Anti HIV Pharmacotherapy

By

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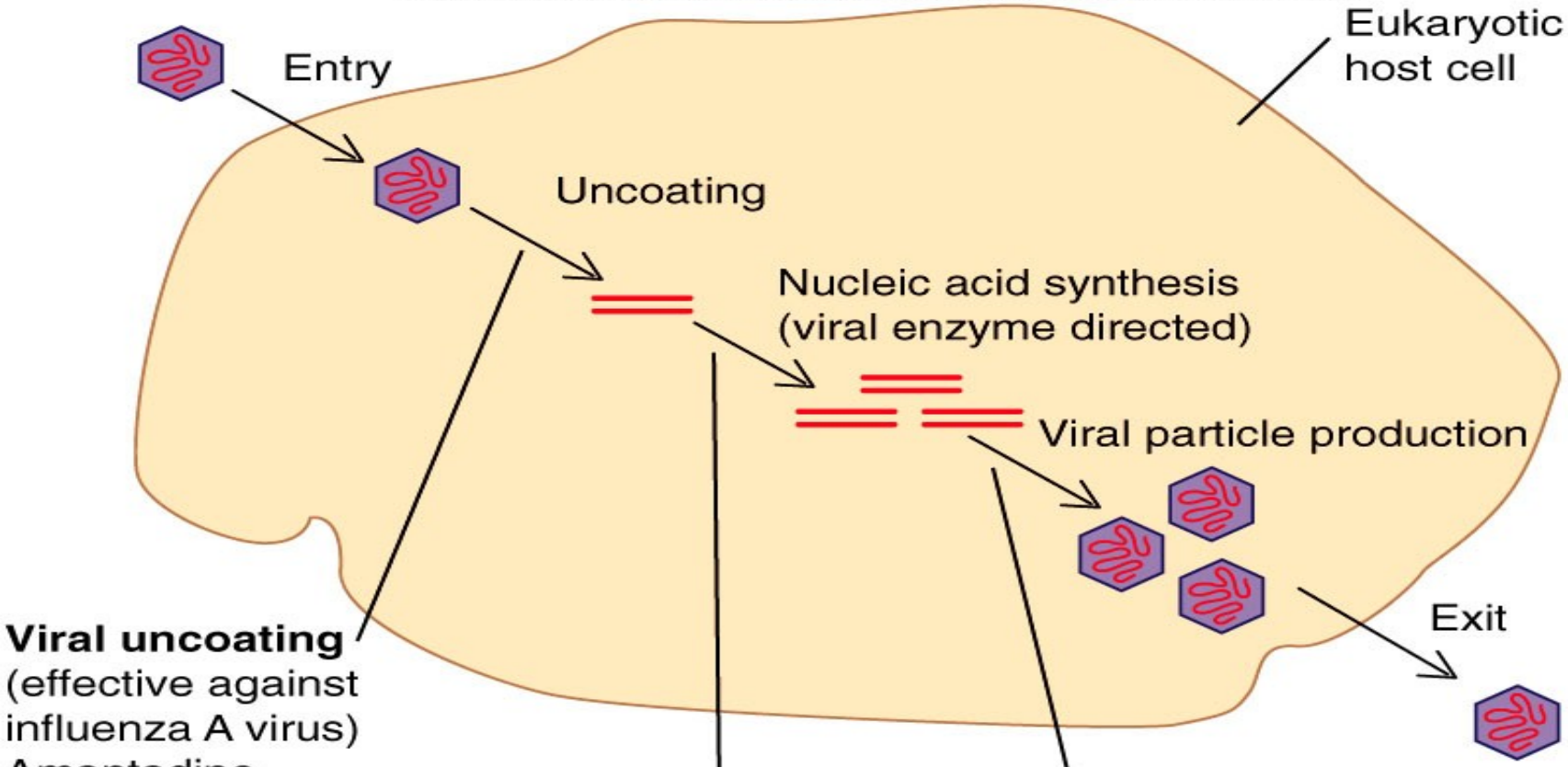
LEARNING OBJECTIVES

- Classify anti HIV drugs
- Describe the role of entry inhibitors, Integrase inhibitors, Protease inhibitors, NRTIs and NNRTIs in HIV treatment
- Describe the adverse effects of Zidovudine and Indinavir
- Describe the rationale of HAART therapy

Classification of Viruses

- **DNA viruses**
- E.g: Papillomavirus (warts), Parvovirus (erythema infectiosum, aplastic anemia), Poxvirus (smallpox), Herpesvirus (Herpes), Hepadenovirus (serum hepatitis), Adenovirus (sore throat, conjunctivitis) etc

- **RNA viruses**
- E.g: Arbovirus (Yellow fever), Arenavirus (Meningitis), Bunyavirus (encephalitis), Coronavirus (URTI), Orthomyxovirus (Influenza), Paramyxovirus (Measles, Mumps), Picornavirus (Polio, Meningitis, URTI), Rhabdovirus (Rabies), **Retrovirus (AIDS, Leukemia)** etc



Viral uncoating
(effective against influenza A virus)
Amantadine
Rimantadine

Nucleic acid synthesis
(effective primarily against herpesviruses and HIV)
Nucleoside analogs
Non-nucleoside polymerase inhibitors
Non-nucleoside reverse transcriptase inhibitors

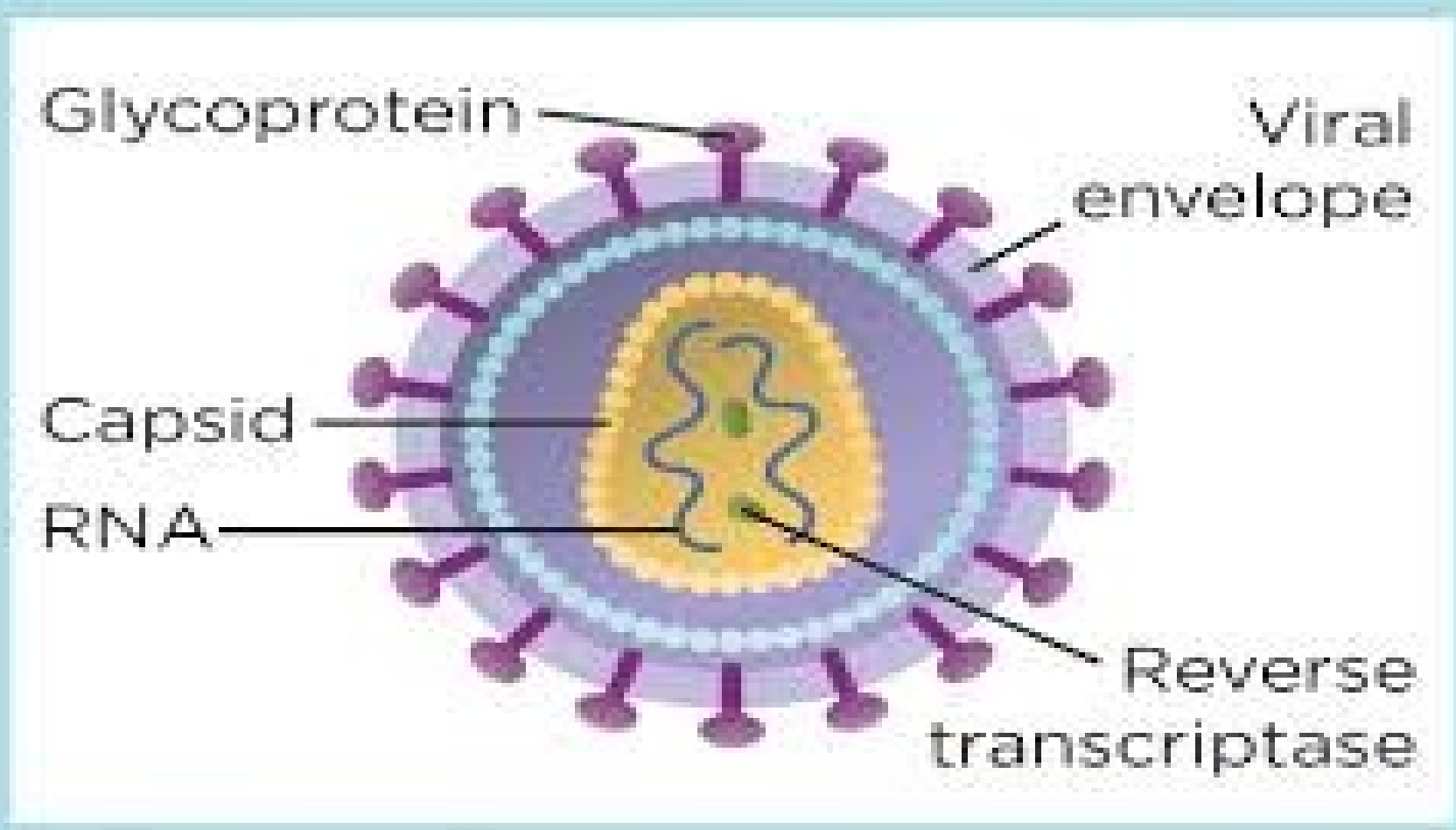
Assembly and release of viral particles
(effective against HIV)
Protease inhibitors
(effective against influenza viruses)
Neuraminidase inhibitors

