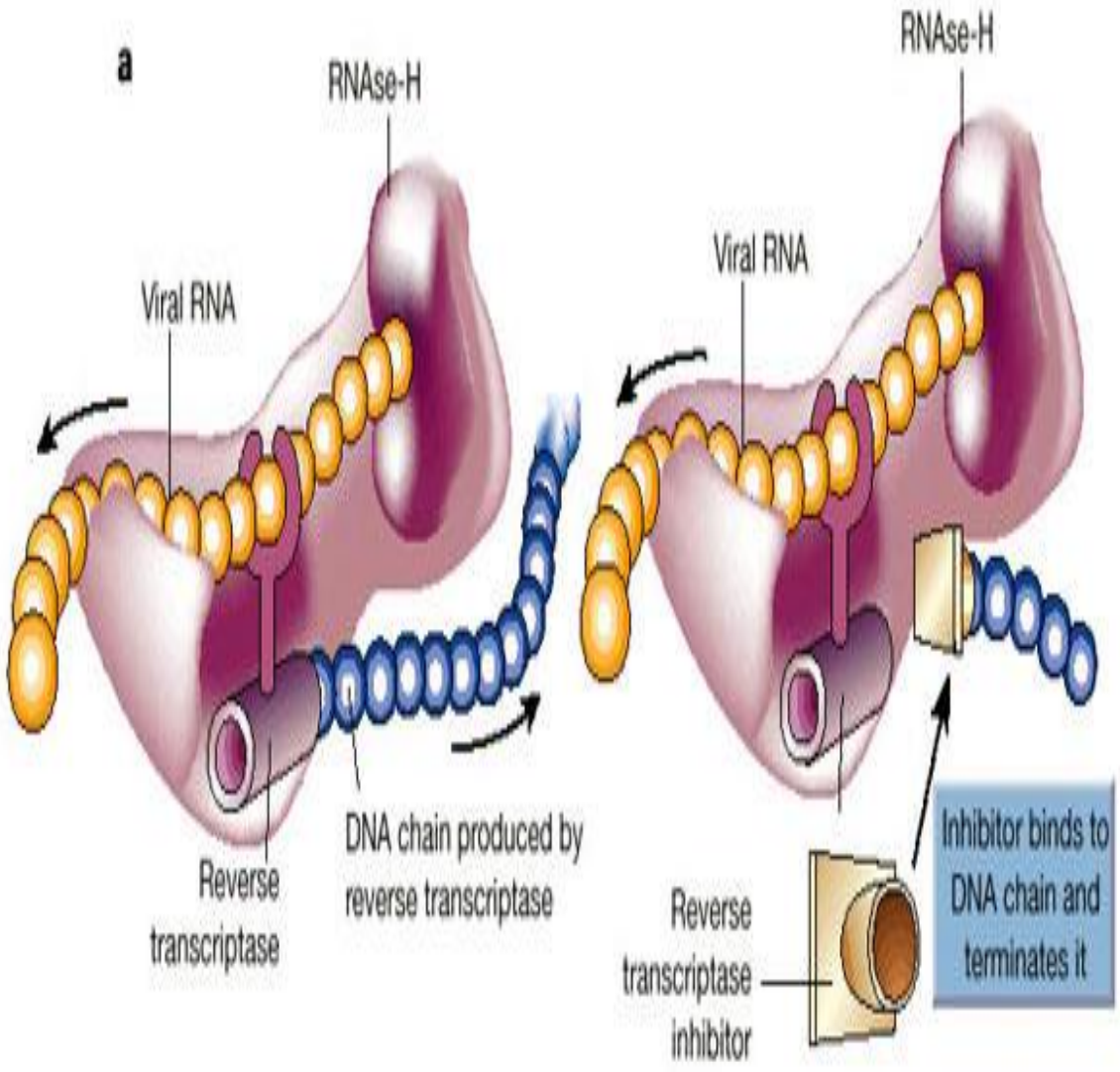
- Reverse transcriptase converts viral RNA into proviral DNA which gets incorporated into host cell DNA

