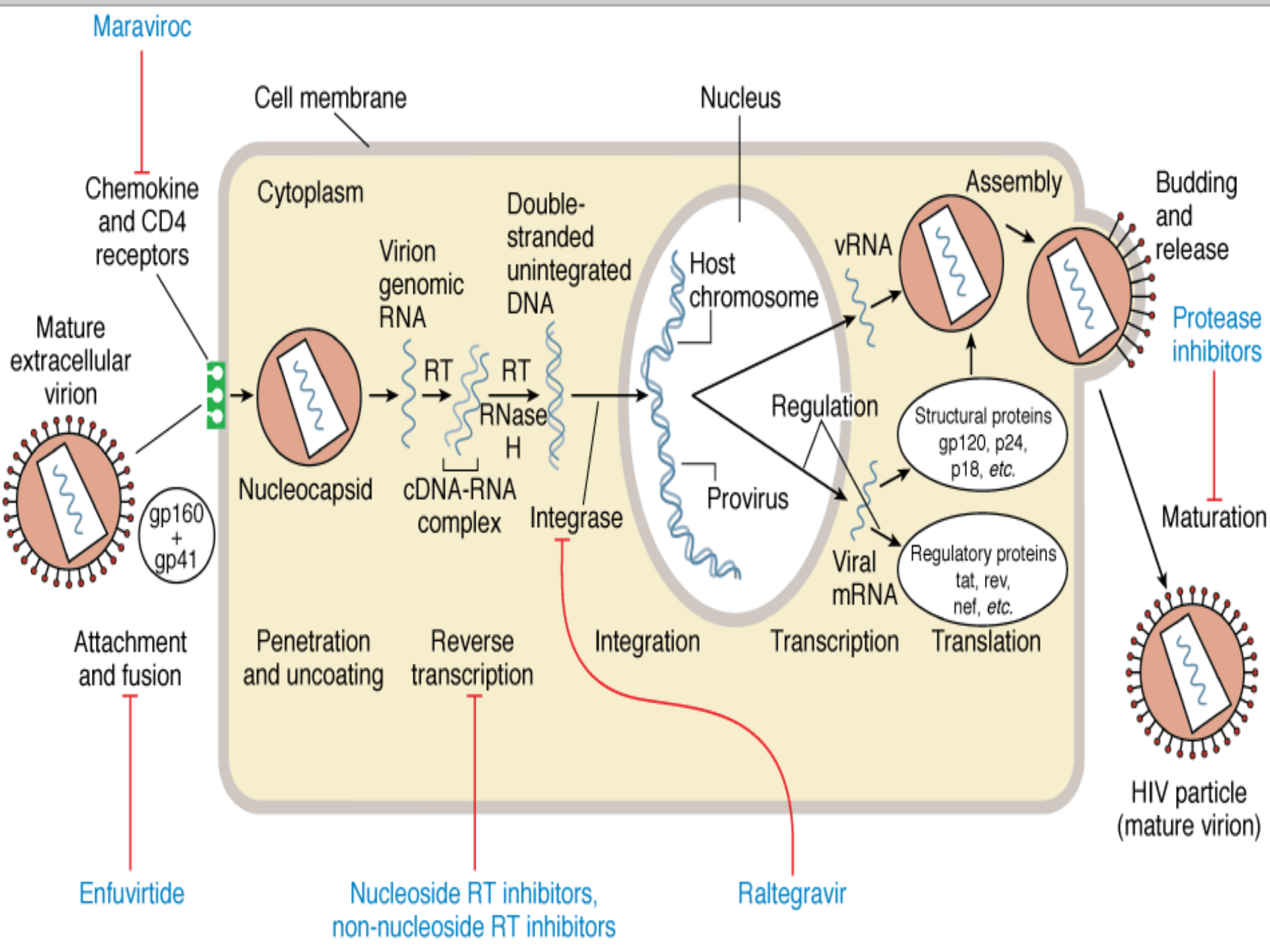
PHARMACOTHERAPY OF HIV INFECTION


Maraviroc
Chemokine and CD4 receptors
Mature extracellular virion
gp160 + gp41
Attachment and fusion
Enfuvirtide
Cell membrane
Cytoplasm
Nucleocapsid
Virion genomic RNA
RT
RT
RNase H
cDNA-RNA complex
Double-stranded unintegrated DNA
Penetration and uncoating
Reverse transcription
Nucleoside RT inhibitors, non-nucleoside RT inhibitors
Integrase
Raltegravir
Nucleus
Host chromosome
Provirus
Integration
Regulation
Viral mRNA
Transcription
Structural proteins gp120, p24, p18, etc.
Regulatory proteins tat, rev, nef, etc.
Translation
vRNA
Assembly
Budding and release
Protease inhibitors
Maturation
HIV particle (mature virion)

