

Drug Interactions, Adherence, and Resistance to Medications

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- Speakers Bureau/Independent Consultant: Gilead Sciences, ViiV Healthcare, Merck & Co

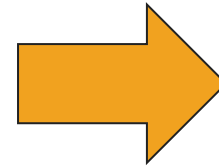
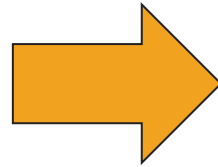
He attests that clinical recommendations are evidence-based and free of commercial bias.

Objectives

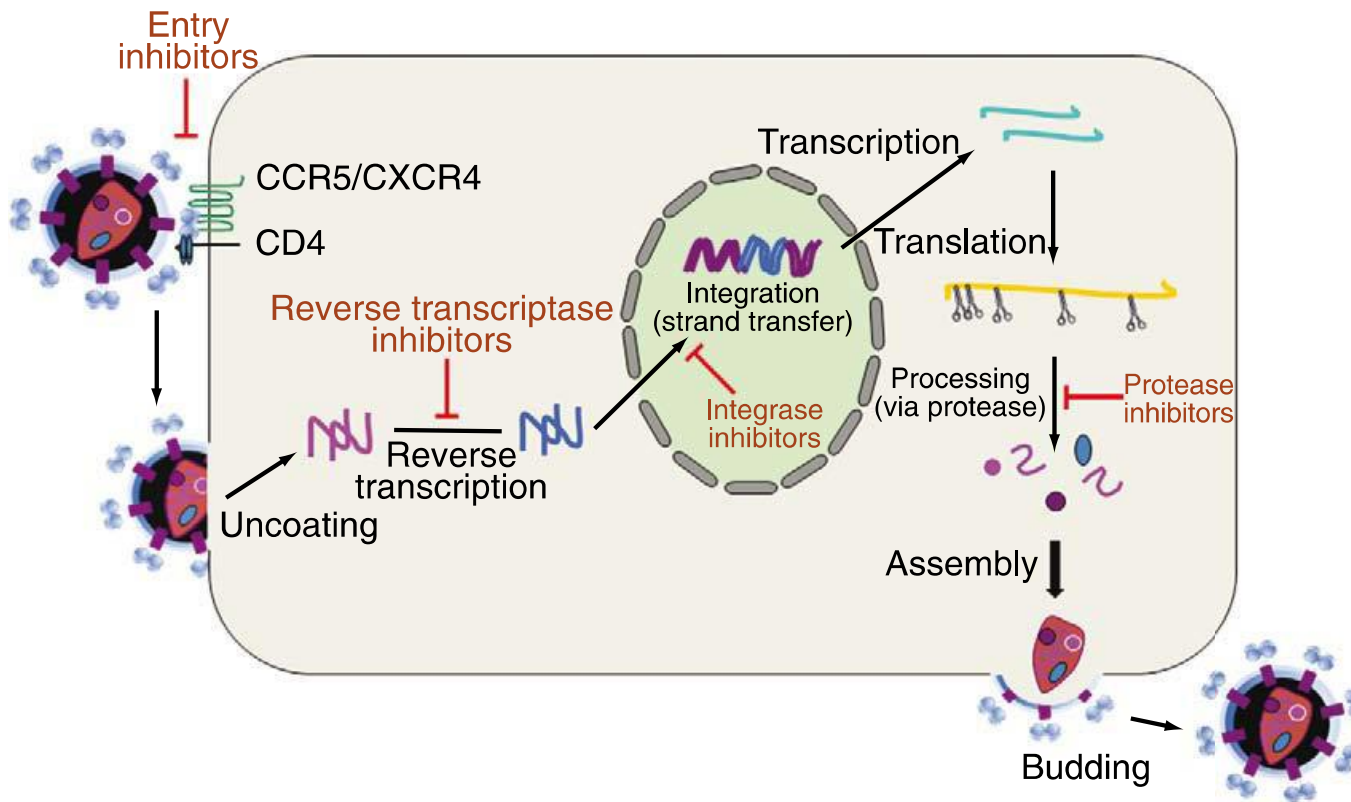
- Discuss treatment considerations and management strategies for antiretroviral-related adverse effects.
- Compare the pharmacokinetics and pharmacodynamics of drug mechanisms and discuss resources for evaluating drug interactions involving antiretroviral medications.
- Discuss clinical management of intermittent and persistently detectable HIV RNA levels in persons receiving ART, including indications for and types of resistance testing for patients with virologic failure.

Introduction

How far we've come!



HIV infection pathophysiology



HIV infection pathophysiology

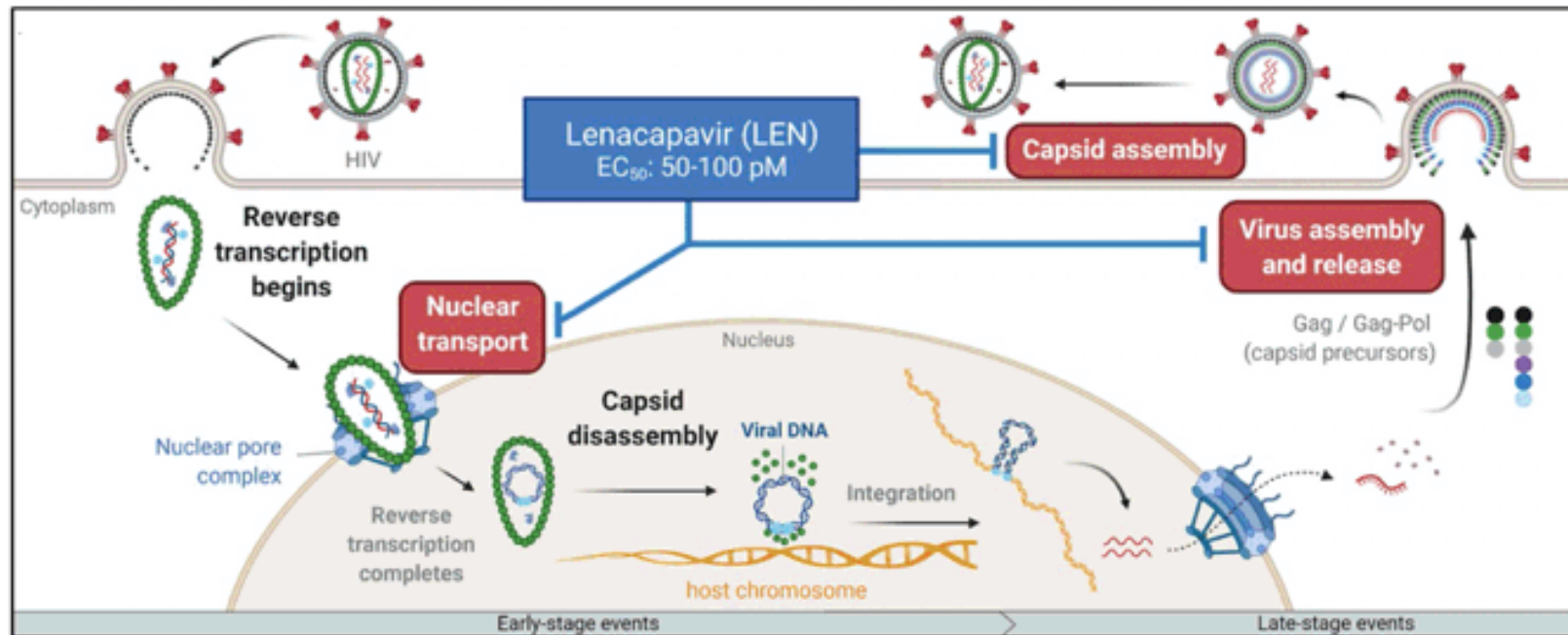
1. HIV virion binds to the CD4 receptor of the CD4 cell using coreceptor CCR5 or CXCR4 and inserts its genetic material (*Entry and Fusion inhibitors*)
2. Reverse transcriptase enzymes convert viral RNA to DNA (*Nucleotide reverse transcriptase inhibitors [NRTIs] and Non nucleotide reverse transcriptase inhibitors [NNRTIs]*)
3. Integrase enzymes insert viral DNA into the host DNA strand (*Integrase inhibitors [INSTIs]*)

HIV infection pathophysiology

4. Normal protein transcription and translation occur
5. “Viral” proteins are processed/excised by protease enzymes (*Protease inhibitors*)
6. Viral assembly occurs from excised proteins / processed components
7. Budding of the new virion from the CD4 cell

Capsid Inhibitor

LEN Targets Multiple Stages of HIV Replication Cycle



AS 2021 Link JO, et al. Nature 2020;584:614-8; Bester SM, et al. Science 2020;370:360-4.