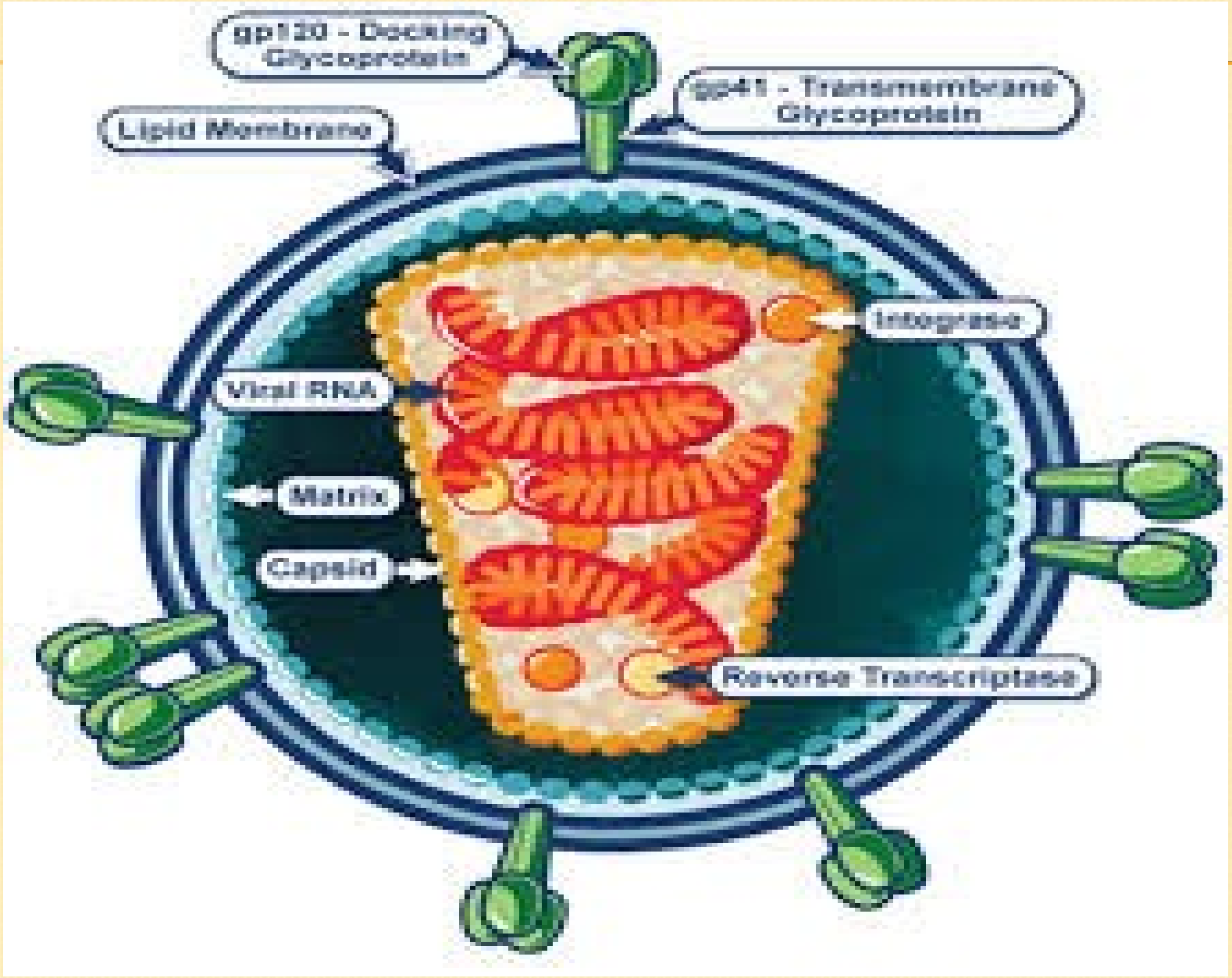
H I V: FACTS

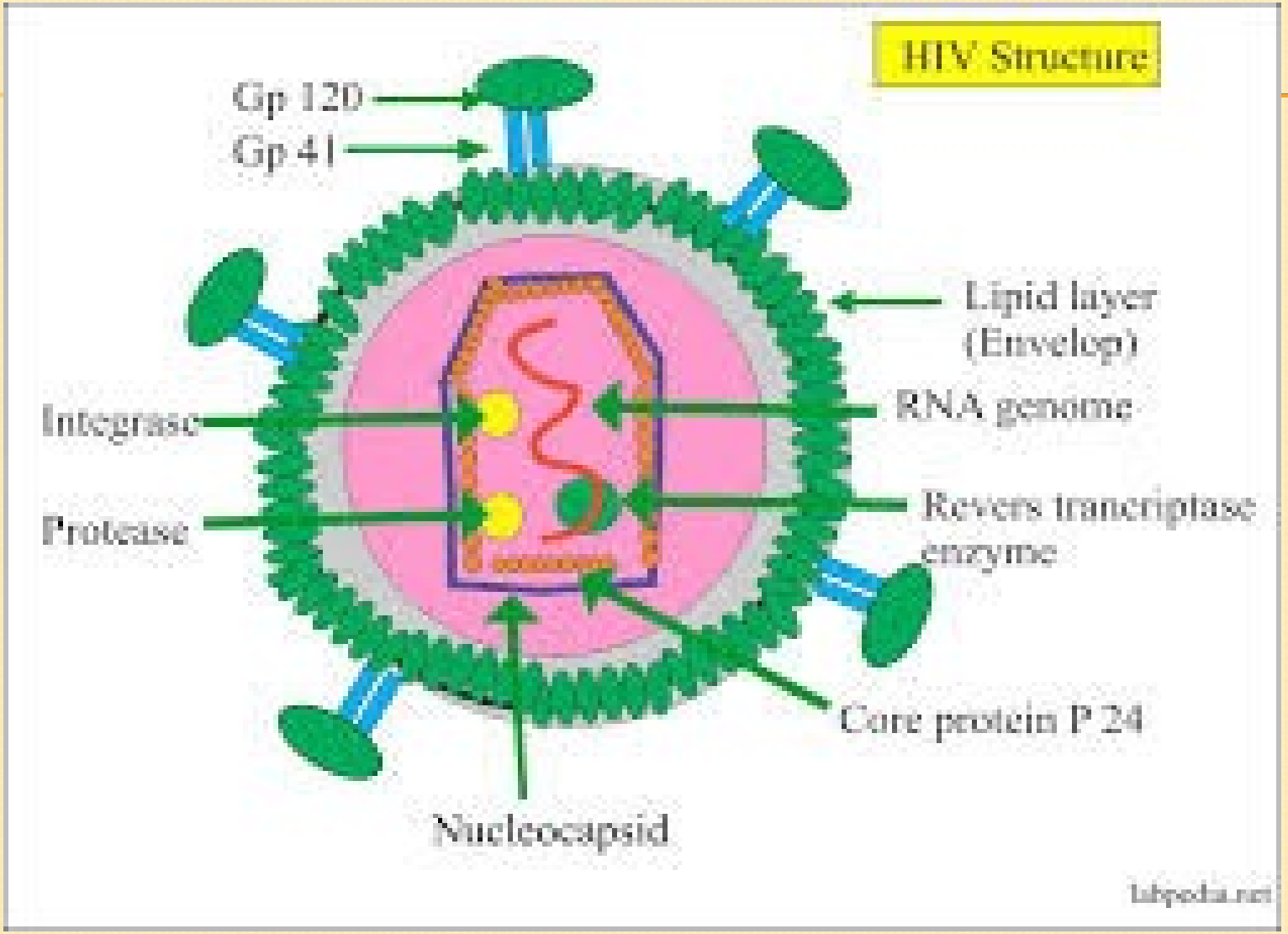
ETIOLOGICAL AGENT

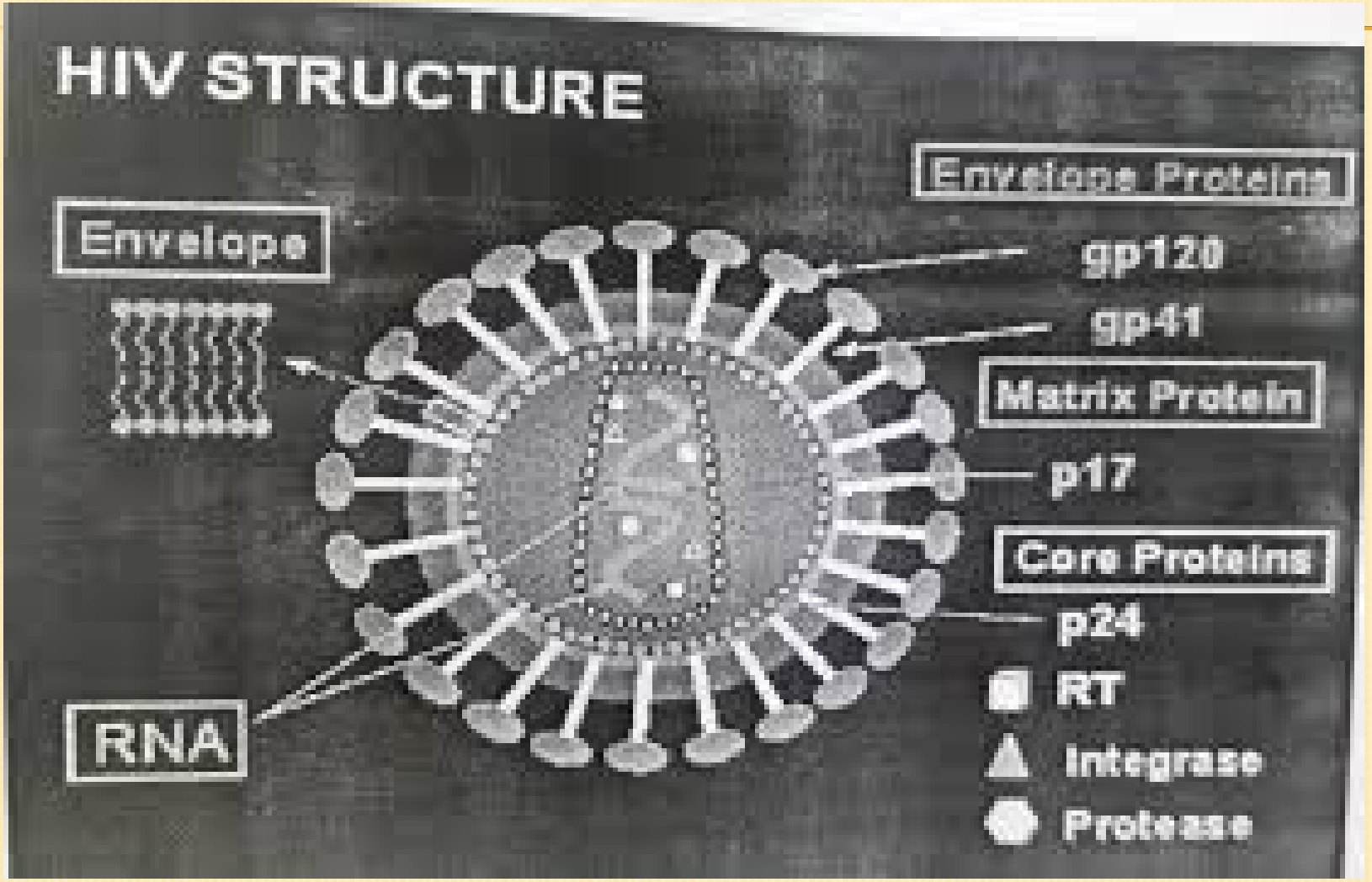
- Human immunodeficiency virus
  1. **HIV-1** → most epidemic,worldwide
  2. **HIV-2** →western Africa,SIV
- Family retroviridae, subfamily lentiviruses.
- Adapted for chronic persistent infection with gradual onset of clinical symptons.
- Reverse Transcriptase(RT) →RNA →DNA
- RT is very error prone & lacks proof reading function, so resistance develops rapidly.
- Transmission routes– hetero/homo-sexual, blood /blood products, transplacental, Injecting drug use.
- Central core contains → RNA & 3 genes gag, pol, env
  - **gag →polyprotein→structural protein**
  - **gag & pol→RT,Protease,Integrase**
  - **Env→envelope protein**

Fig 1. **HIV virus structure**




gp120 - Docking Glycoprotein
gp41 - Transmembrane Glycoprotein
Lipid Membrane
Integrase
Viral RNA
Matrix
Capsid
Reverse Transcriptase