Nucleoside reverse transcriptase inhibitors : Zidovudine (AZT), Didanosine, Stavudine, Lamivudine, Abacavir, Tenofovir, Emtricitabine

Nonnucleoside reverse transcriptase inhibitors : Nevirapine, Efavirenz, Etravirine

Protease inhibitors: Ritonavir, Atazanavir, Indinavir, Nelfinavir, Saquinavir, Lopinavir, Fosamprinavir, Darunavir

Entry (Fusion) inhibitor: Enfuvirtide

CCR5 receptor inhibitor: Maraviroc

Integrase inhibitor: Raltegravir, Dolutegavir

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Zidovudine, **Stavudine** --- Thymidine analogues

Didanosine, **Tenofovir** --- Adenosine analogues

Lamivudine, Emtricitabine --- Cytosine analogue

Abacavir --- Guanosine analogue

Agent	Adverse Effects	Comments
Zidovudine (AZT) 200 mg tid or 300 mg Bid Fixed-dose formulation with lamivudine + - Abacavir	Macrocytic anemia, neutropenia Lipoatrophy, dyslipidaemia, insulin resistance	Avoid concurrent stavudine and myelo-suppressive drugs (eg, ganciclovir, ribavirin) Safe in pregnancy

Agent	Adverse Effects	Comments
Didanosine (ddl) 400 mg od or 200 mg bid Gap between meals	• Peripheral neuropathy, pancreatitis, hyperuricemia. • Possible increase in myocardial infarction. • Reports of retinal changes and optic neuritis	• Avoid concurrent neuropathic drugs (e.g. stavudine, isoniazid, ribavirin). • Stavudine and ribavirin predispose to pancreatitis

Agent	Adverse Effects	Comments
Stavudine 30–40 mg bid, depending on weight	• Peripheral neuropathy • Pancreatitis, lipodystrophy , Hyperlipidemia. • Progressive ascending neuro-muscular weakness (rare)	• Avoid concurrent zidovudine and neuropathic drugs (Didanosine, zalcitabine, isoniazid)

Agent	Adverse Effects	Comments
Lamivudine 150 mg bid or 300 mg od 100mg /day in HBV FDC with Zidovudine & Abacavir	• Least toxic, headache, nausea. • Neutropenia • Pancreatitis in pediatric patients	• Also effective against HBV • Trimethoprim-sulfamethoxazole increase bio-availibility • Safe in pregnancy

Agent	Adverse Effects	Comments
Emtricitabine 200 mg Od, only as FDC tablets • With tenofovir for preexposure prophylaxis	• Least toxic, Fatigue headache, nausea, diarrhoea • Discoloration of exposed skin	• Also effective against HBV • Safe in pregn • one of first li HIV drugs

Agent	Comments	Adverse Effects
Abacavir 300 mg bid or 600 mg OD • FDC with Lamivudine Zidovudine	• Testing to rule out presence of HLA-B5701 allele is recommended prior to initiation of therapy. • Avoid alcohol.	• Rash, hyper-sensitivity Reaction (8%), nausea. • Possible increase in myocardial Infarction.

Agent	Adverse Effects	Comments
Tenofovir 300 mg od • Also for HBV infection • Di-phosphate active	• Renal Insufficiency • Excessive renal phosphate and calcium losses • Osteomalacia	• Avoid concurrent Probenecid, didanosine. • FDC with Emtricitabine Efavirenz • Take with food

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Agent	Comments	Adverse Effects
Nevirapine • Safe in pregnancy. • Not in HIV 2 • Not with	• Dose escalate from 200 mg daily over 14 days to decrease frequency of rash. • Microsomal enzyme inducer	• Rash, hepatitis (occasionally fulminant). • Adjust dose in hepatic Insufficiency.

Etravirine

2nd Generation

For resistant cases

Potent inducer of CYP3A4

Only in combination with 1NRTI + 1NNRTI

Agent	Recommend-ations	Adverse Effects
Efavirenz 600 mg od • Not in HIV2	• Take on an empty stomach. • Bedtime dosing recommended initially to minimize CNS side effects	• Central nervous system effects, rash, ↑ Liver enzymes. • Teratogenic in primates

HIV PROTEASE INHIBITORS
Saquinavir, **Atazanavir**, **Indinavir**, **Lopinavir/ ritonavir**, **Nelfinavir**, **Ritonavir, Fosamprenavir, darunavir**

Adverse effects

GI intolerance, asthenia, headache, dizziness, limb and facial tingling, numbness and rashes. Lipodystrophy (abdominal obesity, buffalo hump with wasting of limbs and face), dyslipidaemia (raised triglycerides and cholesterol) and insulin resistance. Indinavir increases risk of urinary calculi.