NRTIs	PIs	NNRTIs		
Abacavir (ABC, Ziagen)	Atazanavir (ATV, Reyataz)	Delaviridine (DLV, Rescriptor)		
Didanosine (ddl, Videx)	Darunavir (DRV, Prezista)	Efavirenz (EFV, Sustiva)		
Emtricitabine (FTC, Emtriva)	Fosamprenavir (FPV, Lexiva)	Etravirine (ETR, Intelence)		
Lamivudine (3TC, Epivir)	Indinavir (IDV, Crixivan)	Nevirapine (NVP, Viramune)		
Islatravir (ISL)	Lopinavir/Ritonavir (LPV/r, Kaletra)	Rilpivirine (RPV, Edurant)		
Stavudine (d4T, Zerit)	Nelfinavir, (NFV, Viracept)	Doravirine (DOR, Pifeltro)		
Tenofovir AF (TAF, Vemlidy)	Ritonavir (RTV, Norvir)	PKE		
Tenofovir DF (TDF, Viread)	Saquinavir (SQV, Invirase)			
INSTIs	Tipranavir (TPV, Aptivuis)	Entry/Attachment inhibitors		
	Capsid Inhibitor		Cobicistat (cobi)	
			Lenacapavir (LEN, Sunlenca)	Maraviroc (MVC, Selzentry)
				Enfuvirtide (T-20, Fuzeon)
				Ibalizumab (Iba, Trogarzo)
				Fostemsavir (FTR, Rukobia)

HIV Medication combinations

- ABC/3TC (Epzicom)
- AZT/ABC/3TC (Trizivir)
- AZT/3TC (Combivir)
- TAF/FTC (Descovy)
- TDF/FTC (Truvada)
- Darunavir/cobicistat (Prezcobix)
- Atazanavir/cobicistat (Evotaz)
- Efavirenz/TDF/FTC (Atripla)
- Rilpivirine/TDF/FTC (Complera)
- Rilpivirine/TAF/FTC (Odefsey)
- Elvitegravir/cobi/TDF/FTC (**Stribild**)
- Elvitegravir/cobi/TAF/FTC (**Genvoya**)
- Dolutegravir/ABC/3TC (**Triumeq**)
- Dolutegravir/Rilpivirine (**Juluca**)
- Bictegravir/TAF/FTC (**Biktarvy**)
- Darunavir/cobi/TAF/FTC (**Symtuza**)
- Doravirine/TDF/3TC (**Delstrigo**)
- Dolutegravir/Lamivudine (**Dovato**)
- Islatravir/Doravirine (**Idvynso**)
- Bictegravir/Lenacapavir (**Bixlenvo**)
- **Cabotegravir/Rilpivirine (Cabenuva)**

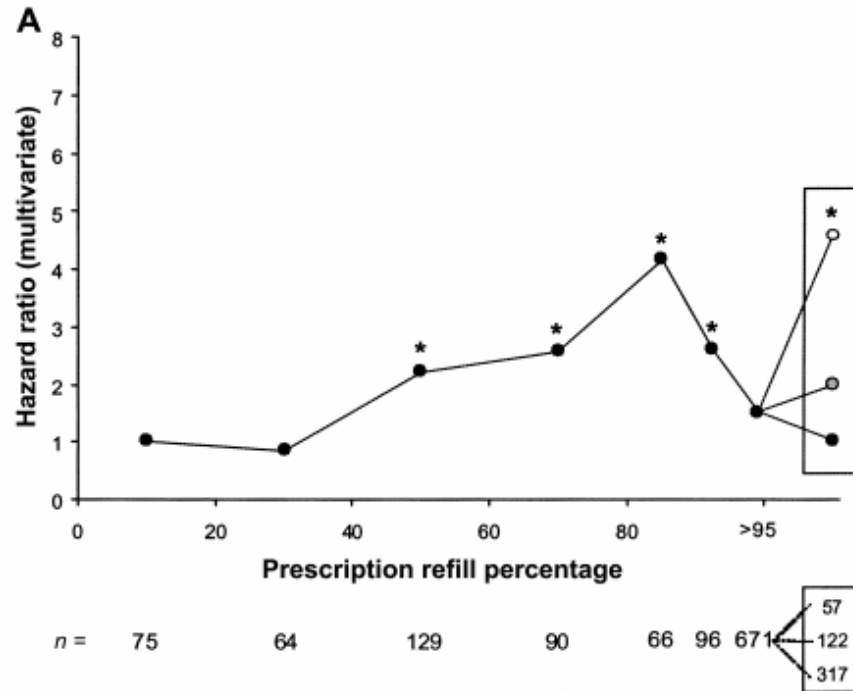
"ART"
isn't easy!



Good vs. Great Adherence

Association between adherence rates and detection of HIV-1 drug resistance mutations

- Goal $\geq 95\%$ adherence
- Highest risk of developing resistance
 - 80-90% adherence
 - Good not great adherence



Factors Associated With Poor Adherence

Characteristics of the patient

- Low level of literacy
- Psychosocial issues
 - Untreated mental health disorders
 - Homelessness
 - Low social support
 - Stressful life events
- Active substance use
- Stigma
- Health Beliefs
- Difficulty with administration
 - trouble swallowing pills
 - daily schedule issues

Characteristics of the regimen

- Complex regimen
 - Pill burden
 - Dosing frequency
 - Food requirements
- Adverse drug effects
- Treatment fatigue
- Lower strength of provider/patient relationship

Adherence to Antiretrovirals

Establish readiness:

- Psychosocial issues
- Active substance use/
risk of relapse
- Low literacy level
- Lack of disclosure
- Health beliefs/skepticism about ART
- Lack of prescription drug coverage/co pays
- Busy daily schedule/travel away from home
- Poor social supports

Strategies to ↑ adherence:

- Patient education
- Use simplified regimens
- Provide resources
 - Case management
 - Substance use tx
 - Support groups
- Reminder devices/ pill boxes
- Aggressive treatment of side effects
- Treat underlying mental health disorders
- Build relationship of trust with patient

Drug-Drug Interactions and Adverse Drug Reactions Due To ART

Drug Interactions

www.hiv-druginteractions.org

The screenshot shows the homepage of the HIV Drug Interactions website. The header includes the site logo, the University of Liverpool affiliation, and an 'Interaction Checker' button. A navigation bar lists 'Interaction Charts', 'Site Updates', 'About Us', 'Pharmacology Resources', and 'Contact Us'. A green banner prompts users to update their HIV iChart app. The main section features the 'HIV Drug Interaction Checker' with a description and a 'Start Now' button. Below this is a table showing drug interactions between various HIV medications and other drugs.

	Atazanavir	Darunavir	Dolutegravir	Efavirenz	Raltegravir	Rilpivirine	Tenofovir-DP
Amiodarone	Potential Interaction	No Interaction Expected	No Interaction Expected	Potential Interaction	No Interaction Expected	Potential Interaction	No Interaction Expected
Antacids	Potential Interaction	No Interaction Expected	No Interaction Expected	No Interaction Expected	Potential Interaction	Potential Interaction	No Interaction Expected
Atazanavir		No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected
Cannabis	Potential Interaction	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected
Carbamazepine	Potential Interaction	Potential Interaction	No Interaction Expected	Potential Interaction	Potential Interaction	No Interaction Expected	No Interaction Expected
Cyclosporin	Potential Interaction	Potential Interaction	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected
Dabigatran	Potential Interaction	Potential Interaction	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected	No Interaction Expected

Below the table, there are two sections: 'Site News & Twitter Updates' with a 'Follow @hivinteractions' button, and 'Discover Our HIV Mobile Apps' with a description of the HIV iChart app.

All in one check

The screenshot shows the HIV Drug Interactions website interface. The header includes the site name, University of Liverpool logo, and navigation links. The main content area is titled "Drug Interaction Checker" and features three columns: HIV Drugs, Co-medications, and Drug Interactions.

HIV Drugs	Co-medications	Drug Interactions
Search HIV drugs...	fluti	Switch to table view
A-Z Class Trade	A-Z Class Trade	Reset Checker
☒ Atazanavir	☒ Fluticasone	Potential Interaction
☒ Cobicistat (with ATV or DRV)	☒ Fluticasone	Atazanavir
☐ Abacavir		Fluticasone
☒ Atazanavir		More Info
☒ Cobicistat (with ATV or DRV)		Potential Interaction
☐ Darunavir		Cobicistat (with ATV or DRV)
☐ Delavirdine		Fluticasone
☐ Didanosine (ddl)		More Info
		No Interaction Expected

This screenshot shows a detailed interaction summary for Atazanavir and Fluticasone. The summary includes a description of the interaction, a summary of the evidence, and a description of the potential interaction.

