

Antiretrovirals 2011

Actions & Common Side Effects

Ty Bingham, Pharm.D., AAHIVE
Federal Bureau of Prisons
Regional Chief Pharmacist
HIV Clinical Pharmacist Consultant



Learning Objectives

Upon completion of this presentation, learners should be better able to:

- Identify the basic antiretroviral drug classes for the treatment of HIV positive individuals and the mechanisms of action unique to each class.
- Discuss with your patients current, FDA approved, antiretroviral medications and the side effects commonly encountered with their use.

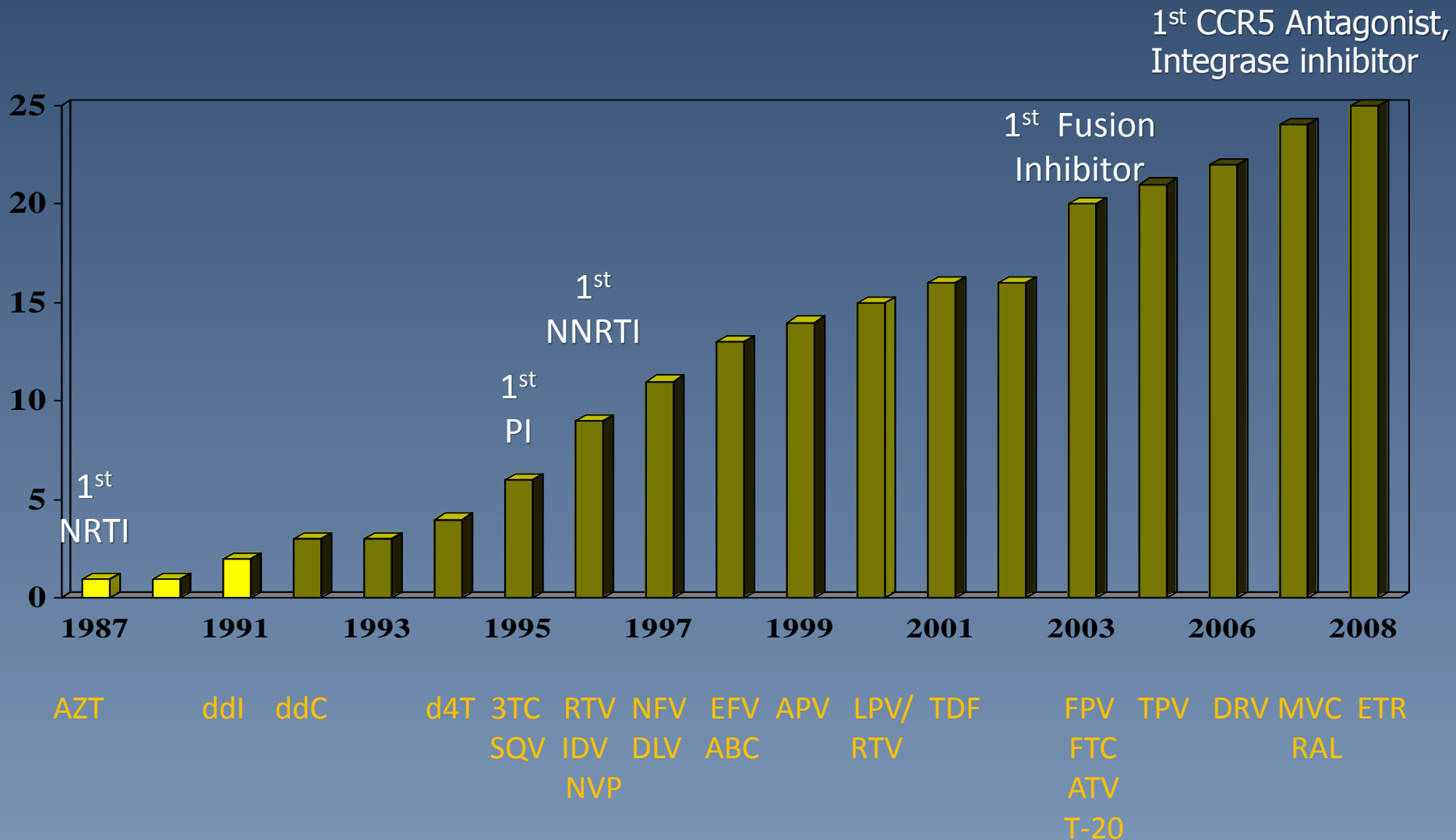


Antiretroviral Classes

1. **NRTI** (Nucleoside OR Nucleotide Reverse Transcriptase Inhibitor)
2. **PI** (Protease Inhibitor)
3. **NNRTI** (Non-nucleoside Reverse Transcriptase Inhibitor)
4. **Fusion Inhibitor**
5. **Integrase Inhibitor**
6. **CCR5 Antagonist** (CC chemokine receptor 5 antagonist)