- There are two types of RTIs:

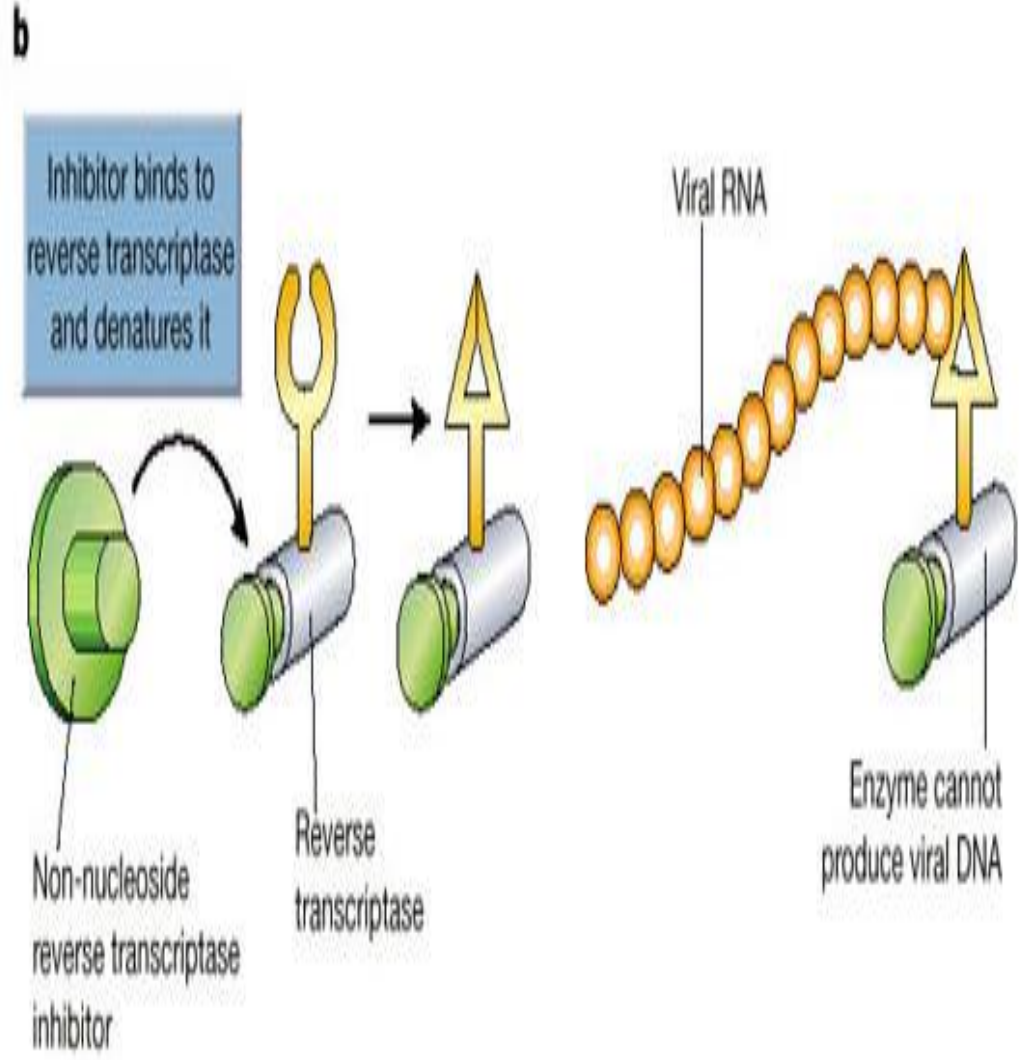
  a)Nucleoside/nucleotide Reverse Transcriptase Inhibitors (NRTI)

  b) Non-nucleoside Reverse Transcriptase Inhibitors(NNRTI)

NRTIs (HIV 1& HIV 2)