Interaction: Atazanavir / Fluticasone

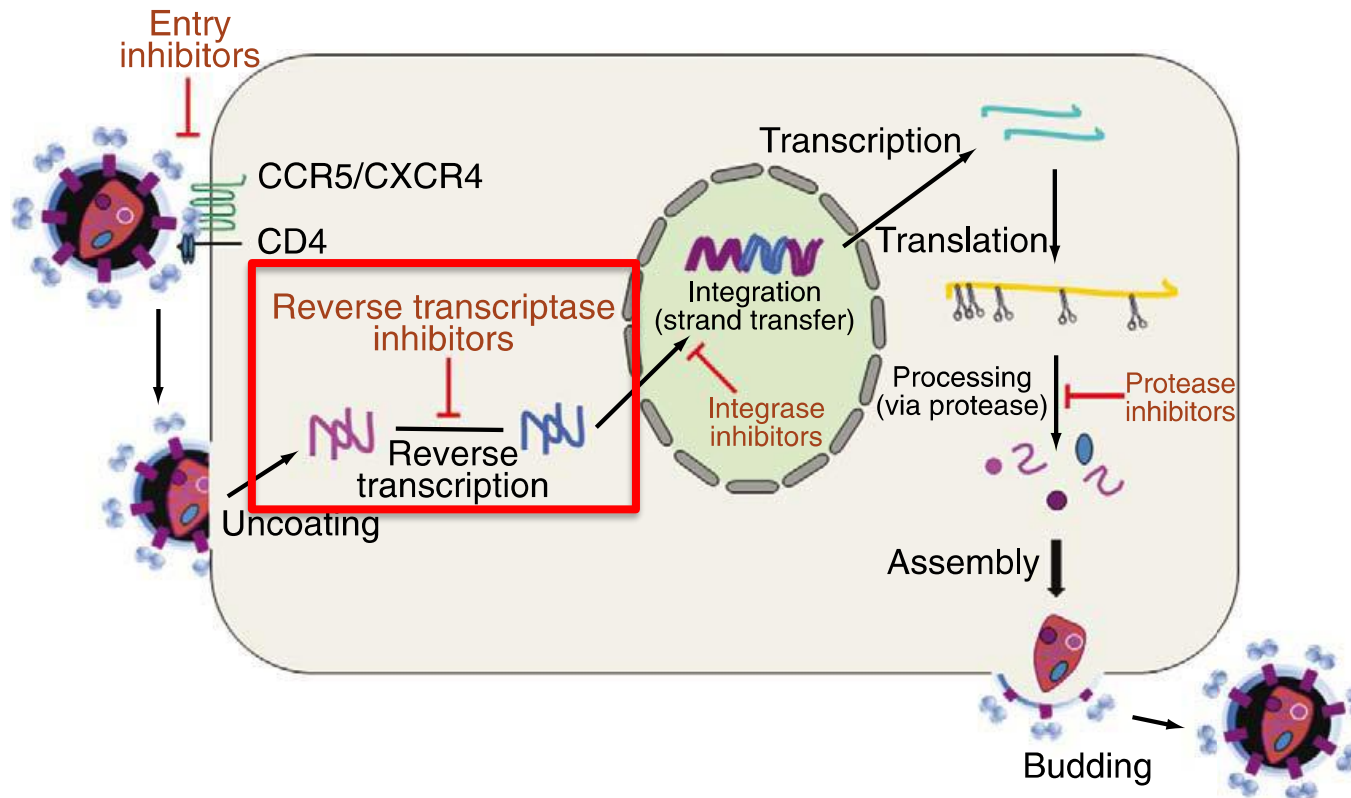
Summary:

Concomitant use of atazanavir and glucocorticoids metabolized by CYP3A4 is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Systemic corticosteroid effects have been reported in patients receiving atazanavir and should be carefully monitored. Atazanavir should be avoided in patients receiving glucocorticoids. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects for a search to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., budesonide). However, in case of withdrawal of glucocorticoid, progressive dose reduction may have to be performed over a longer period.

Description:

Concomitant use of atazanavir (300 mg 3 times daily for 7 days) and atazanavir (300 mg twice daily) was studied. The atazanavir plasma levels increased significantly, whereas the atazanavir levels decreased by approximately 80% (95% confidence interval 62-89%). Greater effects may be expected when atazanavir is administered. Systemic corticosteroid effects including Cushing's syndrome and adrenal suppression have been reported in patients receiving atazanavir and should be carefully monitored. Atazanavir should be avoided in patients receiving glucocorticoids. A dose reduction of the glucocorticoid should be considered with close monitoring of local and systemic effects for a search to a glucocorticoid, which is not a substrate for CYP3A4 (e.g., budesonide). However, in case of withdrawal of glucocorticoid, progressive dose reduction may have to be performed over a longer period.

Nucleoside/tide Reverse Transcriptase Inhibitors (NRTIs)



Generic Name	Trade Name	Abbreviation	Year Approved
Abacavir	Ziagen	ABC	1998
Didanosine	Videx	ddI	1991
Emtricitabine	Emtriva	FTC	2003
Islatravir	***	ISL	2026
Lamivudine	Epivir	3TC	1995
Stavudine	Zerit	d4T	1994
Tenofovir DF	Viread	TDF	2001
Tenofovir AF	***	TAF	***
Zidovudine	Retrovir	AZT	1987
Zalcitabine	Hivid	ddC	1992
	Epzicom	ABC/3TC	2004
	Descovy	FTC/TAF	2016
	Truvada	FTC/TDF	2004
	Combivir	3TC/AZT	1997
	Trizivir	ABC/3TC/AZT	2000

NRTI Pharmacokinetics

- Absorption
 - Well absorbed, with or without food
 - Exception: didanosine
- Low protein binding with intracellular drug target
- Renal elimination
 - Exception: abacavir
- Minimal hepatic metabolism
 - Exception: abacavir

Major NRTI class adverse effects

- Mitochondrial toxicity
- Lactic Acidosis
- Hepatic Dysfunction
- Peripheral Neuropathy
- Lipoatrophy

Note: These are more common with older agents (eg: didanosine, stavudine, zidovudine)

Zidovudine

- Retrovir, AZT
- Tablet, liquid, and IV formulations
- Good CSF penetration and crosses placenta
- 300 mg BID
 - Renal dose adjustment

- Adverse reactions
 - Nausea/vomiting
 - Headache
 - Anorexia
 - Fatigue
 - Nail/skin hyperpigmentation
 - Myopathy
 - **Neutropenia**
 - Lipoatrophy
 - Lactic acidosis
 - **MACROcytic Anemia**



Lamivudine

- Epivir, 3TC
- Dosing: 150 mg q12h or 300 mg daily
 - Renal dosing
 - 300 mg, 150 mg, 100 mg tablet strengths
- Tablet and liquid formulations
- Active against Hepatitis B
 - Epivir HBV 100 mg

- Adverse reactions
 - NOT MANY!
 - GI: nausea, vomiting, diarrhea



Emtricitabine

- Emtriva, FTC
- Capsule and liquid
- Dosing: 200 mg daily (capsule)
 - Renal dose adjustment
 - Liquid dosing: 240 mg

- Adverse reactions
 - Minimal toxicity
 - Hyperpigmentation, skin discoloration



Abacavir

- Ziagen, ABC
- 300 mg tablet and liquid
- Metabolism
 - Glucuronidation
 - Alcohol dehydrogenase
- Dosing: 300 mg q12h or 600 mg once daily
 - Child Pugh
 - 5-6: 200 mg BID
 - > 6: contraindicated

- Adverse reactions
 - Relatively few systemic side effects
 - Hypersensitivity reaction (5-10%)
 - Myocardial infarction
 - Conflicting data from multiple trials



Abacavir Hypersensitivity and Pharmacogenomics

- Symptoms
 - **NONSPECIFIC**
 - Fever, skin rash (66%), malaise, nausea, diarrhea, headache, abdominal pain, dyspnea
 - If continued: hypotension, respiratory distress, vascular collapse
- HLA-B*5701 Screening
 - Prior to initiating therapy with ABC
 - Positive patients should not be given ABC
 - Record as abacavir allergy
 - Negative predictive value: 100%
 - Positive predictive value: 48%