Timeline of ARV Approvals



HIV LIFE CYCLE

1. Free Virus

2. Binding and Fusion

3. Infection

CD4 Receptor
CCR5 Coreceptor
CXCR4 Coreceptor

4. Reverse Transcription

CD4 Cell

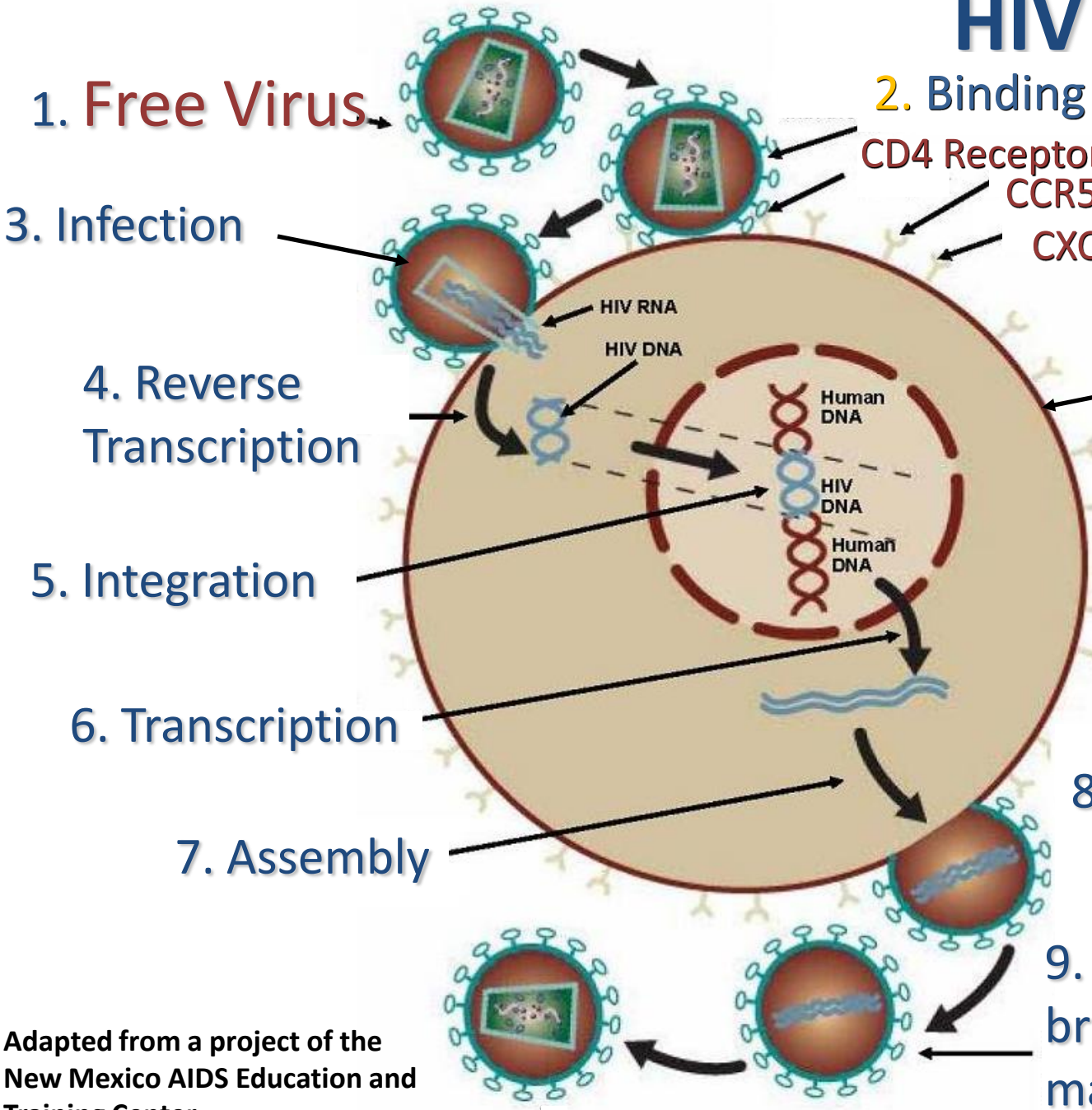
5. Integration

6. Transcription

7. Assembly

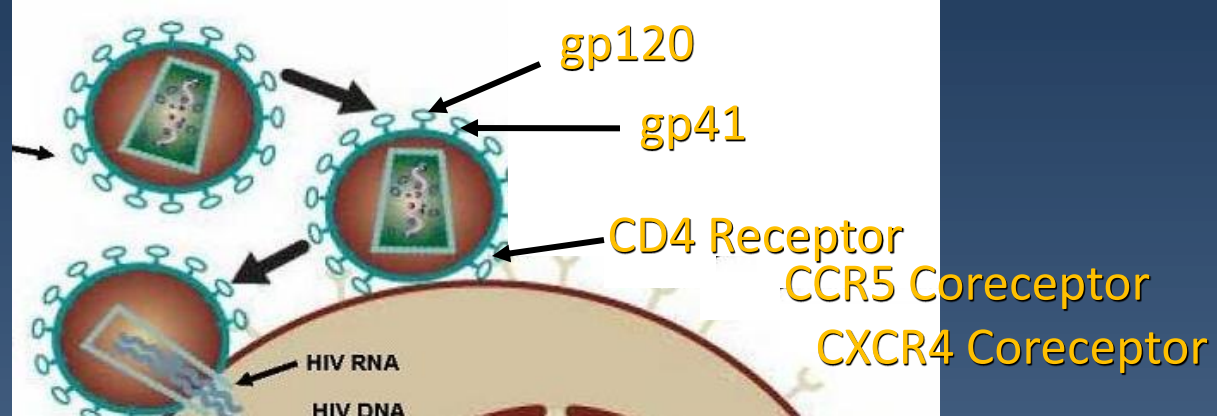
8. Budding

9. Immature virus breaks free and matures



Adapted from a project of the New Mexico AIDS Education and Training Center

Free Virus



Fusion Inhibitor & CCR5 Antagonist

Fusion inhibitors & CCR5 Antagonists prevent HIV from entering human immune cells.