To be taken with food --- Saquinavir, Atazanavir , Lopinavir, Nelfinavir, Ritonavir

To be taken on empty stomach --- Indinavir

Adjust dose in hepatic insufficiency --- Atazanavir, Indinavir, Lopinavir

Ritonavir --- Inhibits metabolism of all current HIV protease inhibitors ; combined with most **(exception nelfinavir**) --- **Boosted Protease inhibitor regimen**

FUSION INHIBITORS

Enfuvirtide

- 90 mg s.c. bid, Store at room temperature as powder; refrigerate once reconstituted.

- **Not active against HIV-2**

- No cross resistance with other classes.
- Reserved for failed therapy with all other feasible antiretroviral regimens.

Adverse effects : injection-site reactions; pain, erythema, induration; nodules or cysts.

CCR5 RECEPTOR INHIBITORS

Maraviroc

- No effect on CXCR4 tropic or dual CCR5/ CXCR4 tropic viruses.

??? impaired immune surveillance and increased risk of infection/malignancy

300 mg bid; 150 bid with CYP3A inhibitors; 600 mg bid with CYP3A inducers.

Muscle and joint pain, diarrhea, sleep disturbance, ↑ liver enzymes. **Avoid rifampin**

INTEGRASE INHIBITOR

Raltegravir --- both HIV-1 and HIV-2.

Adverse effects --- nonspecific; myopathy, Diarrhea, nausea, fatigue, headache, dizziness, muscle aches, ↑ creatine kinase.

Avoid rifampin

400 mg bid. Increase dose to 800 mg bid if administered with rifampin, Separate dosing from antacids by ≥ 4Hrs

Dolutegravir, OD dosing

- 2nd Generation
- Active against both HIV 1 and HIV 2
- Cations affect absorption
- Dose doubled with enzyme inducers
- Good tolerability with infrequent rashes and hypersensitivity
- Now being used as a first line agent in Treatment naïve patients

PRINCIPLES OF HIV CHEMOTHERAPY

- 'Highly active antiretroviral therapy' (**HAART**) --- combination of 3 or more drugs.

- Relapse when treatment discontinued --- rate of mutation high.

- Resistant mutants are selected by anti- HIV therapy.

- Each failing regimen limits future treatment options.

First Line Antiretroviral regimens for adults and adolescents

Prefered Regimens

1. Tenofovir + Lamivudine + Efavirenz[1]
2. Tenofovir + Emtricitabine + Efavirenz[1]

Alternative regimens

1. Lamivudine + Zidovudine + Efavirenz[1]
2. Lamivudine + Zidovudine + Nevirapine[1]
3. Lamivudine + Tenofovir + Dolutegavir
4. Emtricitabine + Tenofovir + Dolutegavir
5. Lamivudine + Nevirapine + Tenofovir[1]
6. Tenofovir+ Emtricitabine+Nevirapine[1]

List of second line regimens*

NRTI components	PI component
Standard regimens	
1. Tenofovir + Abacavir	1. Lopinavir/r**
2. Didanosine + Abacavir	2. Atazanavir/r
3. Tenofovir + Zidovudine	3. Saquinavir/r
± Lamivudine (continued)	4. Indinavir/r
	5. Nelfinavir

FDC of Ritonavir boosted darunavir can be used as alternative PI (Cobicistat)

Therapy not to be discontinued in case of acute opportunistic infection except in case of intolerance, interactions and toxicity.

Pre exposure Prophylaxis

Tenofovir 300mg daily± Emtricitabine 200mg daily

POST EXPOSURE PROPHYLAXIS OF HIV

Preferred NNRTI: Tenofovir 300 mg + **Emtricitabine** 200 mg) ±

Preferred PI: **Lopinavir/r** (400+100mg)

Or **Atazanavir/r** (300+100mg) daily daily **for 4 weeks**

Alternative 3 drug

Darunavir/r (600=100mg) Bd or

Raltegravir (400mg)Bd or **Efavirenz** 600mg daily

POST EXPOSURE PROPHYLAXIS OF HIV

For children < 10 years

Preferred 2NRTI

Zidovudine+ lamivudine

Alternative NRTI: Abacavir+lamivudine or Tenofovir+Lamivudine/Emtrcitabine

Prefered Pi: Lopinavir

Alternative 3rd drug: Atazanavir/Darunavir/ Efavirenz/Raltregavir

Duration 4 weeks

HIV Infection and Pregnancy

Tenofovir 300mg+ Lamivudine 300mg+ Efavirenz 600mg (FDC Tablet) once daily

Neonate: Given Syrup Nevirapine for 6 weeks.

Delivery by cesarean section is adviced if HIV RNA copies are > than 1000 copies /µl