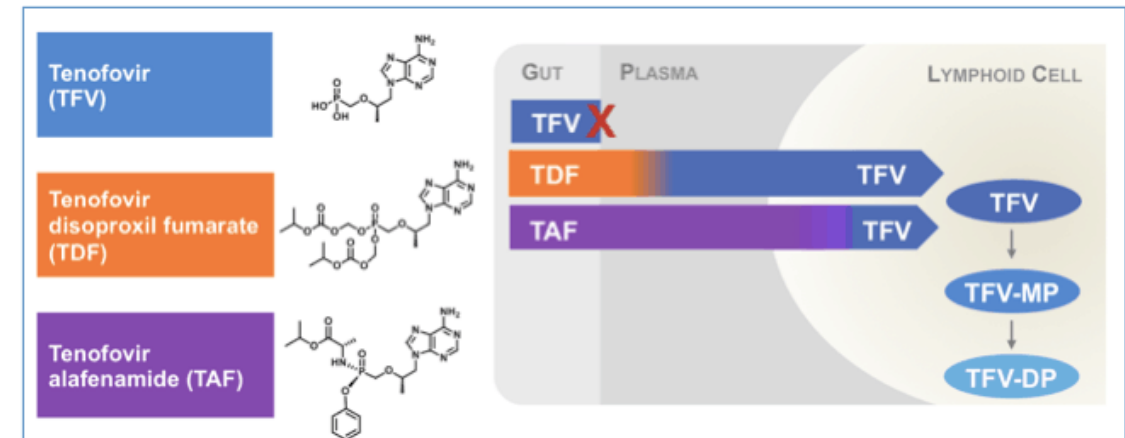
Tenofovir Disoproxil Fumarate



- Viread, TDF
- **Nucleotide** reverse transcriptase inhibitor
- Tablet and pediatric powder
- Dosing: 300 mg daily
 - Renal dose adjustment
 - 300 mg tablet strength
- Active against Hepatitis B
 - Including lamivudine-resistant strains
- Drug interactions
 - Competitive tubular secretion
 - Cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir
- Adverse Reactions
 - Osteomalacia; decreased bone mineral density
 - Renal impairment
 - Fanconi's Syndrome

Tenofovir Alafenamide (TAF)

- Only available in combination products for HIV indication
- Amidate vs Ester molecule
 - 90% less serum concentrations
 - Greater intracellular concentration of active drug
- Active against hepatitis B



TAF - Vemlidy

TAF/FTC - Descovy

TAF/FTC/RPV - Odefsey

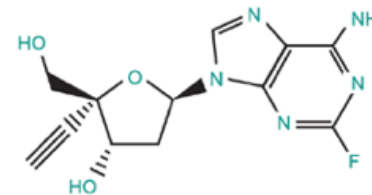
TAF/FTC/EVG/cobi - Genvoya

Islatravir

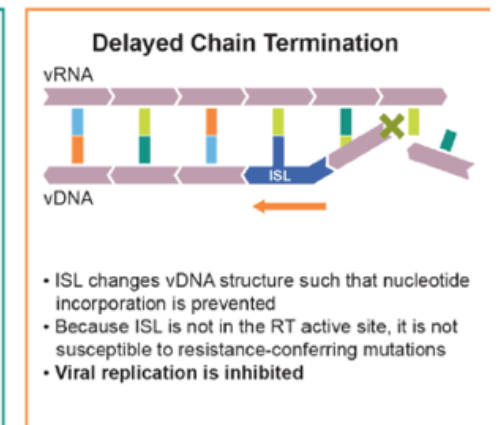
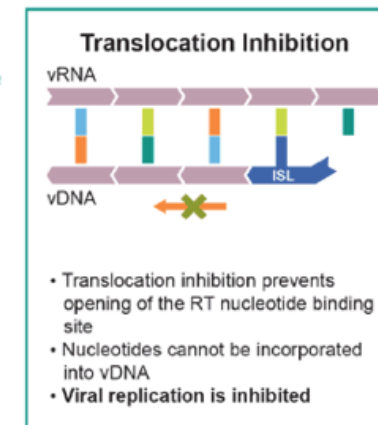
- Islatravir, ISL
- Nucleotide reverse transcriptase inhibitor
 - Also affects translocation
- Tablet and pediatric powder
- Dosing: 0.25mg daily
 - Combined with Doravirine 100mg (Idvynso)
 - Cannot be used with CrCl <30mL/min

- Drug interactions
 - Cannot be coadministered with 3TC/FTC

Islatravir (ISL) Has Multiple Mechanisms of Action¹⁻³

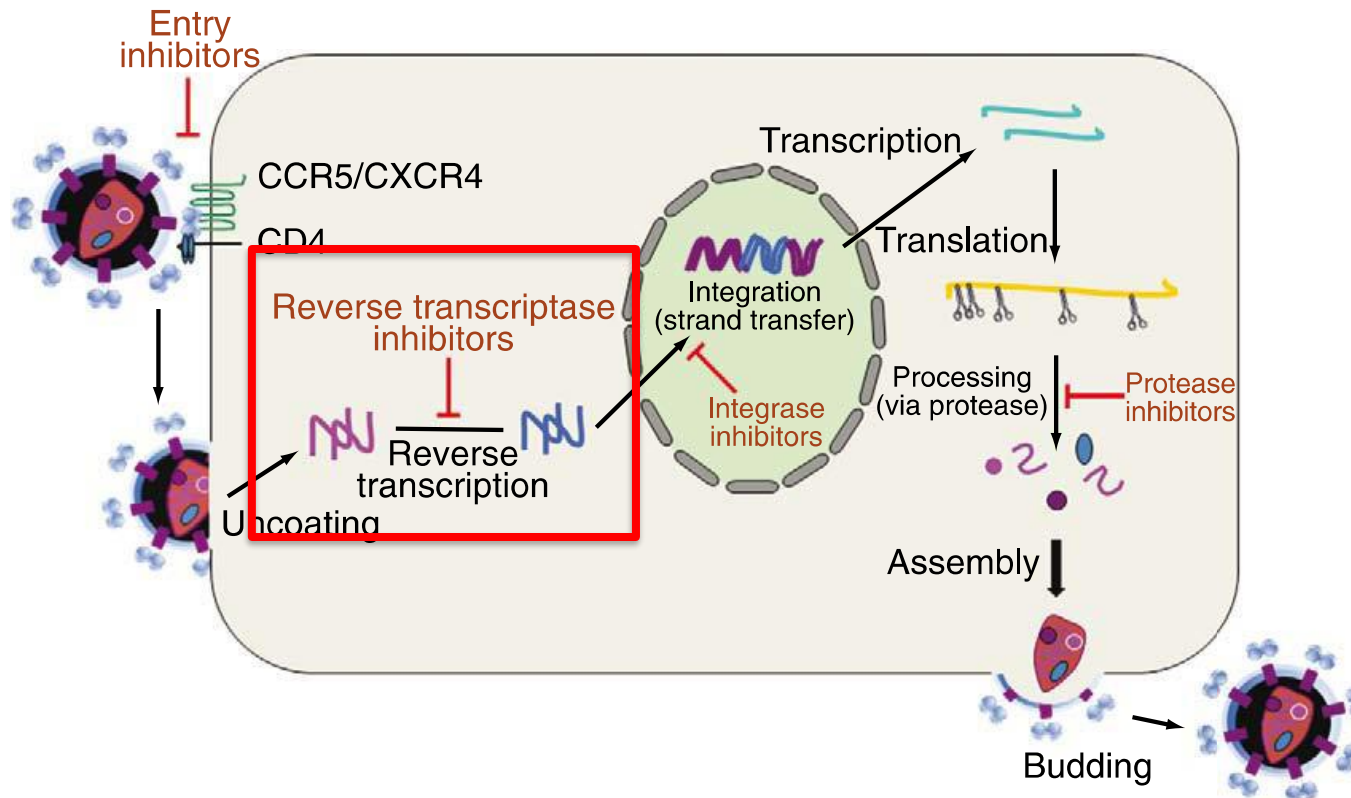


Multiple mechanisms contribute to the high potency of ISL against HIV-1 (including drug-resistant variants) and its high barrier to resistance



ISL, islatravir; RT, reverse transcriptase; vDNA, viral DNA; vRNA, viral RNA.
 1. Kawamoto et al. *Int J Biochem Cell Biol* (2008) 40:2410-2420. 2. Michalidis et al. *J Biol Chem* (2014) 289:24533-24548. 3. Sato et al. *PNAS* (2016) 113:9274-9279.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)



NNRTIs

NNRTI	Trade Name	Year Approved
Nevirapine	Viramune	1996
Delavirdine	Rescriptor	1997
Efavirenz	Sustiva	1998
Etravirine	Intelence	2007
Rilpivirine	Edurant	2011
Doravirine	Pifeltro	2018
Efavirenz + TDF + FTC	Atripla	2006
Rilpivirine + TDF + FTC	Complera	2011
Rilpivirine + TAF + FTC	Odefsey	2016
Doravirine + 3TC + TDF	Delstrigo	2018

NNRTI Pharmacokinetics

- Absorption: > 90 %
- Distribution: Generally highly protein-bound
- Renal Elimination
 - Minimal
- Long serum half-life, caution when discontinuing combination therapy
- Metabolism
 - CYP enzyme substrates
 - Variable CYP enzyme inhibition and induction depending upon agent