Key proteins involved in the HIV entry process:

CD4 – a glycoprotein found on the surface of T4-lymphocytes that serves as the receptor for HIV

CCR5/CXCR4 – a chemokine receptors found on the surface of T4-lymphocytes that serve as the coreceptor for HIV

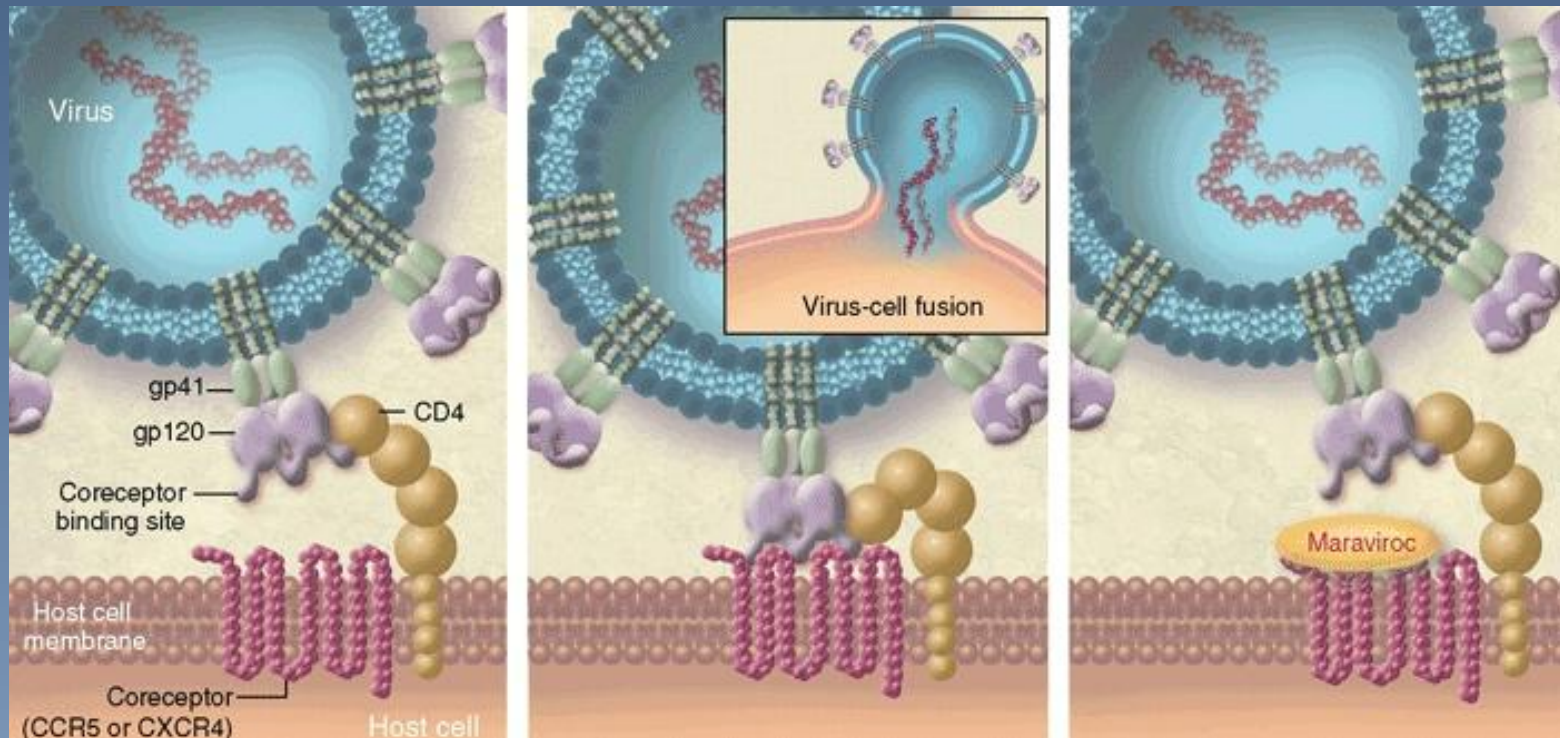
Gp120 – a glycoprotein on the HIV external envelope that binds to the CD4 receptor

Gp41 – a glycoprotein, closely associated with gp120, that penetrates the cell membrane once gp120 binds with CCR5 → Cell fusion

Maraviroc, MVC (Selzentry) CCR5 Inhibitor

Mechanism of Action:

MVC blocks CCR5 cell surface receptors and halts the viral entry process. The effect is limited to CCR5-tropic (R5) virus, (no activity against CXCR4-tropic (X4) or mixed-tropic HIV-1.)