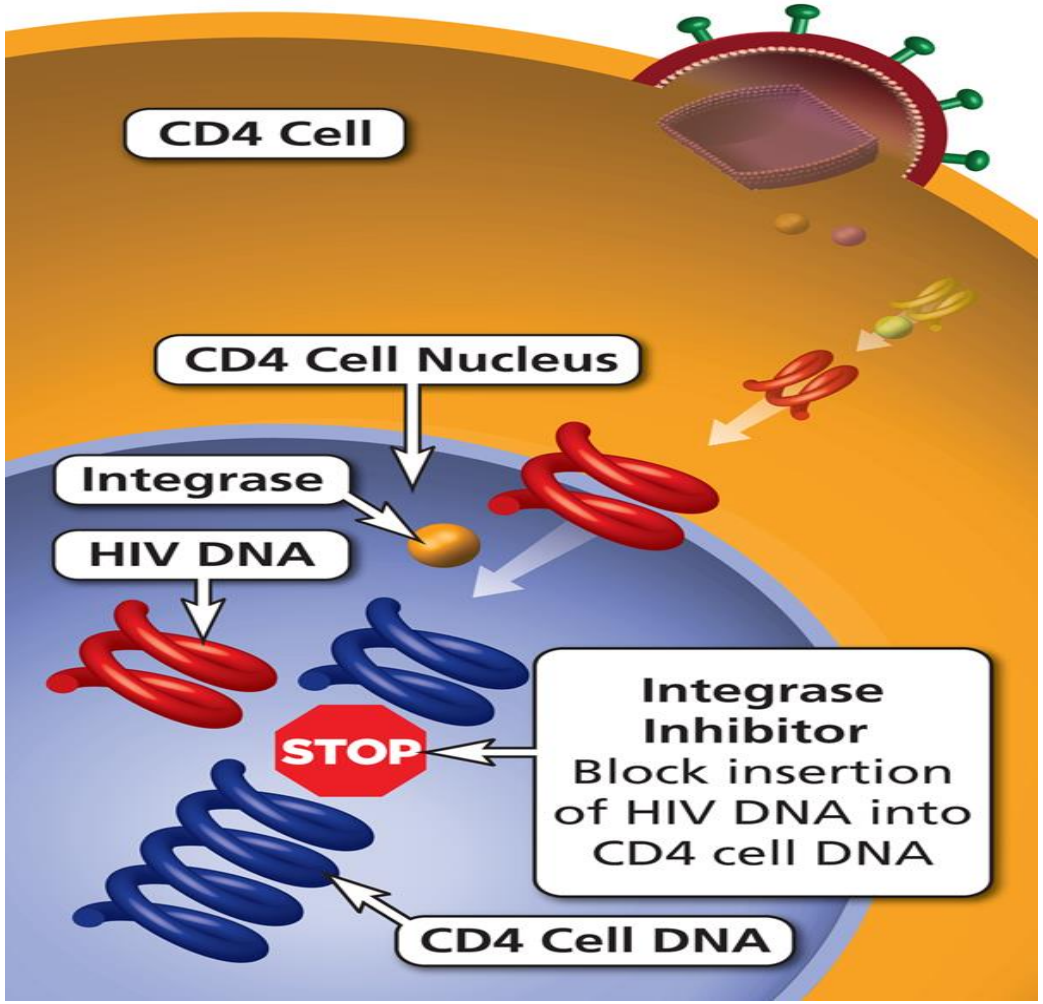


NNRTIs (HIV-1)