CYP 450 Metabolism

	Substrate	Inhibits	Induces
Delavirdine	3A4 (major) 2D6 (minor)	3A4 (strong) 2C9 (strong) 2C19 (strong) 2D6 (strong)	--
Efavirenz	3A4 (major) 2B6 (major)	3A4 (moderate) 2C9 (moderate) 2C19 (moderate)	3A4(strong) 2B6 (weak)
Etravirine	3A4 (major) 2C9 (major) 2C19 (major)	2C9 (moderate) 2C19 (moderate)	3A4 (strong)
Nevirapine	3A4 (major) 2B6 (minor) 2D6 (minor)	1A2 (weak) 2D6 (weak) 3A4 (weak)	3A4 (strong) 2B6 (strong)
Rilpivirine	3A4 (major)	--	--
Doravirine	3A4 (major)		

Rilpivirine

- RPV, Edurant
- RPV + TDF + FTC: Complera
- RPV + TAF + FTC: Odefsey
- RPV + CAB: Cabenuva
- Dosing: 25 mg daily
 - With normal caloric meal
 - NOT protein shake
 - Exposure 40% lower in fasted state
- Half life: 38-47 hrs

- Adverse Effects
 - Depression, insomnia
 - Headache
 - Rash
- Requires acidic environment for absorption



Rilpivirine and Acid Suppressors

Antacids

- Give antacids 2 hour before or 4 hours after rilpivirine

H2 Blockers

- Give H2 blocker at least 12 hours before rilpivirine

PPIs

- Contraindicated

Doravirine



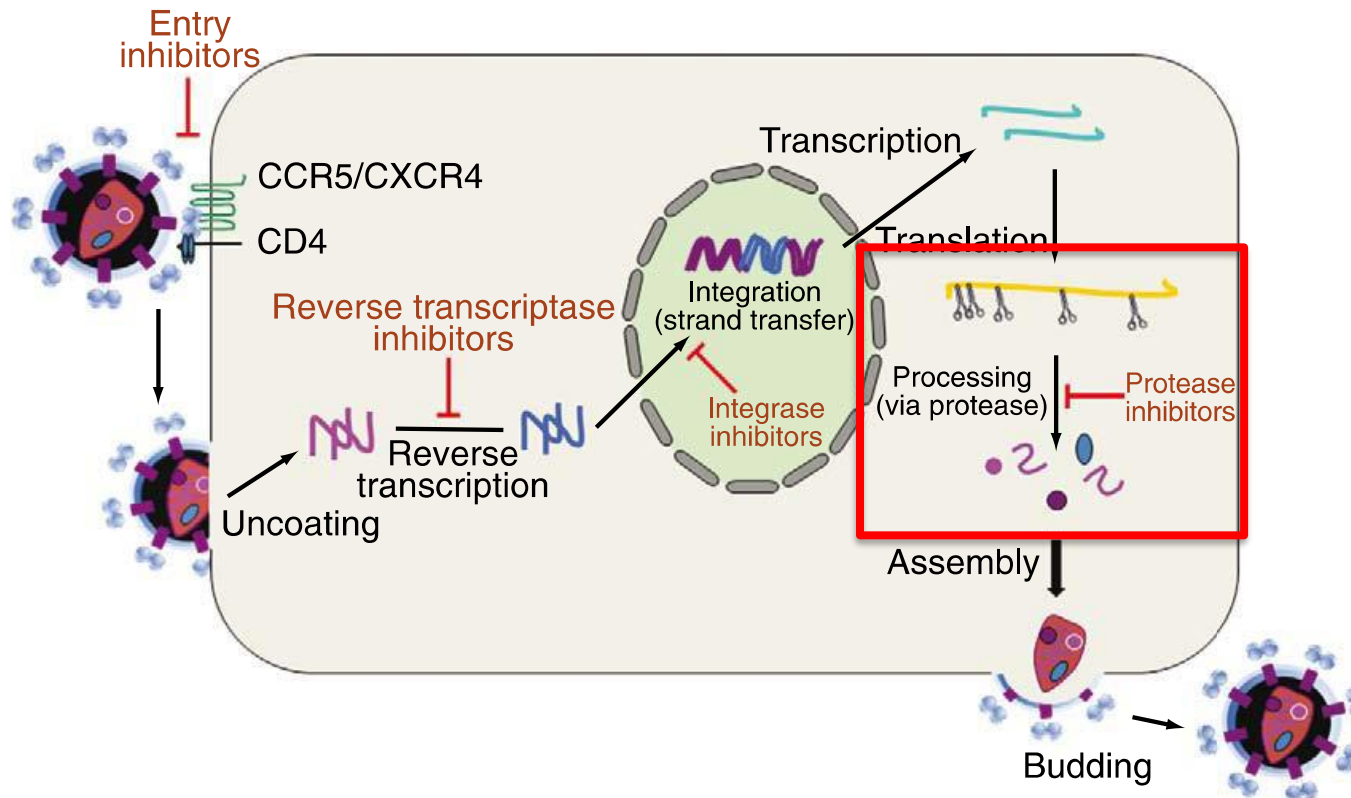
- DOR, Pifeltro
- DOR + 3TC + TDF: Delstrigo
- Dosing: 100 mg daily
 - Without regards to food
- Half-life: 15 hrs
- Unique resistance mechanism (can possibly be used if patient has resistance to multiple other in-class agents)

- Adverse Effects

- Fatigue
- Headache
- Rash



Protease Inhibitors (PIs)

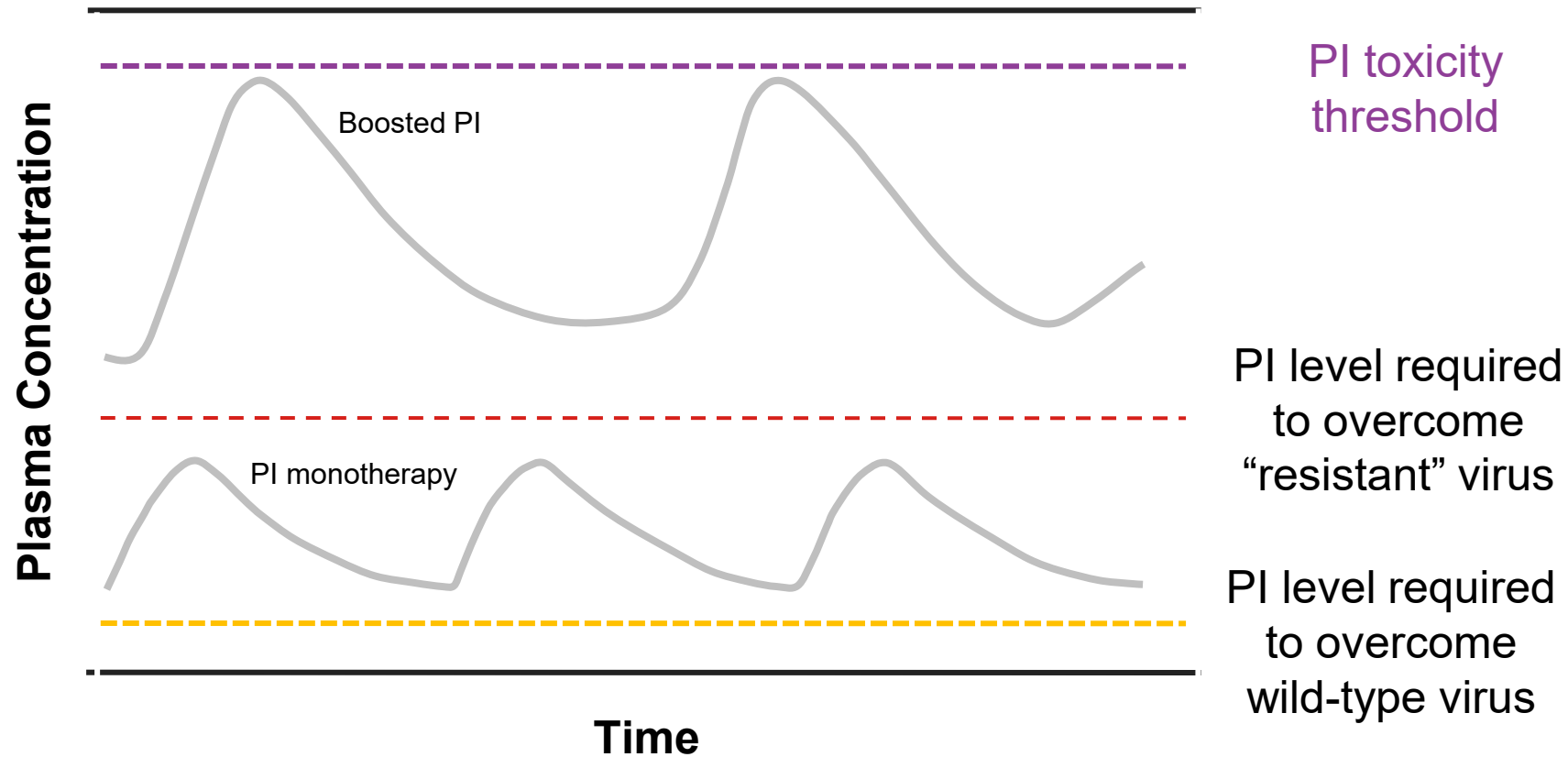


Generic Name	Trade Name	Abbreviation	Year Approved
Atazanavir	Reyataz	ATV	2003
Darunavir	Prezista	DRV	2006
Fosamprenavir	Lexiva	FPV	2003
Lopinavir	Kaletra	LPV/r	2000
Nelfinavir	Viracept	NFV	1997
Ritonavir	Norvir	RTV	1996
Saquinavir	Invirase	SQV-hgc	1995
Tipranavir	Aptivus	TPV	2005
Atazanavir/cobicistat	Evotaz	ATV/COBI	2015
Darunavir/cobicistat	Prezcobix	DRV/COBI	2015
Amprenavir	Agenerase	APV	1999
Indinavir	Crixivan	IDV	1996
Saquinavir	Fortovase	SQV-sgc	1997
Darunavir/cobi/TAF/FTC	Symtuza	D/c/F/TAF	2018