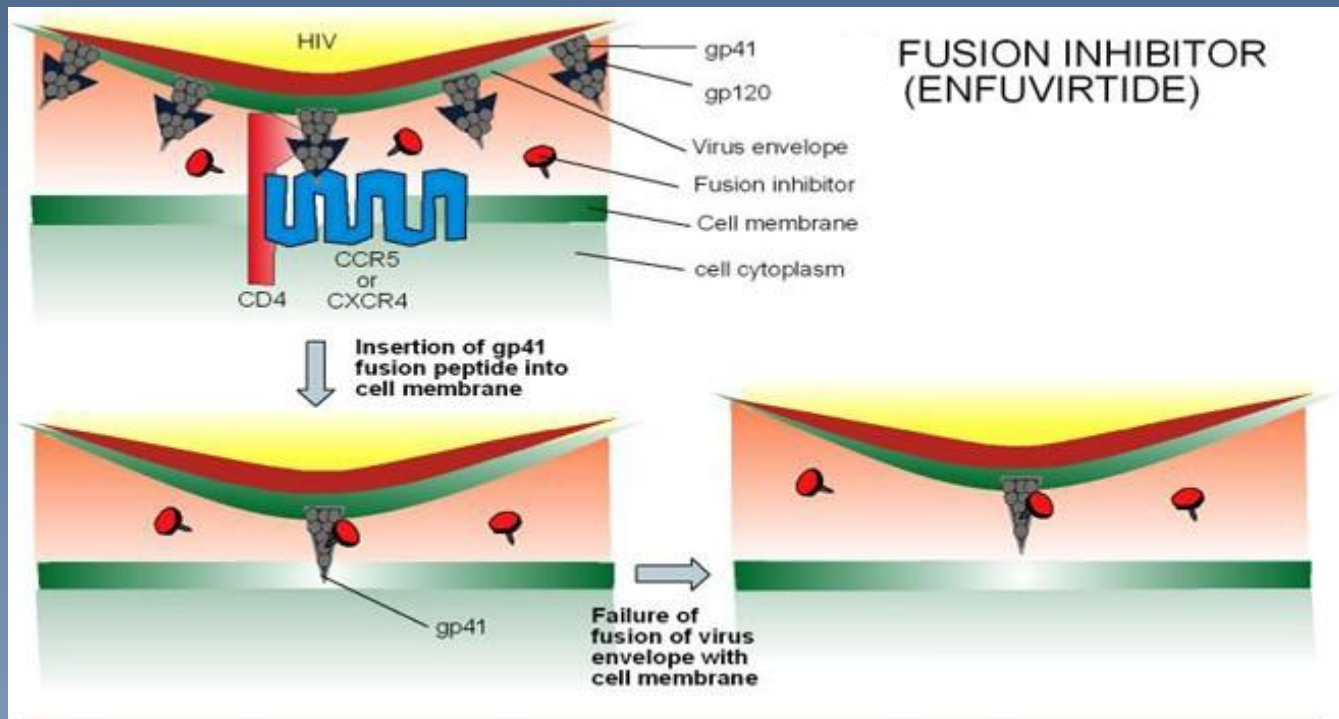
CCR5 Inhibitor

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism (Hepatic)</u>
Maraviroc (MVC) Selzentry	150mg bid with CYP3A inhibitors 300mg bid with NRTIs 600mg bid with CYP3A inducers (without inhibitor)	150, 300mg tablets	Colds, cough, fever, rash, dizziness Hepatotoxicity	CYP3A4 substrate

Enfuvirtide, T-20 (Fuzeon) Fusion Inhibitor

Mechanism of Action:

Enfuvirtide binds to gp41 preventing the creation of an entry pore and subsequent entry of the viral capsid.

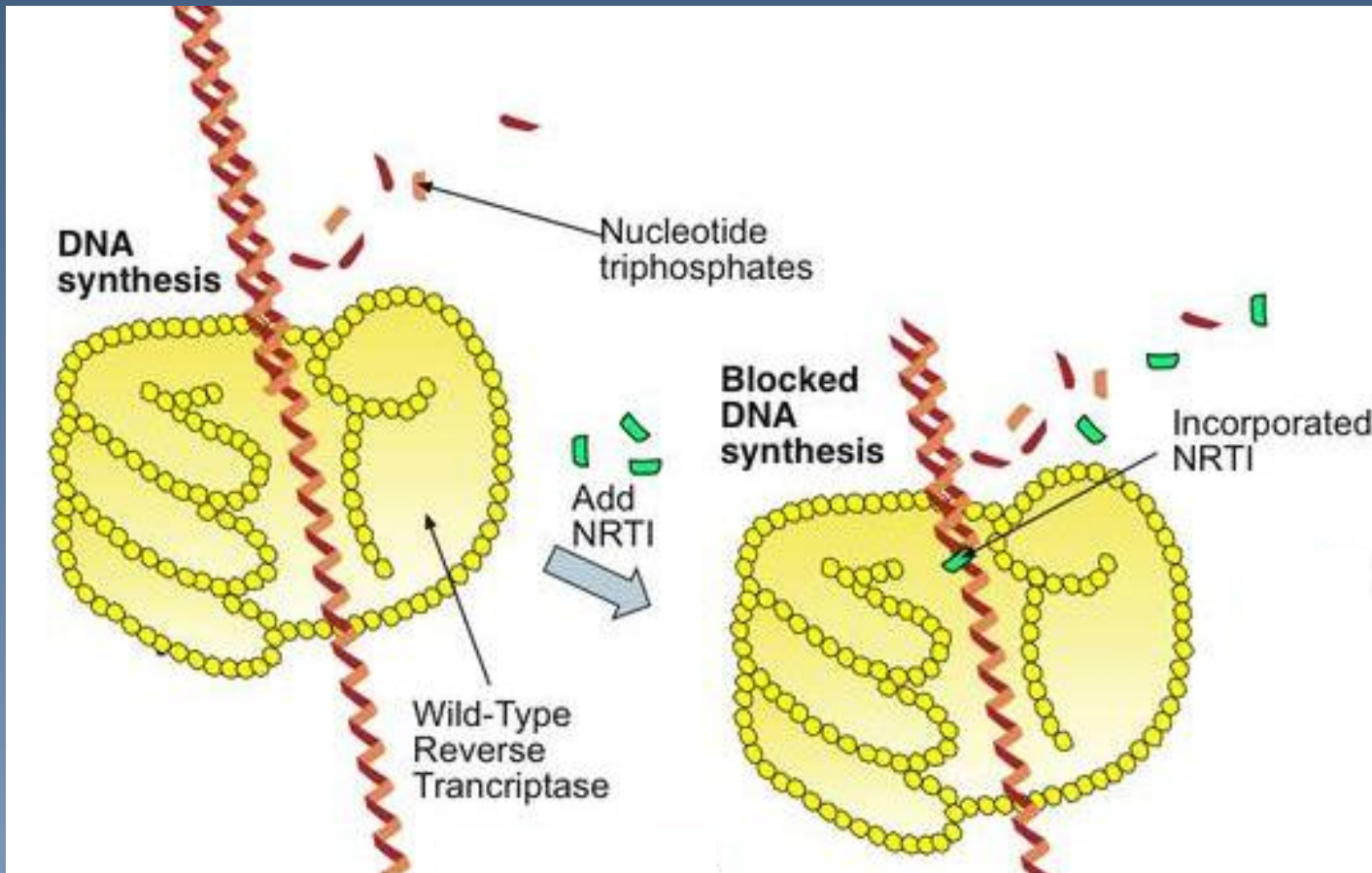


Fusion Inhibitor

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism</u>
Enfuvirtide (T-20) Fuzeon	90mg (1ml) SQ q12h	Single use vial (lyophilized power for reconstitution)	Injection site rx (pain, induration, erythema , nodules) Bacterial pneumonia	Completely absorbed and largely catabolized

Nucleoside/tide Reverse Transcriptase Inhibitors

Mechanism of Action: NRTIs/NtRTIs are analogs of natural deoxynucleotides competing for incorporation into the growing DNA chain. They lack a 3'-hydroxyl group necessary to bond with the incoming deoxynucleotides, resulting in DNA chain termination.