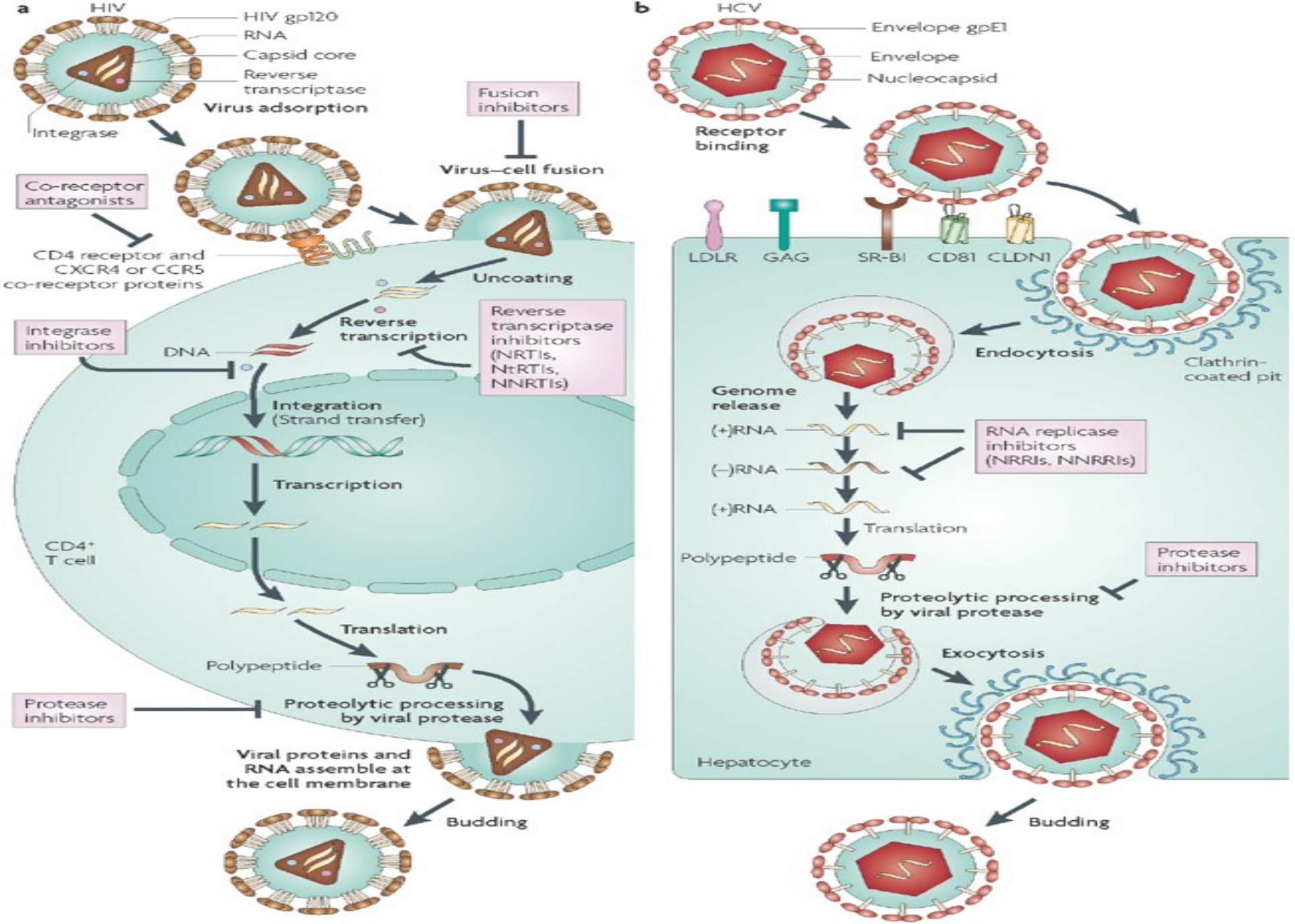

HIV Structure
Gp 120
Gp 41
Lipid layer
(Envelop)
RNA genome
Integrase
Protease
Revers trancriptase
enzyme
Core protein P 24
Nucleocapsid


HIV STRUCTURE
Envelope
Envelope Proteins
gp120
gp41
Matrix Protein
p17
Core Proteins
p24
RT
Integrase
Protease
RNA

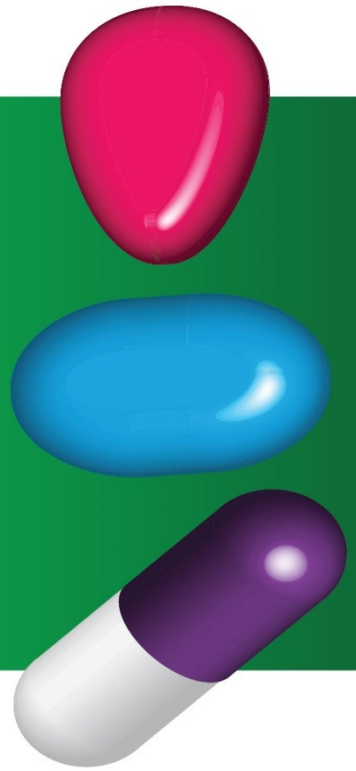
Antiviral drug classification

A. Non-Retroviral Antiviral Agents
   1. Anti-herpesvirus Agents
   2. Anti-influenza Agents
   3. Anti-hepatitis Agents

B. Antiretroviral Agents
   1. Nucleoside Reverse Transcriptase Inhibitors (NIRTI)
   2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)
   3. Protease Inhibitors (PI)
   4. Entry Inhibitors
   5. Integrase Strand Transfer Inhibitors


a
HIV
HIV gp120
RNA
Capsid core
Reverse transcriptase
Integrase
Virus adsorption
Fusion inhibitors
Virus–cell fusion
Co-receptor antagonists
CD4 receptor and CXCR4 or CCR5 co-receptor proteins
Uncoating
Reverse transcription
Reverse transcriptase inhibitors (NRTIs, NtRTIs, NNRTIs)
Integrase inhibitors
DNA
Integration (Strand transfer)
Transcription
CD4+ T cell
Translation
Polypeptide
Protease inhibitors
Proteolytic processing by viral protease
Viral proteins and RNA assemble at the cell membrane
Budding
b
HCV
Envelope gpE1
Envelope
Nucleocapsid
Receptor binding
LDLR
GAG
SR-BI
CD81
CLDN1
Endocytosis
Clathrin-coated pit
Genome release
(+)RNA
(–)RNA
(+)RNA
RNA replicase inhibitors (NRRIs, NNRRIs)
Translation
Polypeptide
Protease inhibitors
Proteolytic processing by viral protease
Exocytosis
Hepatocyte
Budding

Antiretroviral Therapy... What does it do?



Antiretroviral therapy (ART) is the daily use of a combination of HIV medicines to treat HIV. ART saves lives, but does not cure HIV.

- Reduces the amount of HIV in the body
- Reduces the risk of HIV transmission
- Prevents HIV from advancing to AIDS
- Protects the immune system

For more information, visit HIVinfo.NIH.gov

Classification of ART Drugs

- Nucleo(t)side Reverse Transcriptase Inhibitors (NRTIs)
- Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Entry Inhibitors – Chemokine (CCR5) co-receptor antagonist
- Fusion Inhibitors
- Integrase Inhibitors (HIV integrase strand transfer inhibitors)

TABLE 1: Classes of antiretroviral agents.