Key Pharmacokinetic Points

- Absorption
 - Most agents are recommended with food
- Half life
 - Similar to NRTIs
 - Shorter than NNRTIs
- Metabolism
 - Major metabolism by CYP 450 enzymes = many drug interactions
 - Ritonavir/cobicistat: Strong CYP3A4 inhibitors

Boosted vs. Non-boosted PIs



Major PI Class Adverse Effects

- Lipodystrophy
 - In vitro inhibition of GLUT4
- Insulin resistance
- Dyslipidemias
 - $\uparrow$ TG / LDL / TC
- Gastrointestinal side effects
 - Nausea/Diarrhea



Darunavir

- Prezista, DRV
- Dosing
 - Naïve – 800mg/100 mg daily
 - Experienced & at least 1 DRV associated mutation:
600mg/100mg BID
 - With food
- Formulation
 - Tablets (800, 600, 400)
 - Suspension
- Available in combination with cobicistat – Prezcobix
- Available as single tablet regimen D/c/F/TAF - Symtuza

- Adverse reactions
 - Diarrhea, nausea
 - Rash (2-7%)
 - Sulfa moiety
 - Caution in patients with sulfa allergy
 - Hyperlipidemia
 - Acute hepatitis



Protease Inhibitors & Statins

Statin	Protease Inhibitor	Recommendation
Atorvastatin	TPV/RTV	Do not co-administer
	DRV/RTV	NTE 20 mg atorvastatin
	DRV/c, LPV/RTV	
Fluvastatin		
Lovastatin		
Pitavastatin		
Pravastatin	DRV/RTV or COBI LPV/RTV	No dose limitations
Rosuvastatin	ATV+/- RTV, LPV/RTV	NTE 10 mg rosuvastatin
	ATV/c, DRV/c, DRV/r	
Simvastatin	All protease inhibitors	Contraindicated

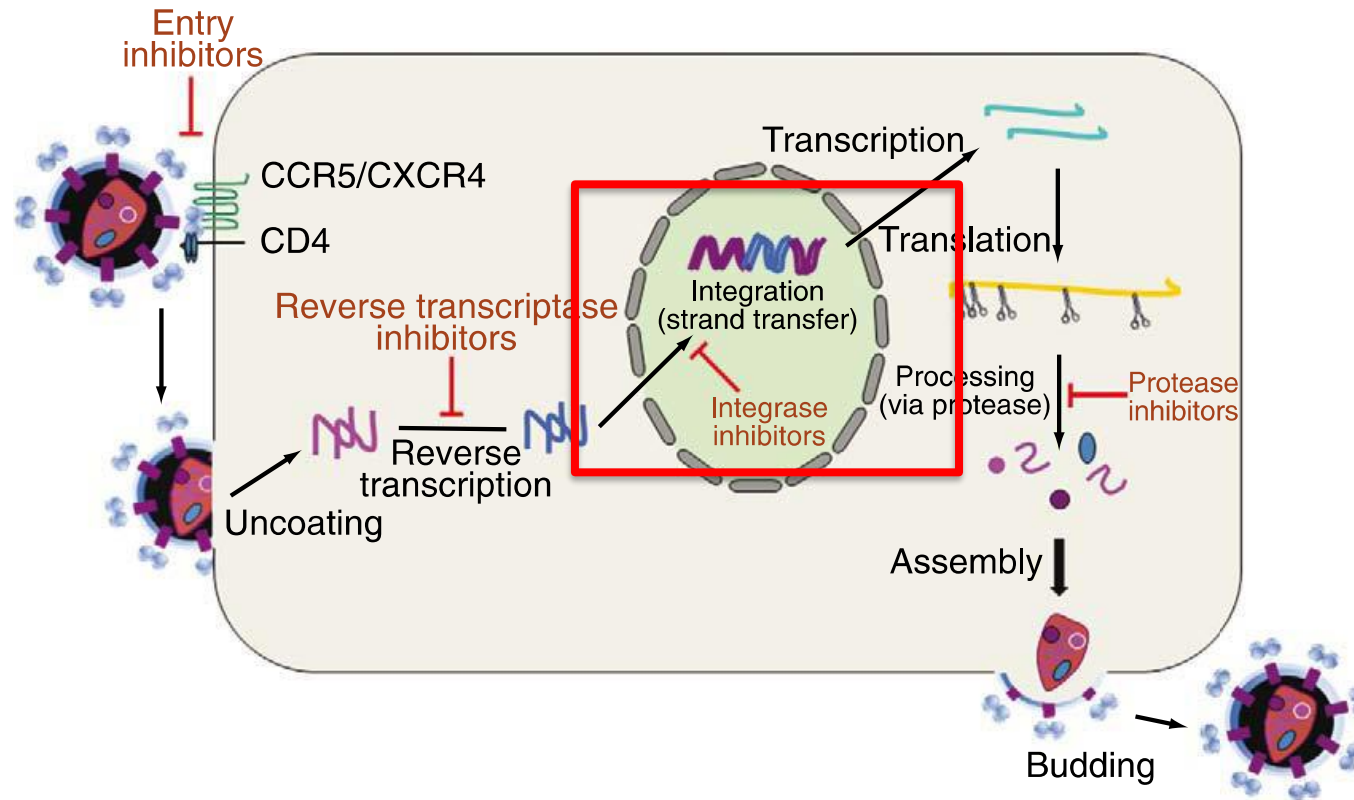
Which statins are contraindicated with protease inhibitors?

Steroids and HAART

- Dexamethasone: avoid NNRTIs or PIs
 - Can decrease ART levels
- Prednisone
 - All PIs can increase prednisone concentrations
 - Use with caution and monitor
- Inhaled or intranasal steroid and PIs/Cobi:
 - Bypass first pass metabolism

Option	Glucocorticoid
Do not use	Budesonide, fluticasone, mometasone: Up to a 350-fold ↑ in AUC
Caution	Flunisolide (monitor)
Safest	Beclomethasone

Integrase Inhibitors (INSTIs)



Integrase Inhibitor	Brand Name	Approval Date
Raltegravir	Isentress	2007
Elvitegravir	-	2015
Dolutegravir	Tivicay	2013
Cabotegravir	Vocabria	2021
Elvitegravir/cobicistat/FTC/TDF	Stribild	2012
Elvitegravir/cobicistat/FTC/TAF	Genvoya	2015
Dolutegravir/3TC/ABC	Triumeq	2014
Dolutegravir/Rilpivirine	Juluca	2017
Bictegravir/TAF/FTC	Biktarvy	2018
Dolutegravir/3TC	Dovato	2019
Cabotegravir/RPV	Cabenuva	2021

Pharmacokinetics of INSTI

	Raltegravir	Elvitegravir	Dolutegravir	Bictegravir	Cabotegravir
Absorption	Inter-patient variability	Improved with acidic environment	Not affected by food	Not affected by food	Slightly increased by food
Administration	With or without food	With food	With or without food	With or without food	With food
Distribution	83% protein bound	98% protein bound	99% protein bound	99% protein bound	99% protein bound
Metabolism	UGT1A1	Substrate CYP 3A4 (major), UGT1A1, UGT1A3 Always administer with booster (RTV or COBI)	CYP3A4 (minor), P-gp, UGT1A1, UGT1A3, UGT1A9	Substrate CYP 3A and UGT1A1	UGT1A1, UGT1A9 (minor)
Elimination	51% feces, 32% urine	95% feces	53% feces, 31% urine	60% feces, 35% urine	60% feces, 27% urine
Half-life	8-9 hours	9 hours	14 hours	17 hours	41 hours