Nucleoside Reverse Transcriptase Inhibitors

Class Toxicities

Mitochondrial Toxicity

Multiple in vitro studies have shown that NRTIs lead to some degree of mitochondrial toxicity which is thought to occur by NRTI inhibition of mitochondrial DNA (mtDNA).

N Engl J Med. 2002;346:811-820

Mitochondrial dysfunction in various tissues may be the cause of several of the side effects and toxicities associated with NRTIs:

lactic acidosis, myopathy, hepatic steatosis, pancreatitis, peripheral neuropathy, and perhaps lipoatrophy

In vitro potency of various NRTIs with respect to their inhibitory effects on mtDNA production is **zalcitabine > didanosine > stavudine > zidovudine > lamivudine = emtricitabine = abacavir = tenofovir**

Antimicrob Agents Chemother. 2002;46:716-723

Nucleoside/tide Reverse Transcriptase Inhibitors

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism/ Elimination</u>
Zidovudine (ZDV/AZT) Retrovir	300mg bid*	300mg tab, 100mg cap, iv, oral soln	Bone Marrow suppression, GI, hyperlipidemia, LA/HS (rare)	Renal
Lamivudine (3TC) Epivir	150mg bid* or 300mg qd	150, 300mg tab, oral soln	Well tolerated	Renal
Emtricitabine (FTC) Emtriva	200mg qd*	200mg cap	Well tolerated	Renal
Didanosine (ddl) Videx	400mg EC qd (≥ 60 kg) 250mg EC qd (<60 kg)*	125,200,250, 400mg cap, pwr for soln	Pancreatitis, peripheral neuropathy, LA/HS, lipoatrophy Insulin resistance	Renal

*dose reduce for renal dysfunction

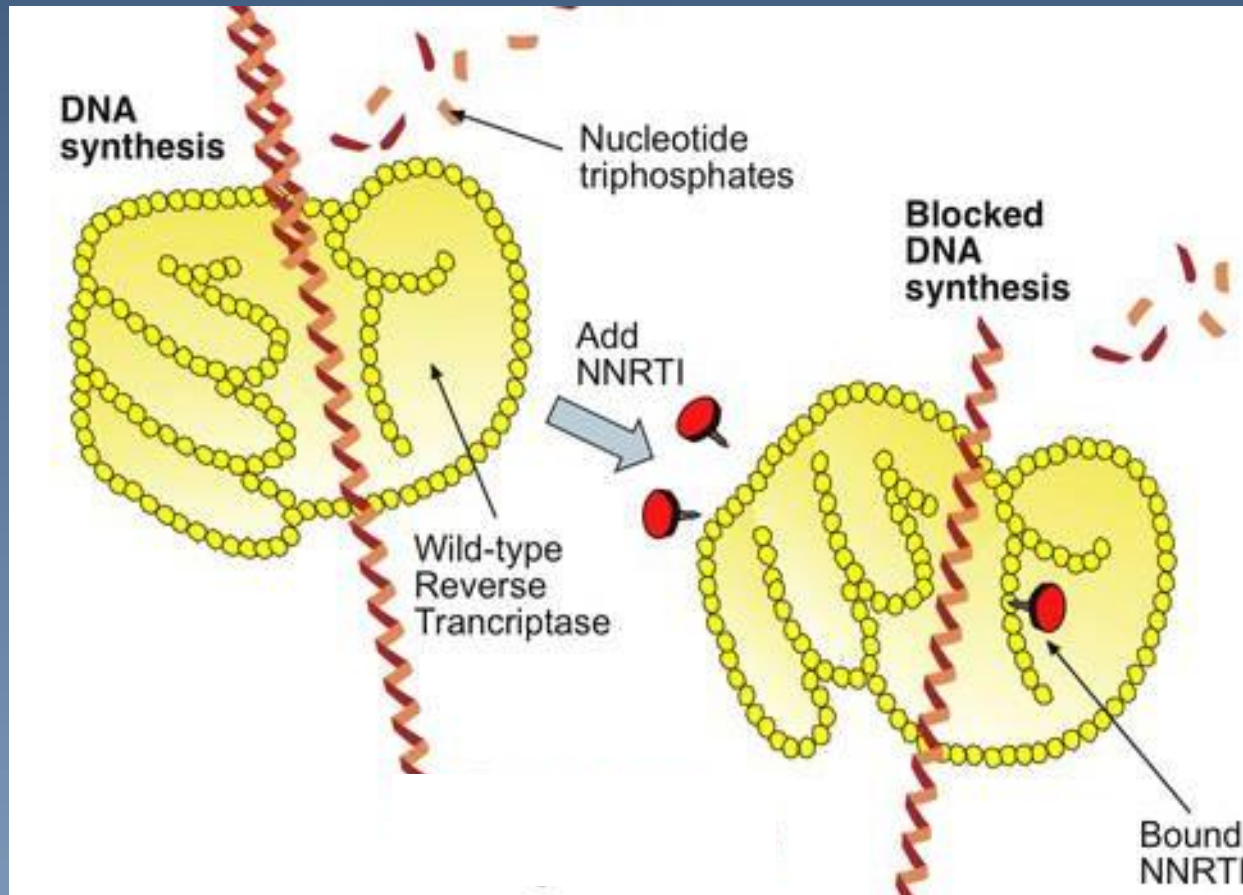
Nucleoside/tide Reverse Transcriptase Inhibitors

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism/ Elimination</u>
Stavudine (d4T) Zerit IR	40mg bid (\geq 60kg) 30mg bid (<60kg) *	15,20,30,40 mg cap,oral soln	Peripheral neuropathy, Lipoatrophy, Pancreatitis, LA/HS, Hyperlipidemia	Renal
Abacavir (ABC) Ziagen	300mg bid, 600mg qd	300mg tabs, oral soln	Hypersensitivity	Hepatic (alcohol dehydrogenase and glucuronyl Transferase)
Tenofovir (TDF) Viread	300mg qd*	300mg tabs	GI, renal toxicity Osteomalacia	Renal

*dose reduce for renal dysfunction

Non-nucleoside Reverse Transcriptase Inhibitors

Mechanism of Action: NNRTI bind directly to the reverse transcriptase enzyme and causes a structural change that disrupts the formation of the active site and leads to impaired polymerization activity.