Class	Abbreviation	Mechanism of action	Specific action
Nucleoside and nucleotide reverse transcriptase inhibitors	NRTIs and NtRTIs	Reverse transcriptase inhibition	Nucleic acid analogues mimic the normal building blocks of DNA, preventing transcription of viral RNA to DNA
Non-nucleoside reverse transcriptase inhibitors	NNRTIs	Reverse transcriptase inhibition	Alter the conformation of the catalytic site of reverse transcriptase and directly inhibit its action
Protease inhibitors	PIs	Protease inhibition	Inhibit the final maturation stages of HIV replication, resulting in the formation of non-infective viral particles
Integrase inhibitors (also termed integrase strand transfer inhibitors)	InSTIs	Inhibition of viral integration	Prevent the transfer of proviral DNA strands into the host chromosomal DNA
Entry inhibitors	—	Entry inhibition	Bind to viral gp41 or gp120 or host cell CD4+ or chemokine (CCR5) receptors

CCR5, C-C chemokine receptor type 5; NRTIs, nucleoside reverse transcriptase inhibitors; NtRTIs, nucleotide reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; InSTIs, integrase inhibitors (integrase strand transfer inhibitors).

CLASSIFICATION OF ANTI HIV DRUGS

NUCLEOSIDE/ NEOCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)

- Abacavir
- Didanosine
- Lamivudine
- Emtricitabine
- Stavudine
- Tenofovir Disoproxil
- Zalcitabine
- Zidovudine

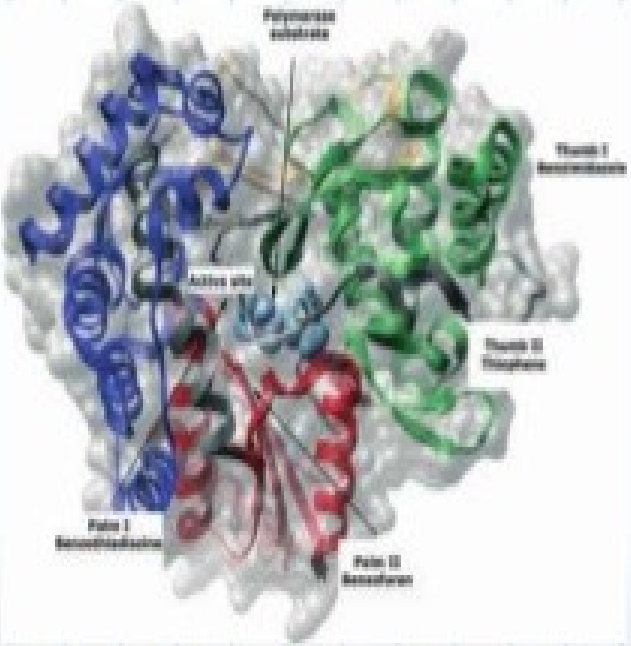
Nucleo(t)side Reverse Transcriptase Inhibitors (NRTIs)

- First agents available for HIV Infection.
- Less potent than NNRTIs) and pIs.
- Have a central role in ART.
- Have activity against HIV-1 and HIV-2.
- Nucleoside and nucleotide an alogues
- Differ from normal substrates only by a minor modification in sugar (ribose) molecule

Drugs

- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (ZDV; formerly azidothymidine [AZT])

Non-nucleoside polymerase inhibitors...



Non-nucleoside inhibitors bind outside the active site and target allosteric sites on the surface of the enzyme.

inhibitors.

Nucleos(t)ide inhibitors	Non-nucleoside inhibitors
Analogues of natural substrate, need to be phosphorylated	≥ 4 target sites at the polymerase
Inhibitory competition	Allosteric inhibition
Similar activity against all genotypes	Genotype-dependent activity, except for the NNI site 4 inhibitor
High genetic barrier to resistance	Rapid selection of resistance
No demonstrated influence of polymorphism on drug activity	Polymorphism may influence activity

CLASSIFICATION OF ANTI HIV DRUGS

NON-NUCLEOSIDE/ NEOCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)

- Dilavirdine
- Efavirenz
- Nevirapine
- Etravirine

Protease Inhibitors

- First introduced in 1995
- Are an integral part of treatment
- Exhibit activity against clinical isolates of both HIV-1 and HIV-2.

Drugs

- Atazanavir sulfate, ATV
- Darunavir
- Fosamprenavir Calcium, FOS-APV
- Indinavir, IDV,
- **lopinavir / ritonavir, LPV/RTV**
- Nelfinavir mesylate, NFV
- Saquinavir mesylate, SQV
- Tipranavir, TPV

CLASSIFICATION OF ANTI HIV DRUGS

PROTEASE INHIBITORS (PI)

- Amprenavir
- Darunavir
- Indinavir
- Saquinavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Ritonavir
- Tiprinavir
- Nelfinavir

CCR5 Receptor Antagonist

- Glycoprotein gp120 of HIV envelope anchors to the CD4 site of host cell by binding to CCR5 chemokine receptor

- **Maraviroc** selectively and reversibly binds CCR5 coreceptor, blocking it and interfering attachment of the virus

Fusion Inhibitors

Enfuvirtide

- 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.

Integrase Inhibitors

- Two main groups of integrase inhibitors;

1. Integrase Strand Transfer inhibitors (INSTI) restrain the binding of pre-integration complex (PIC) and host DNA
2. Integrase Binding Inhibitors (INBI) restrain integrase and viral DNA binding