Raltegravir



- Isentress, RAL
 - 400 mg BID
 - 800mg BID with rifampin
- 1200mg Daily (HD)
- Formulations
 - 400 mg tablet
 - 600mg tablet (HD)
 - 100mg chewable tablet
 - 20mg/mL suspension
- Adverse reactions
 - Fatigue
 - Nausea
 - Insomnia, headache
 - Elevations to ALT/AST
 - Increases in CK

Elvitegravir

- EVG
- Formulations
 - Stribild 150/150/200/300 (EVG/COBI/FTC/TDF)
 - Genvoya 150/150/200/10 (EVG/COBI/FTC/TAF)
- Adverse Reactions
 - Nausea
 - Diarrhea
 - LFT elevation
 - Increased SCr (COBI)
- Stribild:
 - CrCl > 70 ml/min: initiation
 - CrCl < 50 ml/min on treatment: discontinue



Dolutegravir (Tivicay)

- Tivicay, DTG
- Tx-naïve or Tx-experienced, INSTI-naïve
 - 50 mg daily
- INSTI-experienced or w/ potent CYP 3A4 inducer,
 - 50 mg BID
- Formulation
 - Tivicay 50 mg tablet
 - Triumeq 50/600/300 mg DTG/ABC/3TC
 - Juluca 50/25 mg DTG/RPV
 - Dovato 50/300 mg DTG/3TC

- Adverse Reactions
 - Diarrhea
 - Nausea, vomiting
 - Elevated transaminases
 - SCr elevation: 0.1 mg/dL



Bictegravir



- BIC
 - Only available in combination
 - TAF/FTC/BIC, Biktarvy
 - Tx-naïve or Tx-experienced (including the M184V)
 - BIC/LEN, Bixlenvo
 - Tx-Experienced only
- Tx-naïve or Tx-experienced, (no mutations)
 - 25/200/50 mg daily
- Substrate of CYP3A AND UGT1A1
 - Not many problems with inhibitors
 - Problems with inducers! (Rifampin/Carbamazepine etc...)
- Adverse Reactions
 - Diarrhea
 - Nausea, vomiting
 - Fatigue
 - SCr elevation: 0.1 mg/dL
 - Possible increases in bilirubin (1-1.5xULN)

Cabotegravir

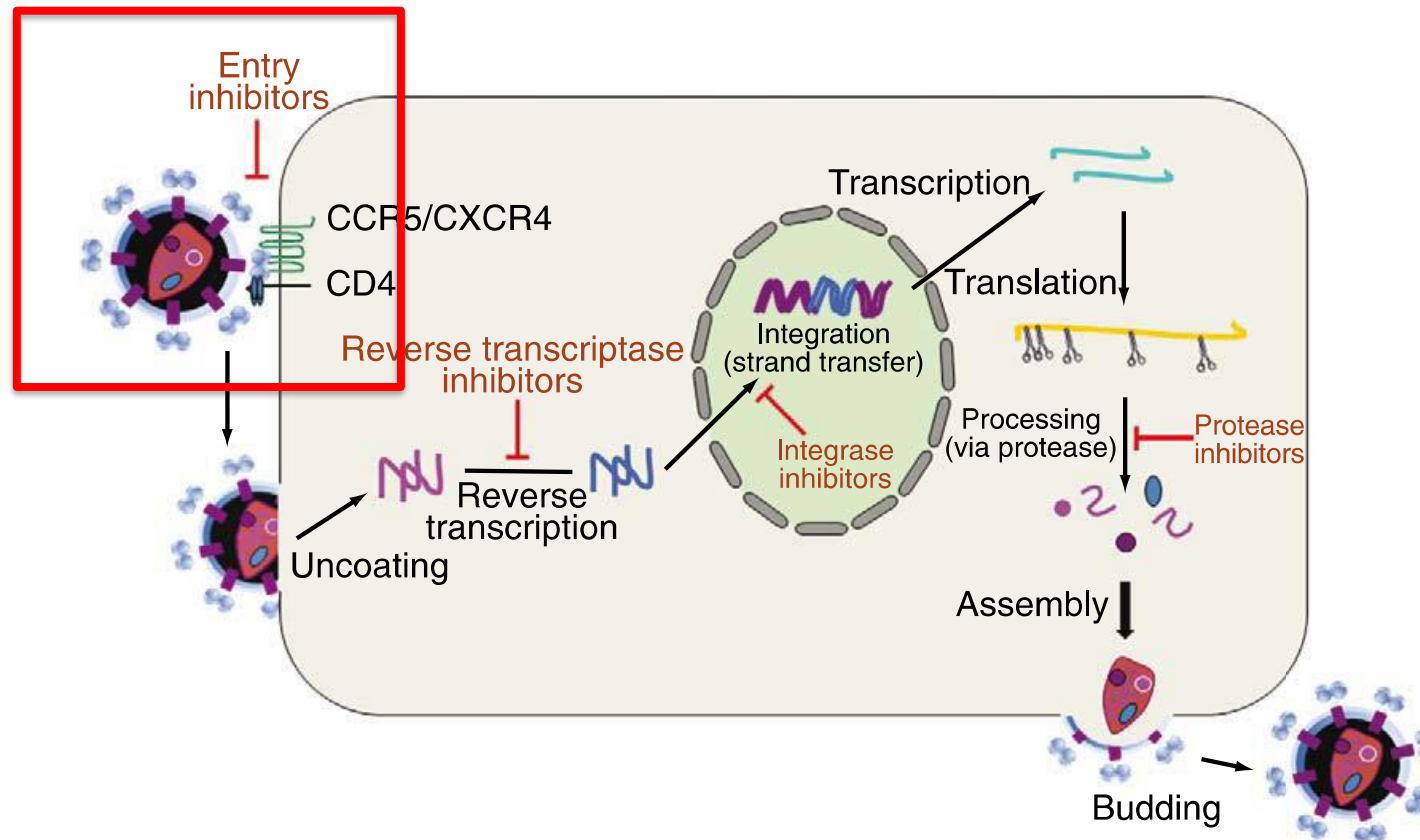
- Vocabria, CAB – 30 mg daily
- CAB/RPV – Cabenuva
 - 600/900 Loading dose (2-3mL injections)
 - 400/600 Maintenance dose monthly (2-2mL injections)
 - 600/900 dose every 2 months!
 - First two injections are spaced one month apart with bimonthly dosing thereafter
- Interesting DDI profile
 - Avoids problems with acid suppression absorption
 - Problems with inducers! (Rifampin/Carbamazepine etc...)
- Adverse Reactions
 - Injection site reactions
 - Pyrexia
 - Fatigue
 - Headache
 - Musculoskeletal pain
 - Possible increases of AST/ALT and/or CPK

Missing injections?

Doses can be administered within a 7 day pre/post window

- Planned interruptions
 - Give oral therapy until the next injection
- Unplanned interruptions for monthly dosing
 - ≤ 2 months: resume 400/600mg dosing
 - ≥ 2 months: re-load with 600/900mg dose
- Unplanned interruptions for bimonthly dosing
 - **Injection 2:**
 - < 2 months: resume regular dosing
 - > 2 months: re-load with 2 monthly shots
 - **All injections thereafter**
 - < 3 months: resume regular dosing
 - > 3 months: re-load with 2 monthly shots

Inhibitors of viral entry



Entry Inhibitor	Brand Name	Approval Date
Enfuvirtide	Fuzeon	2003
Maraviroc	Selzentry	2006
Ibalizumab	Trogarzo	2018
Fostemsavir	Rukobia	2020

Maraviroc (CCR5 Antagonist)

- Lone Rx with human receptor
- Requires Trofile Co-receptor Tropism Assay
- 300mg BID (alternative dosing with inducers/inhibitors) Adverse reactions
 - Fever
 - Rash
 - Abdominal pain
 - Dizziness, orthostatic hypotension
 - Arthralgias, myalgias
 - Elevated transaminases

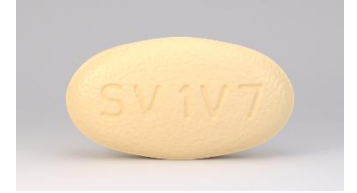


Ibalizumab (Post-Attachment Inhibitor)

- Tx experienced only in combination with other medications
- Degraded by internalization of bound receptors
- 2 gram initial dose followed by 800mg every 2 weeks
- Intravenous Infusion or push
 - Headache
 - Rash



Fostemsavir



- Rukobia, FTR
- HIV attachment inhibitor
- Tx-experienced, MDR virus only in conjunction with other ART
 - 600mg BID
 - Cannot be crushed/split/halved
- Rapidly metabolized to active component which is THEN a CYP3A4 substrate
- Cannot be given with CYP Inducers (eg. Carbamazepine, rifampin etc.)
- Adverse Reactions
 - Nausea
 - Diarrhea
 - Headache