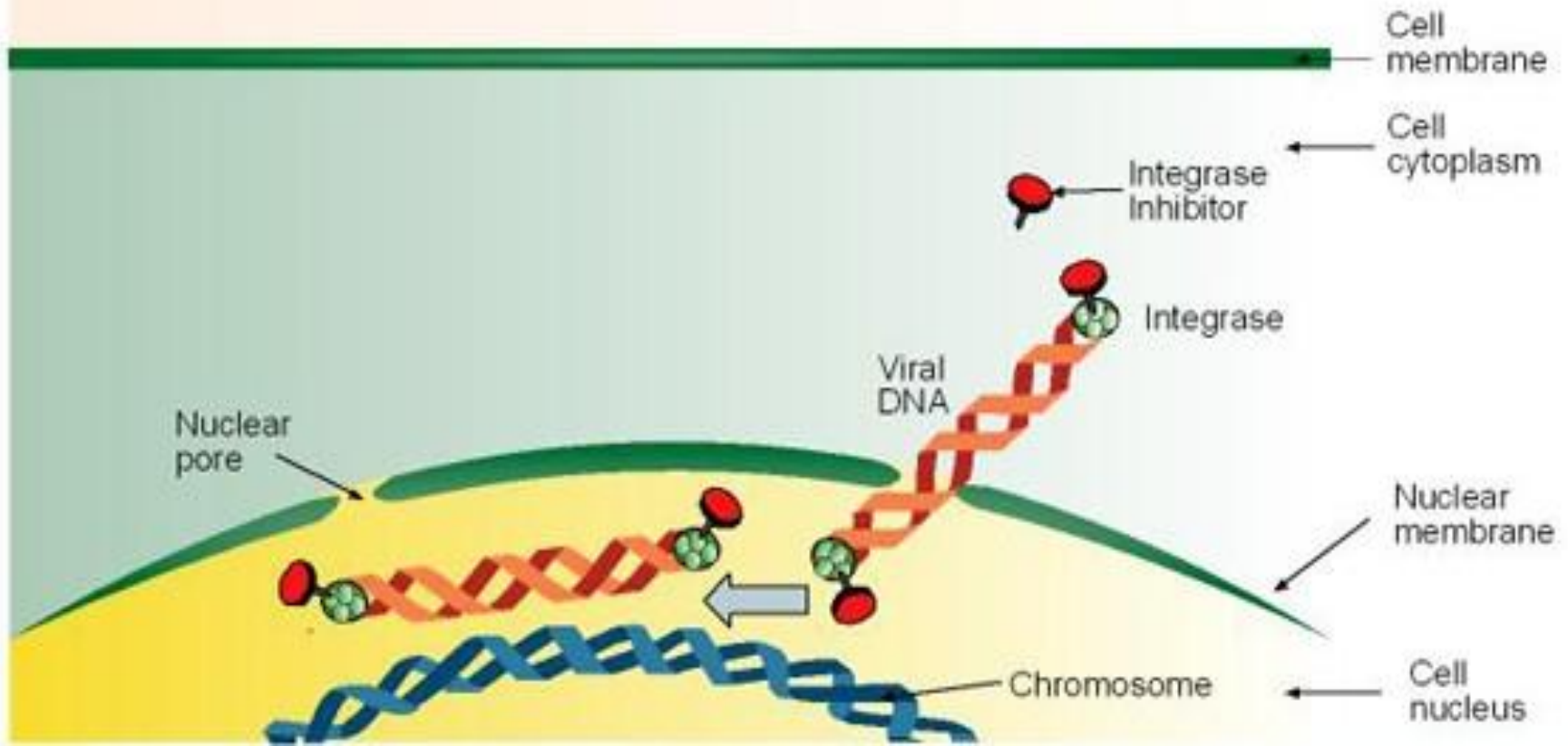


Non-nucleoside Reverse Transcriptase Inhibitors

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism (Hepatic)</u>
Efavirenz (EFV) Sustiva	600mg qd	50, 200mg caps 600mg tabs EFV-FTC-TDF tabs	Rash - 20% onset 11 days CNS – 50% onset 1 day Potentially teratogenic	Substrate CYP2P6>3A4 T½ 36-100 hr Inducer>Inhib. CYP3A4
Nevirapine (NVP) Viramune	200mg qd x 14 days then 200mg bid thereafter	200mg tabs, oral soln	(Possibly fatal) hepatotoxicity and skin reaction – may occur together	Substrate CYP3A4 Autoinducer of CYP3A4
Delavirdine (DLV) Rescriptor	400mg tid	100, 200mg tabs	Rash – 18% Increased LFTs Headaches	CYP3A4 substrate and inhibitor
Etravirine (ETR) Intelence	200mg bid	100mg tabs	Rash–9% (rarely severe) Nausea Hypersensitivity with Hepatotoxicity appears safe in HepB/C	Substrate CYP3A4,2C9, 2C19 Inducer 3A4 Inhibitor 2C9 & 2C19