ANTIRETROVIRAL DRUGS

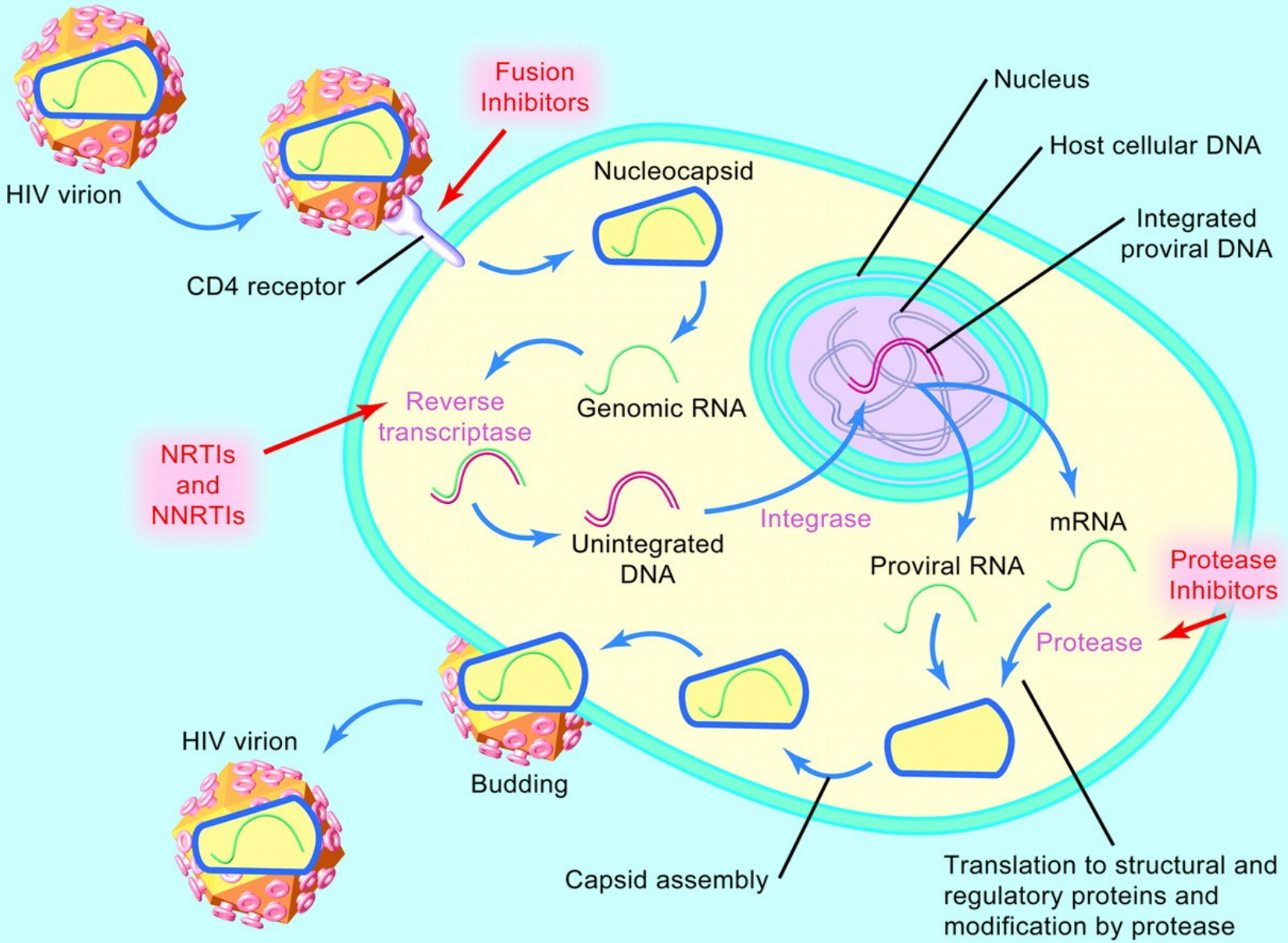
MNEMONICS

NRTIs
- Abacavir
- Didanosin
- [illegible]icitabine
- [illegible]line

Protease Inhibitors
- Ataza navir
- Daru navir
- Fosampre navir
- Indi navir
- Lopi navir
- Rito navir

Integrase Inhibitors
- Ral tegravir
- Elvi tegravir
- Dolu tegravir

RTIs
- [illegible]dine


HIV virion
Fusion Inhibitors
CD4 receptor
Nucleocapsid
Nucleus
Host cellular DNA
Integrated proviral DNA
Reverse transcriptase
Genomic RNA
NRTIs and NNRTIs
Unintegrated DNA
Integrase
Proviral RNA
mRNA
Protease Inhibitors
Protease
HIV virion
Budding
Capsid assembly
Translation to structural and regulatory proteins and modification by protease

HAART THERAPY

(2+1 Strategy)

GENERAL PRINCIPLES

- HAART(**Highly Active Anti Retroviral Therapy**)
- Classical: 2 NRTIs + 1 protease inhibitor or 1 NNRTI
- May be life long therapy
- Avoid two same nucleoside analogue e.g. stavudine and zidovudine (both are thymidine analogues)
- Avoid toxicity and genotypic overlap

GENERAL PRINCIPLES

- Human nuclear DNA should not be affected; mitochondrial DNA may be involved
- All NRTIs cause lactic acidosis and hepatic steatosis
- All NRTIs have urinary excretion except abacavir (hepatic)
- Dideoxynucleoside group causes more chances of neuropathy, pancreatitis and lipodystrophy (Zalcitabine,didanosine, stavudine)

WHO recommendations of ART

- **WHAT TO START:**
- **First-line therapy should consist of**
- NNRTI(1) + NRTIs (2), one of which should be zidovudine (AZT) or tenofovir (TDF).
- Take steps to progressively reduce the use of stavudine (d4T) in first-line regimens because of its well-recognized toxicities.
- **Second-line ART should consist of**
- A Ritonavir-boosted PI + NRTIs (2), one of which should be AZT or TDF, based on what was used in first-line therapy.
- Ritonavir-boosted atazanavir (ATV/r) or lopinavir/ritonavir (LPV/r) are the preferred PIs.

NRTI: BASIC PHARMACOLOGY

MOA

- Interrupt HIV replication cycle via competitive inhibition of HIV reverse transcriptase and termination of the DNA chain
- Reverse transcriptase.
  - An HIV-specific DNA polymerase
  - Allows HIV RNA to be transcribed into ss and ultimately ds proviral DNA and incorporated into host-cell genome.
  - Proviral DNA chain elongation is necessary before genome incorporation can occur
- Acting as "false building blocks causes Chain termination,
- Once incorporated, work by preventing other nucleosides from also being incorporated b/c of absence of a 3' OH group.

NRTI: BASIC PHARMACOLOGY

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Mechanism of Action :

- All drugs require intra-cytoplasmic activation via phosphorylation by cellular enzymes to tri-phosphate form
- Inhibit reverse transcriptase
- Incorporate into ***viral*** DNA and cause chain termination

Resistance :

- Mutation in reverse transcriptase - Monotherapy

NRTI: BASIC PHARMACOLOGY

- NRTI resistance=viral codon 184 mutation
- NRTIs need intracellular phosphorylation
- NRTIs are competitive inhibitors of HIV-I reverse trascriptase
- Stop NRTIs
  - ALT rises
  - Hepatomegaly
  - Metabolic acidosis

NRTI: BASIC PHARMACOLOGY

ARV Components in Initial Therapy: NRTIs

ADVANTAGES

- Established backbone of combination therapy
- Minimal drug interactions
- PI and NNRTI preserved for future use

DISADVANTAGES

- Lactic acidosis and hepatic steatosis reported with most NRTIs (rare)
- 3-NRTI regimens show inferior virologic response compared with EFV- and IDV-based regimens*

* 3-NRTI regimen of ABC + 3TC + ZDV to be used only when a preferred or alternative NNRTI- or PI-based regimen cannot or should not be used as first-line therapy.

NNRTI: BASIC PHARMACOLOGY

- NNRTIs are non competitive inhibitors of HIV-I reverse transcriptase inhibitors.
- Direct binding at distinct site
- Block both DNA and RNA dependant polymerases .
- Do not compete with nucleoside tri PO4
- Nor they require phosphorylation
- Resistance =K 103 N mutation

NNRTI: BASIC PHARMACOLOGY

MOA

- 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 noncompetitive binding induces a conformational change in enzyme
- 1st generation NNRTIs are more rigid in structure
- Resistance can quickly be developed .
- 2nd generation NNRTIs have a more flexible structure,
- Adjust readily and resist mutation more effectively

NNRTI: BASIC PHARMACOLOGY

- Metabolized by cyt: p450 3A4
- Inducer ; nevirapine
- Inhibitor ; dilavirdine
- Mixed ; efavirenz
- Adverse = rash, S.J syndrome
- Advantages
  - No bone marrow toxicity
  - No interaction with NRTIs

PI: BASIC PHARMACOLOGY

PI: Mechanism of Action

- HIV protease is a 99-amino-acid, aspartic acid protein
- Responsible for maturation of virus particles late in viral life cycle
- Competitive inhibitors
- Directly bind to HIV protease and prevent subsequent cleavage of polypeptides

PI: BASIC PHARMACOLOGY

- PIs absorption is affected by fatty meal
  - Increased =nelfinavir, saquinavir
  - Decreased =indinavir
- P glycoprotein substrate
- Act on Gag /Gag pol polyproteins
- Block budding / maturation
- 1000 times more avidity for viral aspartyl protease (human renin and cathepsin)

PI: BASIC PHARMACOLOGY

- All PIs except atazanavir cause central obesity ,muscle wasting ,gynecomastia ,and cushingoid appearance.
- All PIs except amprenavir cause hypertriglyceridemia ,glucose intolerance ,and insulin resistance.
- More chances of spontaneous bleeding in hemophilia A and B.