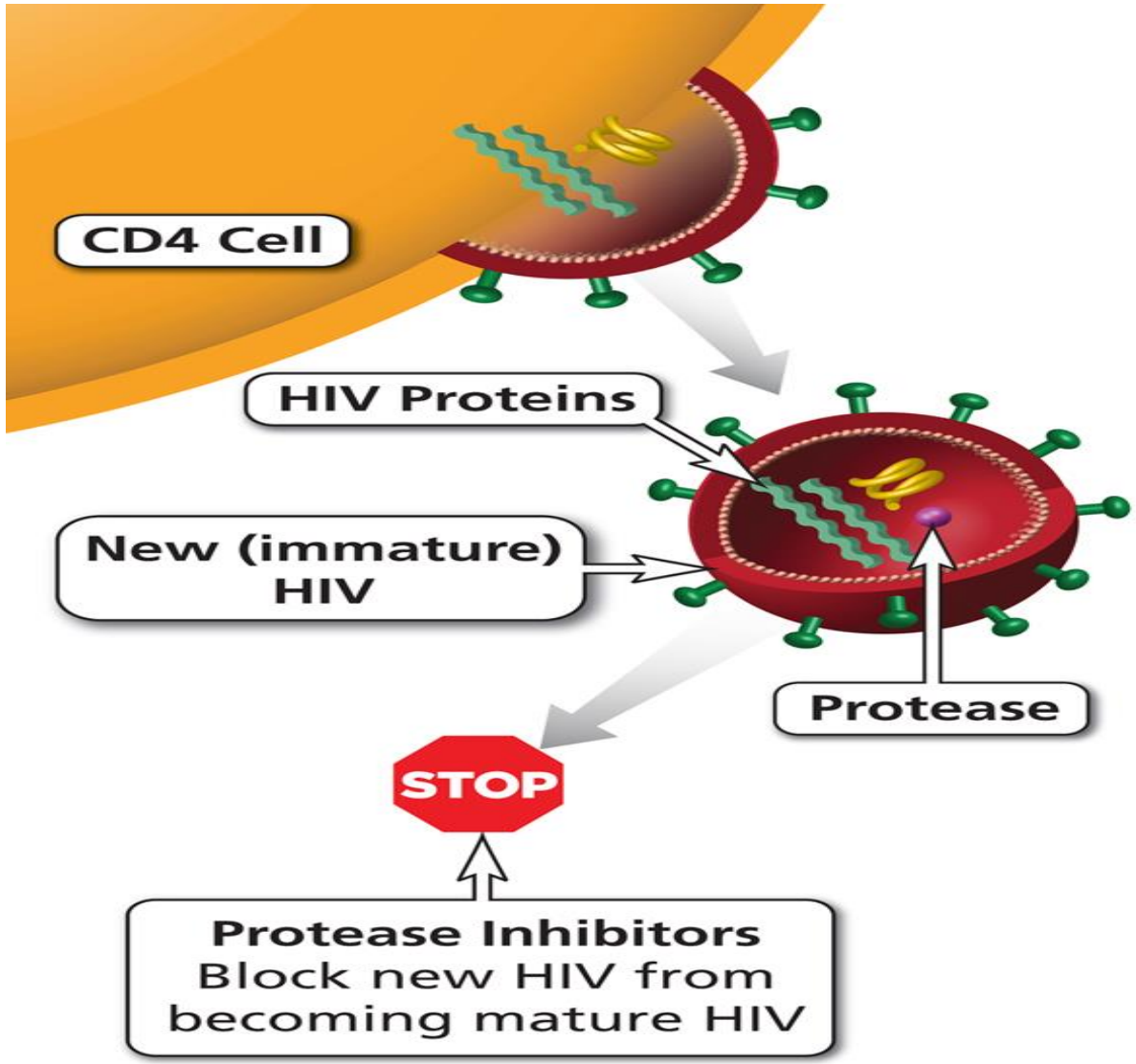
DRUG	ADVERSE EFFECTS AND INTERACTIONS
NRTIs	
All NRTIs	Lactic acidosis, hepatic steatosis, and lipodystrophy (all higher with stavudine)
Abacavir	Hypersensitivity reactions
Didanosine	Pancreatitis, peripheral neuropathy, gastrointestinal intolerance
Emtricitabine	Headache, nausea, diarrhea, fatigue, depression, insomnia
Stavudine	Pancreatitis, peripheral neuropathy
Tenofovir	Headache, gastrointestinal intolerance, renal impairment
Zidovudine	Headache, gastrointestinal intolerance, bone marrow suppression
NNRTIs	
All NNRTIs	Rash, drug interactions
Efavirenz	Neuropsychiatric reactions, teratogenic effects
Etravirine	Diarrhea, peripheral neuropathy, redistribution of body fat
Nevirapine	Hepatotoxicity, rash including Stevens-Johnson syndrome; increases metabolism of protease inhibitors, contraceptive steroids, and other drugs
Rilpivirine	Insomnia and sleep disturbances, headache, dizziness, redistribution of body fat