Integrase Inhibitors

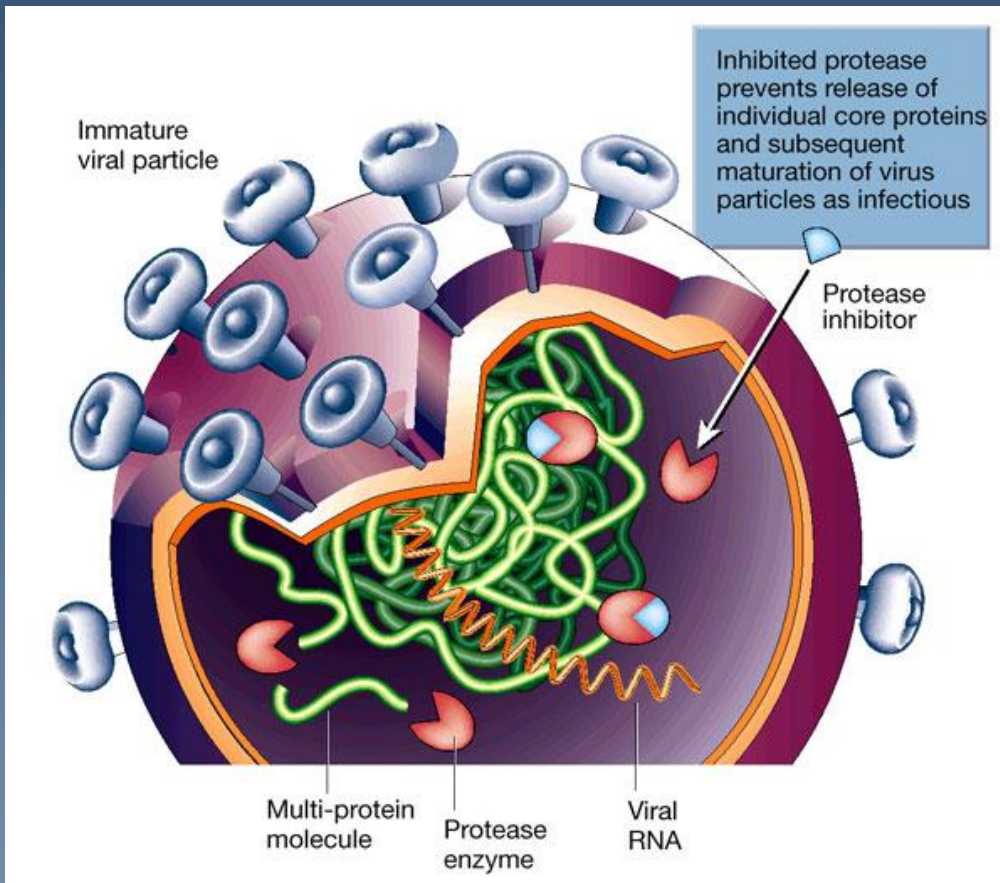
Mechanism of Action: Viral DNA is transported through the nuclear pore and integrated into the host DNA by the action of the virus encoded integrase. Raltegravir renders integrase incapable of viral DNA strand transfer into the host chromosome.



Integrase Inhibitor

<u>Drug</u>	<u>Standard Dose*</u>	<u>Dosage forms</u>	<u>Common Side Effects</u>	<u>Metabolism (Hepatic)</u>
Raltegravir (RAL) Isentress	400mg bid	400mg tabs	Generally well tolerated = Placebo GI, HA Slight increases in myopathy/creatine phosphokinase	(UGT)1A1– mediated glucuronidation

Protease Inhibitors



Protease inhibitors (peptide-like compounds) competitively inhibit the HIV Protease enzyme and prevent the post-translational cleavage of polyproteins → (processing of viral proteins into functional form) → production of immature, non-infectious viral particles

Nature 410, 995-1001

Protease Inhibitors

Class Toxicities

Class toxicities include:

- Hyperlipidemia
- Fat maldistribution (peripheral fat wasting/central fat accumulation)
- Insulin resistance/hyperglycemia
- GI complaints
- Bleeding episodes in hemophiliacs

Protease Inhibitors

	<u>Standard Dose</u>	<u>Dosage Forms</u>	<u>Common Side Effects</u>	<u>Metaolism (Hepatic)</u>
Atazanavir (ATV) Reyataz	300/100mg rtv qd 400mg qd (ARV-naïve)	100, 150, 200, 300mg caps	Unconjugated Hyperbilirubinemia PR prolongation	CYP3A4 inhibitor and substrate
Darunavir (DRV) Prezista	600/100mg rtv bid or 800/100mg rtv qd (ARV-naïve)	75, 400, 600mg tabs	Skin rash (10%) Hepatotoxicity Metabolic effects GI 2-3%, HA 1-4%	CYP3A4 inhibitor and substrate
Lopinavir/ ritonavir (LPV/r) Kaletra	400/100 bid or 800/200mg qd (not recommended with ≥ 3 LPV mutat.)	200/50mg tabs, 100/25mg tabs, Solution 400/100mg/5ml	GI Intolerance Metabolic effects \uparrow LFTs PR prolongation QT prolongation	CYP3A4 inhibitor and substrate
Fosamprenavir (FPV) Lexiva	1400mg bid 700/100mg rtv bid 1400/100-200mg qd (PI-naïve)	700mg tabs Suspension 50mg/ml	Skin rash (12-19%) GI intolerance, \uparrow LFTs Metabolic effects	CYP3A4 inhibitor, substrate, and inducer
Ritonavir (RTV) Norvir	Used as a PK booster 100- 400mg/day	100mg tab & cap Solution 80mg/mL	GI intolerance Hepatitis (SEs are dose related)	CYP3A4 $>2D6$ substrate; potent 3A4, 2D6 inhibitor