PI: BASIC PHARMACOLOGY

Serious Adverse Effects of PIs

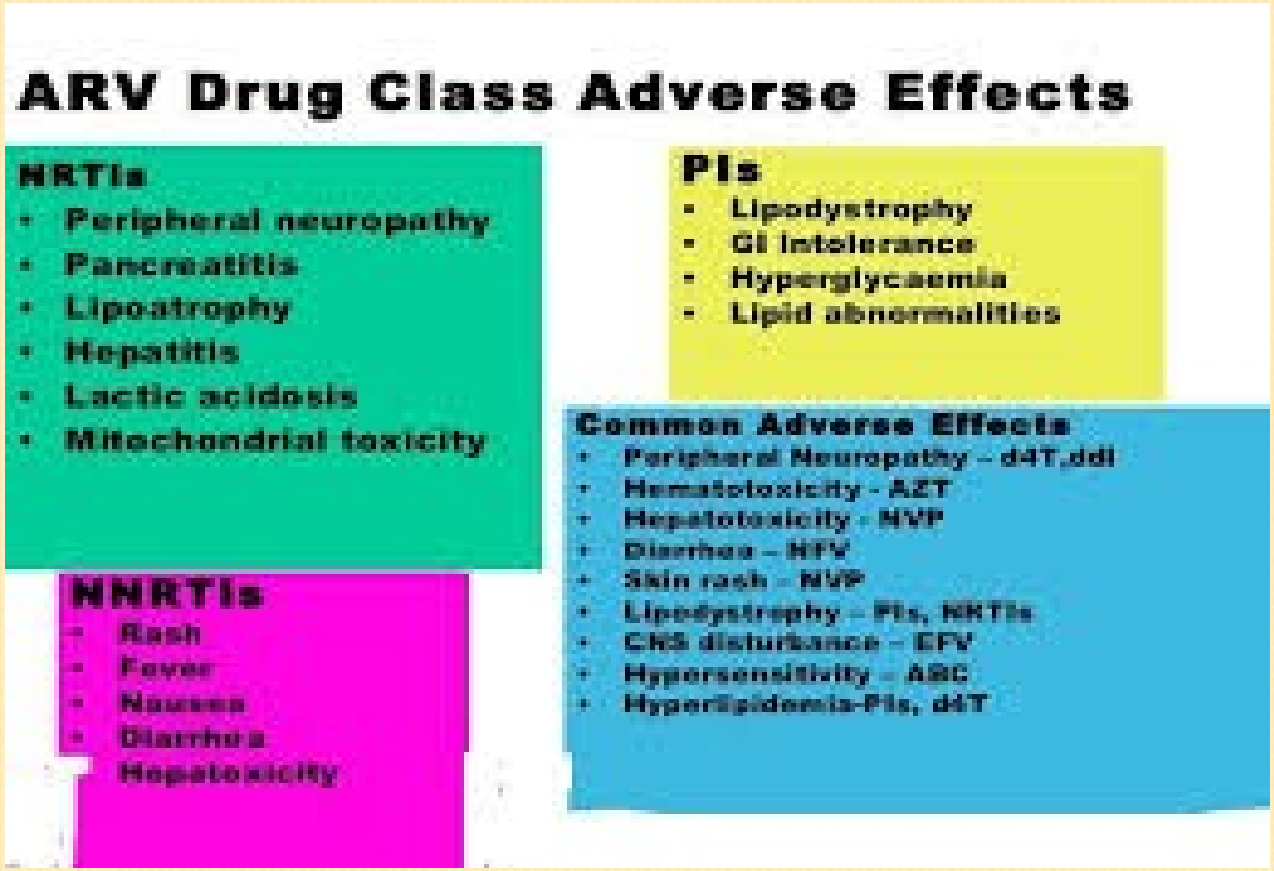
- All PIs
  - Insulin resistance ⇒ hyperglycemia and diabetes
  - Elevated serum lipids
  - Abnormal fat accumulation
  - Liver toxicity*

***Potentially life-threatening**

PI: BASIC PHARMACOLOGY

- All PIs are substrates/inhibitors of Cyt: p 450 3A4
- Ritonavir = most potent inhibitor ; pharmacologic booster
- Saquinavir = least potent inhibitor
- Avoid PIs concomitant with
  - Statins= rhabdomyolysis
  - Midazolam, fentanyl ,ergots ,rifampin

BASIC PHARMACOLOGY



CLINICAL PHARMACOLOGY

Table 2. **Recent improvements in antiretroviral drug formulations and new dosing options to improve adherence**

Antiretroviral drug	*Dosing*
Nucleoside analogue reverse transcriptase inhibitors	
abacavir	600-mg once-daily dosing
abacavir/lamivudine	Fixed-dose combination, once-daily dosing
didanosine EC (enteric-coated formulation)	Once-daily dosing
lamivudine	300-mg once-daily dosing
tenofovir/emtricitabine	Fixed-dose combination, once-daily dosing
zidovudine/lamivudine	Fixed-dose combination, twice-daily dosing
zidovudine/lamivudine/abacavir	Fixed-dose combination, twice-daily dosing
Nonnucleoside reverse transcriptase inhibitors	
efavirenz	600-mg pill
nevirapine	400-mg once-daily dosing*
Protease inhibitors	
fosamprenavir	Prodrug of amprenavir; fewer pills
lopinavir/ritonavir	Fixed-dose combination, once-daily* or twice-daily dosing, 200/50-mg tablet
nelfinavir	625-mg pill
ritonavir	Pharmacokinetic enhancement for once-daily dosing of amprenavir, atazanavir, fosamprenavir, lopinavir*
saquinavir	Tablet formulation, 500 mg

*Once-daily dosing is not approved by the US Food and Drug Administration.

CLINICAL PHARMACOLOGY

Recently approved drugs

DRUGS	CATEGORY	YEAR OF APPROVAL
Extended-release nevirapine	NNRTIs	March 25, 2011
Rilpivirine	NNRTIs	May 20, 2011
Dolutegravir	Integrase Inhibitors	August 13, 2013
Elvitegravir	Integrase Inhibitors	September 24, 2014
Cobicistat	Pharmacokinetic Enhancers	September 24, 2014

CLINICAL PHARMACOLOGY

Commercial Fixed-dose combinations

Combination	Name
Zidovudine + lamivudine	Combivir
Zidovudine + abacavir	Epzicom
Zidovudine + lamivudine + abacavir	Trizivir (combivir +ABC)
Tenofovir + emtricitabine	Truvada
Tenofovir + emtricitabine + efavirenz	Atripla (Truvada +EFV)
Stavudine + lamivudine + nevirapine	Triomune[a]
Lopinavir + ritonavir	Kaletra
Rilpivirine + tenofovir/emtricitabine	Complera
Elvitegravir+ cobicistat+ tenofovir + emtricitabine	Stribild

CLINICAL PHARMACOLOGY

Recommendations for Coadministering Antiretroviral Drugs with RIFAMPICIN

DRUG WITH WHICH RIFAMPIN IS CO-ADMINISTERED	DOSE OF CO-ADMINISTERED DRUG	DOSE OF RIFAMPIN
EFAVIRENZ	600 mg/day (recommend 800 mg for patients > 50 kg)	NO CHANGE
NEVIRAPINE	200 mg twice daily	NO CHANGE
RITONAVIR BOOSTED INDINAVIR	should not be used together	should not be used together
RITONAVIR BOOSTED ATAZANAVIR	should not be used together	should not be used together
RITONAVIR BOOSTED LOPINAVIR	should not be used together	should not be used together