INTEGRASE INHIBITOR



- Bind to the integrase enzyme when the integrase enzyme is attached to the viral DNA and prevent formation of covalent bonds between host and viral DNA
- Reduced BA with divalent cations
- Can be given with cobicistat as PK booster (elvitegravir)
- Metabolised by UGT and CYP
- Use is associated with hypersensitivity reactions (rash),GIT & musculoskeletal effects
- Raltegravir safe in pregnancy

PROTEASE INHIBITOR



- Protease cleaves HIV precursor proteins at appropriate places to produce functional proteins that are needed for a mature virion
- PI bind to active site of protease preventing cleavage resulting in immature non infectious HIV virus.
- Orally available and metabolized before fecal excretion
- Synergistic with NRTIs
- GIT, lipodystrophy, fat redistribution, hepatotoxicity, osteomalacia, QT interval prolongation and bleeding tendency, hyperglycemia
- Potent CYP inhibitor (ritonavir)-used to **boost** the levels of other PIs

ADVERSE EFFECTS OF ART

Protease Inhibitors	
All protease inhibitors	Lipodystrophy (fat accumulation), hyperlipidemia, insulin resistance and diabetes, liver dysfunction and hepatitis; inhibit metabolism of other drugs including protease inhibitors, antiarrhythmic agents, opioids, and tricyclic antidepressants
Atazanavir	PR interval prolongation
Fosamprenavir	Gastrointestinal intolerance, rash
Lopinavir, ritonavir	Gastrointestinal intolerance
Other Drugs	
Enfuvirtide	Injection site reactions, hypersensitivity reactions
Maraviroc	Upper respiratory symptoms, possible hepatotoxicity
Raltegravir	Headache, diarrhea, nausea, vomiting

HAART

Highly Active Anti-Retroviral Therapy

Multidrug/combination therapy used in the treatment of HIV/AIDS to delay progression and prolong survival by suppressing viral replication

It provides synergistic antiviral effect (sequential block of the steps of viral replication) and reduces the development of resistance

HAART

MAIN COMPONENTS

- It usually involves using **three** agents from **two** different classes working by different mechanism at different phases of the viral life cycle.
- The most frequently used combinations employ a backbone of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus a third drug (anchor drug)
- The third anchor drug that is paired with two NRTIs is typically either an NNRTI, a ritonavir-boosted protease inhibitor, or an integrase inhibitor
- Three NRTIs are only used when NNRTIs and PI can not be used (due to drug interactions)
- Alternative combinations are used if clinical variables deteriorate or unwanted drug effects occur

REGIMENS FOR PREVENTING TRANSMISSION OF HIV

PRE-EXPOSURE PROPHYLAXIS (PrEP)

- Tenofovir + Emtricitabine

POST-EXPOSURE PROPHYLAXIS (PEP)

- Tenofovir + Emtricitabine+Raltegravir

PREGNANCY

- Zidovudine + Lamivudine+ Ritonavir boosted lopinavir or atazanavir
- Zidovudine to infant for 6 weeks