Protease Inhibitors

	<u>Standard Dose</u>	<u>Dosage Forms</u>	<u>Common Side Effects</u>	<u>Metabolism (Hepatic)</u>
Tipranavir (TPV) Aptivus	500/200mg rtv bid	250mg caps Solution 100mg/ml	Hepatotoxicity, Skin rash (3-21%) Rare intracranial hemorrhages Metabolic effects	CYP3A4 inducer and substrate (with rtv → CYP 3A4/2D6 inhibitor)
Nelfinavir (NFV) Viracept	1250 bid, 750mg tid	250mg, 625mg tabs, 50mg/g oral pwr	Diarrhea Metabolic effects ↑ LFTs	CYP2C19 and 3A4 substrate— metabolized to active M8 metabolite; CYP 3A4 inhibitor
Saquinavir (SQV) Invirase	1000/100mg rtv bid	200mg caps, 500mg tabs	SQV/r → ↑ QT & PR interval GI intolerance ↑ LFTs, HA,	CYP3A4 inhibitor and substrate
Indinavir (IDV) Crixivan	800/100-200mg bid 800mg q8h	100, 200, 400mg caps	Nephrolithiasis ⇒ Drink 7-8 glasses of water per day; hyperbilirubinemia GI intolerance	CYP3A4 inhibitor and substrate

Toxicities and Side Effects

Lactic acidosis (LA) +/- hepatic steatosis

Associated with NRTIs, specifically d4T, AZT, ddI

Consider switch: d4T, AZT, ddI to TDF or ABC or another class

Hepatic steatosis: D/C or switch as above. Follow liver enzymes

Pancreatitis

Strongly associated with ddI (+/- d4T, hydroxyurea, ribavirin).

May also occur with PI-induced hypertriglyceridemia

D/C all ARTs if severe and restart with different NRTIs

Diarrhea

Associated with many PIs, especially NFV

Usually controlled with fiber supplements

Calcium supplements and anti-diarrheals may also be helpful

If severe, switch from PI to NNRTI, alternate PI or another class

Toxicities and Side Effects

Hepatotoxicity

NNRTIs, PIs, most NRTIs, MVC: Clinical hepatitis or asymptomatic transaminase elevation.

NNRTIs: Often due to hypersensitivity, especially NVP.

Occurs in first wks of therapy, often accompanied by rash.

Can be life-threatening: D/C or switch usually necessary

PIs: Greatest risk with TPV/r. More common with HBV or HCV coinfection. Consider single-drug. D/C of all therapy may be required in symptomatic patients or if ALT > 5-10x upper limit of normal.

Hyperbilirubinemia

Indirect: benign side effect of ATV or IDV

Switch to different PI or NNRTI in pts with visible jaundice or scleral icterus (ATV only).

Direct: not typical drug side effect; evaluate for cholestasis

Toxicities and Side Effects

Hypersensitivity

Most commonly NNRTIs, ABC. Among PIs, DRV and FPV most likely to cause rash.

ABC: Systemic HSR in 5-8%, progressive with each dose. Substitute other NRTI, DO NOT rechallenge with ABC. Pre-screen for HLA B*5701.

NNRTIs: Mild-moderate rash common, D/C not required. Stop or switch for severe rash, systemic sx, or rash with hepatotoxicity (most common w/ NVP).

Lipoatrophy

Most strongly associated with use of d4T, AZT, ddl. Slowly and partially reversible with switches to ABC or TDF. Complete reversibility of severe lipoatrophy not likely. Facial LA often not reversible. Switching when lipoatrophy mild more likely to result in resolution.

Toxicities and Side Effects

Rash

Most common w/ NNRTIs, ABC, FPV, DRV

NNRTIs: Mild-moderate rash common, D/C not required
Stop or switch for severe rash (mucosal involvement or desquamation), systemic symptoms, or rash with hepatotoxicity (most common w/ NVP).

Do not increase to full-dose NVP until rash resolved. Rule out hepatotoxicity with NVP rash.

DRV and FPV: sulfa-allergic pts may be at increased risk (but not contraindicated for mild-moderate sulfa allergy).

CNS effects

Common with EFV therapy during first days-weeks; usually improves with time. If no improvement after 3-4 wks, may not resolve.

Toxicities and Side Effects

Peripheral Neuropathy

Most often associated with d4T or ddI, but can also occur with HIV itself. Switch to TDF, ABC, or AZT or another class.

Renal insufficiency

Switch from IDV to other PI or NNRTI. Adjust TDF dose based on calculated creatinine clearance, or switch from TDF to ABC or AZT or to NRTI-sparing regimen.

Anemia and Neutropenia

If AZT-related, switch to another agent.

Fat Accumulation

Studies changing ART, including eliminating PIs, have failed to demonstrate significant impact on FA. There may be less FA with ATV especially if insulin resistant, although data not conclusive.

Toxicity and Side Effects

Nausea and Vomiting (possible with all approved ART)

Initiation of ART – Sx may improve within 1-2 wks
(N&V varies widely among individuals)

Symptomatic treatment: Prochlorperazine, Promethazine,
Trimethobenzamide, Metoclopramide, others

If Sx do not improve significantly consider changing ART

CASTLE study: diarrhea and nausea of pts taking ATV/r
+ TDF/FTC < LPV/r twice-daily + TDF/FTC

Take with food if possible

NRTIs: ddl - take on empty stomach. Others - may be
better tolerated w/ food, especially AZT.

NNRTIs: EFV - take on empty stomach initially, to decrease
CNS side effects. Others - may be better tolerated w/ food

PIs: IDV - take on empty stomach. Others - may be better
tolerated w/ food

MVC & RAL – no food restrictions

Toxicity and Side Effects

Insulin Resistance

PI effect on IR: IDV >> NFV, RTV, LPV/r > SQV, APV >> ATV.
Consider switching from PI to NNRTI-based regimen provided viral control not jeopardized.
ATV may cause less insulin resistance.

Hyperlipidemia

PIs: most cause elevation in TC, LDL and triglycerides TG.
Highest risk: RTV, TPV/r and LPV/r.

Least or no risk: ATV and SQV.

TC and LDL increase an average of 30 mg/dL on PIs. TGs may be severely elevated.

NRTIs: d4T highest risk for TG and LDL increase. Low or no risk with TDF and ABC.

NNRTIs: EFV > NVP associated with TG, LDL increase.

NNRTIs increase HDL. Increase in TG, TC and LDL less than for PIs.