- SQV 400/RTV 400, LPV/RTV 4 tab BD, Super boosted LPV/RTV

CLINICAL PHARMACOLOGY

Recommendations for Coadministering Antiretroviral Drugs with RIFABUTIN

DRUG WITH WHICH RIFABUTIN IS CO-ADMINISTERED	DOSE OF RIFABUTIN
EFAVIRENZ	450-600 mg/day
NEVIRAPINE	300 mg/day
RITONAVIR BOOSTED DARUNAVIR	150 mg daily
RITONAVIR BOOSTED ATAZANAVIR	150 mg daily
RITONAVIR BOOSTED LOPINAVIR	150 mg daily

CLINICAL PHARMACOLOGY

Drugs in Pregnancy

Class	Preferred Drug	Alternate Drug
NRTI	Zidovudine, Lamivudine	Didanosine, Stavudine, Emtricitabine, Abacavir
NNRTI	Nevirapine	-
PI	Nelfinavir, Saquinavir	Lopinavir+ Ritonavir, Indinavir, Ritonavir

CLINICAL PHARMACOLOGY

Infant born to HIV+ women not taking ART

Zidovudine 300mg BD started during 2nd trimester and continued through delivery to post natal period.

with treatment of the neonate for 6 weeks at a dose of 2mg /kg has been found to reduce mother-to-child transmission by 2/3rd.

CLINICAL PHARMACOLOGY

Table 24. Classes of antiretroviral drugs recommended for use in children

Nucleoside analogue reverse transcriptase inhibitors	
Zidovudine	ZDV (AZT)
Lamivudine	3TC
Abacavir	ABC
Emtricitabine	FTC
Tenofovir	TDF
Non-nucleoside analogue reverse transcriptase inhibitors	
Nevirapine	NVP
Efavirenz	EFV
Protease inhibitors	
Lopinavir/ritonavir	LPV/RTV
Atazanavir	ATZ

CLINICAL PHARMACOLOGY

Table 25. First-line treatment regimens for children

WHO-recommended preferred first-line antiretroviral regimens for infants and children	
First-line regimens for children < 3 years	**First-line regimens for children ≥ 3 years up to 12 years**
Abacavir (ABC)[a] or zidovudine (ZDV) *plus* Lamivudine (3TC) *plus* Lopinavir/ritonavir (LPV/RTV)[a]	Abacavir (ABC)[b] or zidovudine (ZDV) *plus* Lamivudine (3TC) *plus* Efavirenz (EFV)[b] or nevirapine (NVP)
Abacavir (ABC) or zidovudine (ZDV) *plus* Lamivudine (3TC) *plus* Nevirapine (NVP)	Tenofovir (TDF) *plus* Emtricitabine (FTC) or Lamivudine (3TC) *plus* Efavirenz (EFV) or nevirapine (NVP)

[a] Preferred regimen for children < 36 months regardless of exposure to nevirapine or other NNRTIs directly or via maternal treatment in preventing mother-to-child transmission.

[b] ABC+3TC+EFV is the preferred regimen for children ≥ 3 years up to 12 years.

CLINICAL PHARMACOLOGY

Immunization of HIV Infected Child

Broad issues in the immunosuppressed child:

- **Some live vaccines can result in severe vaccine associated disease- BCG**
- **Immune response to vaccines may be reduced**
- **Immune response may not be sustained**

Zidouvidine (AZT, ZDV)

- First antiviral drug used against HIV.
- It is a thymidine analogue that is effective against HIV-1, HIV-2, and HTLV I and II.
- Zidovudine, in combination with one or more other antiretroviral agents, is approved for the treatment of HIV infection in adults and children and for post-exposure prophylaxis. It is used alone or in combination for the prevention of prenatal and perinatal transmission to the baby by HIV-infected pregnant women.
- **Adverse effects:** Headache, nausea, vomiting, anorexia, fatigue, confusion, insomnia, malaise, hepatitis, myopathy, myositis, bone marrow toxicity, anaemia, neutropenia, and other haematological abnormalities.

ZIDOVUDINE: Drug Interactions

- Increased serum levels of Zidovudine may occur with simultaneous administration of:
  - Fluconazole
  - Probenecid
  - Phenytoin
  - Methadone
  - Valproic acid
- Zidovudine may decrease the levels of Phenytoin
- Potentiating hematologic toxicity of other cytotoxic agents and myelosuppressive drugs

Zidovudine (ZDV, AZT, Retrovir)

- Precautions
  - Bone marrow suppression (combined effect w/ganciclovir & interferon alpha or B12 & other deficiencies)
  - Elevated MCV (megaloblastic change MUST r/o B12 or folate deficiency)
  - Probenecid increases drug levels → flulike Sx's
  - Trimethoprim increases serum levels
  - Alters dilantin levels
  - In combo with acyclovir → drowsiness & lethargy
  - Methodone increases serum concentration & toxicity risk

Zidovudine (ZDV, AZT, Retrovir)

- Warnings
  - Hypersensitivity: rash & anaphylaxis
  - Metabolized by liver excreted in kidney → dosage reduction in renal impairment
  - Impaired liver function → increased toxicity risk
  - RARE BUT FATAL: lactic acidosis w/o hypoxemia & severe hepatomegaly w/steatosis (esp. in obese women)

AZT induced Anaemia

- Zidovudine can cause severe anaemia as a side effect.
- Make sure the anaemia is not caused by malaria or other infectious causes
- Subsitute zidovudine with stavudine or tenofovir drugs.
- Always consult with a colleague before making the drug substitution
- Give folic acid or transfuse if signs of failure are present.
- Signs of failure include palpitation, fast heart beat and swollen feet.

Didanosine (DDI)

- It is an adenosine analogue
- Active against HIV-1, HIV-2, and HTLV-I.
- It is approved as part of a multidrug regimen for the therapy of HIV infection and is also used as Postexposure HIV prophylaxis.

- **Adverse effects:** Diarrhea, abdominal pain, nausea, vomiting, anorexia and dose-related peripheral neuropathy, pancreatitis, hyperuricemia, bone marrow suppression, retinal depigmentation, and optical neuritis.

PHARMACOKINETIC ENHANCERS

Cobicistat

- Investigational drug
- Cobicistat has no anti-HIV activity but is a potent inhibitor of CYP3A
- It increases the blood level of certain ARV drugs, allowing once-daily dosing.
- It is found to be safe and well-tolerated in escalating single and multiple dose-ranging studies in healthy volunteers.
- It is under trial as a standalone boosting agent for PIs, especially atazanavir and integrase inhibitor elvitegravir as FDC and found to be comparable with ritonavir.

Virologic Response Definitions

- **Virologic Suppression:** A confirmed HIV RNA level below the lower limit of detection of available assays.
- **Virologic Failure:** The inability to achieve or maintain suppression of viral replication to an HIV RNA level <200 copies/mL.
- **Incomplete Virologic Response:** Two consecutive plasma HIV RNA levels ≥200 copies/mL after 24 weeks on an ARV regimen in a patient who has not yet had documented virologic suppression on this regimen.
- **Virologic Rebound:** Confirmed HIV RNA level ≥200 copies/mL after virologic suppression.

Gene therapy for HIV/AIDS treatment

- Nanotechnology platforms for delivery of siRNA for HIV/AIDS treatment are in their early stages but recent work has been met with optimism.

- Single-walled nanotubes, dendrimers, fusion proteins, peptide–antibody conjugates have all been used for delivery of siRNA to HIV-specific cells.

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THANK YOU