	Drugs	Comments
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)	Tenofovir, abacavir, zidovudine,* stavudine,* lamivudine, emtricitabine	Tenofovir is associated with renal and perhaps bone dysfunction. Abacavir is associated with hypersensitivity reactions in at risk individuals (HLA B5701) and is associated in some studies with an increased risk of cardiovascular disease. Abacavir might be less potent than tenofovir in patients with high viral loads. Zidovudine and stavudine are associated with profound fat redistribution (lipoatrophy). All NRTIs are associated with potential to cause risk of severe lactic acidosis. The combination of tenofovir and emtricitabine is the preferred first-line regimen in most regions
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz, nevirapine,* etravirine	Efavirenz can cause CNS toxicity (which is usually time limited). Efavirenz has teratogenic potential and should be used with caution in woman who might become pregnant. Nevirapine can cause severe hepatoxicity when used in patients with higher CD4 cell counts (more than 250 cells per µL for women and more than 400 cells per µL for men). Etravine is given twice daily and has generally been used as second-line regimen
Integrase inhibitors	Raltegravir	Raltegravir has no short-term and no known long-term toxic effects, although data are scarce
Protease inhibitors	Fosamprenavir, atazanavir, darunavir, lopinavir, saquinavir (ritonavir)	Most protease inhibitors are extensively metabolised by the P450 CYP3A system; ritonavir is generally given at low doses (100–200 mg per day) to inhibit P450 and boost the co-administered protease inhibitors. Most protease inhibitors are associated with hyperlipidaemia and other metabolic abnormalities such as insulin resistance. Long-term protease inhibitor exposure has been associated with increased risk of cardiovascular disease
CCR5 inhibitors	Maraviroc	Maraviroc is only active in patients who do not have virions that use CXCR4 for cell entry. A specialised assay is therefore needed to screen for coreceptor tropism. By contrast with other antiretroviral drugs, maraviroc binds to a host rather than a viral target. Maraviroc has an immunomodulatory effect that is independent of its effect on HIV replication; the clinical significance of this activity is unknown.
Fusion inhibitors	Enfuvirtide	Enfuvirtide must be given subcutaneously twice daily and is very expensive. The drug is generally used only in patients with no other therapeutic options

*Some drugs such as zidovudine, stavudine, and nevirapine are generally used in resource-limited regions because of cost considerations. These drugs are generally not recommended as preferred agents in resource-rich regions in view of their potential toxic effects.

Table: **Antiretroviral drugs generally used in clinical practice**

RESEARCH

Newly Approved HIV Medications

Ian Villaluz, PharmD Candidate 2021
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Crestview, Florida
Glenn R. Grantner, PharmD, BCPS
Clinical Pharmacist
Sacred Heart Hospital
Pensacola, Florida

US Pharm. 2020:45(10):17-25

ABSTRACT: The available antiretroviral (ARV) drugs for the treatment of HIV have expanded since 2018. Novel types of ARVs with new mechanisms of action have been approved, including ibalizumab-uiyk and fostemsavir. There have also been approvals of combination tablets of previously available drugs, such as bictegravir/emtricitabine/tenofovir alafenamide and dolutegravir/lamivudine. Finally, there has been an expansion in approved indications for previously available ARVs themselves, such as emtricitabine/tenofovir alafenamide for use in pre-exposure prophylaxis.

BIOETHICS

National

Private healthcare facilities countrywide denying treatment to HIV patients

By M. Waqar Bhatti | June 13, 2023

END OF LECTURE ASSESSMENT

1. Which of the following is not an important property of anti-viral drugs?

A. They are nucleoside/nucleotide prodrugs
B. They are activated inside infected host cells only
C. They use viral and host enzymes for activation
D. They don't require host immune system for their action
E. They use phosphorylation for activation

2. Which point in the replication cycle appears most easily blocked by antivirals?

A. Virus absorption
B. Virus penetration
C. Virus RNA and DNA replication
D. Virus protein synthesis
E. Exit of viruses from the cell

3. Choose the following correct combination of drug and virus:

A. Amantadine versus influenza B
B. Daclatasvir versus hepatitis C
C. Zidovudine versus hepatitis B
D. Saquinavir versus influenza A
E. Acyclovir versus HIV-AIDS