Capsid Inhibitor	Brand Name	Approval Date
Lenacapavir	Sunlenca	2022

Lenacapavir

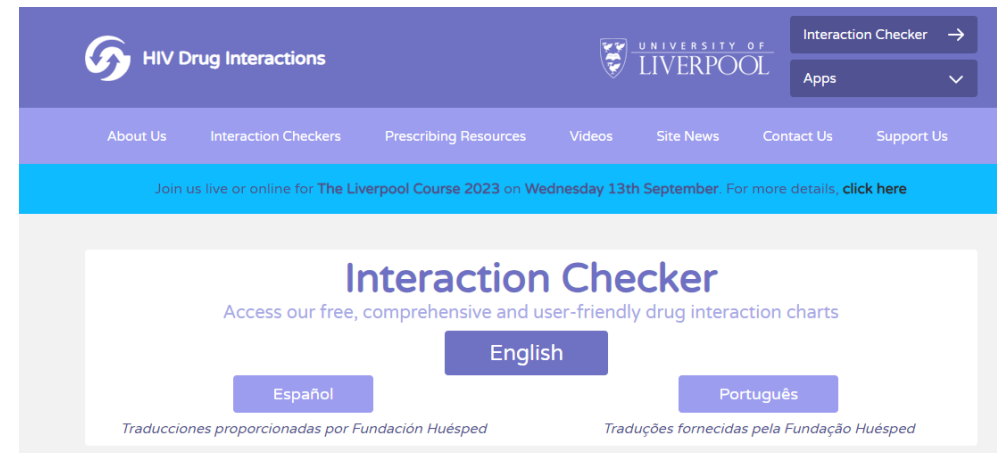
- Sunlenca, LEN
- HIV capsid inhibitor
 - Multiple action sites
- Tx-experienced, MDR virus only in conjunction with other ART
 - Induction: 927mg SC on day 1, 600mg orally on days 1 and 2
 - Maintenance 927mg every 26 weeks
- Cannot be given with CYP Inducers (eg. Carbamazepine, rifampin etc...)
- May moderately increase concentrations of other CYP medications!
- Adverse Reactions
 - Injection site reactions
 - Nausea

Resistance to ART

Part 1: Which? When?

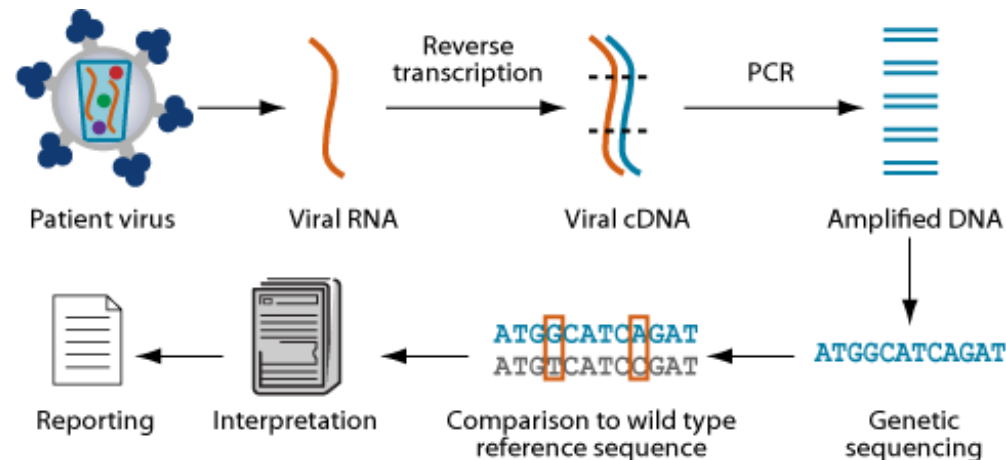
Pre-testing questioning

- Adherence assessments
 - Barriers to procurement
- Pharmacokinetic treatment issues
 - Absorptive (e.g., PPI and Rilpivirine, di-/poly-valent cations with INSTIs)
 - Metabolic (CYP450 inductive)



Genotype assay

- Patient viral RNA is converted to DNA by reverse transcription, amplified, sequenced, and compared to wild-type reference sequence
- Prediction of drug susceptibility made based on differences in sequences
- Requires plasma viral load of at least 500copies/mL (though may vary depending on lab)



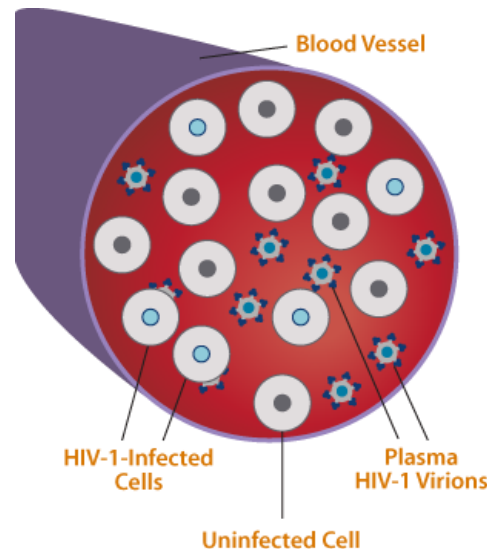
Phenotype Assay

- Performed by exposing sample of individual's HIV to known/available ARVs
- Measures ability of virus to grow in different concentrations of ARVs
- Can determine which ARVs will be individually susceptible / resistant as well as a replication capacity determination

	DRUG		PHENOSENSE® SUSCEPTIBILITY				Evidence of Susceptibility		NET ASSESSMENT	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing	Drug Susceptibility	Decreasing	Pheno Sense	Gene Seq	
PI	Atazanavir	Reyataz	(2.2)	11				N	N	Resistant 1
		Reyataz / r*	(5.2)	11				N	N	Resistant 1
	Darunavir	Prezista / r*	(10 - 90)	5.89				Y	N	Sensitive
	Fosamprenavir	Lexiva / r*	(4 - 11)	14				N	N	Resistant
	Indinavir	Crixivan / r*	(10)	2.20				Y	N	Resistant 1
	Lopinavir	Kaletra	(9 - 55)	7.43				Y	N	Sensitive
	Nelfinavir	Viracept	(3.6)	4.77				N	N	Resistant 1
	Ritonavir	Norvir	(2.5)	15				N	N	Resistant 1
	Saquinavir	Invirase / r*	(2.3 - 12)	1.77				Y	N	Resistant 1
	Tipranavir	Aptivus / r*	(2 - 8)	1.56				Y	N	Sensitive
	PI Mutations		L10F, V32I, L33F, M36M/L, M46M/L, I62I/V, L63C/S/T, A71V, I84V							

Proviral DNA “Archive”

- Provides information across classes when standard testing cannot be performed due to insufficient viral load
- Amplification of HIV-1 DNA from infected cells in whole blood, however limited information based on sample size



But when?

- At baseline
- Confirmed virologic **failure**
 - Undetectable is defined as <200copies/mL
 - Sufficient viral load persistently present (not “blip”)
 - While patient is taking
- Suboptimal viral load reduction

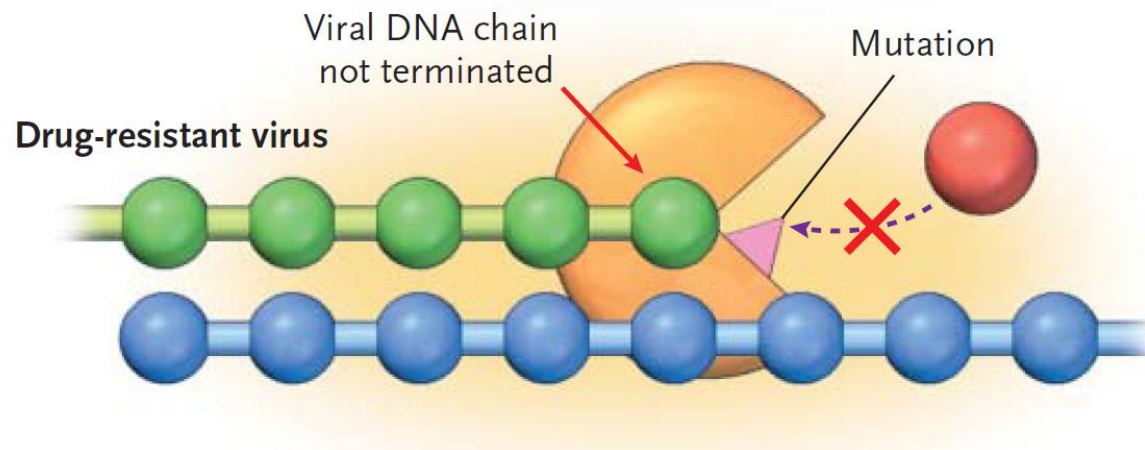
Also, which?

- Genotypic testing is generally preferred
 - Genotypic information is always additive!
- Phenotypic testing recommended in a patient with known or suspected complex drug-resistance mutation patterns
- Archive testing useful in unique circumstances when other testing may prove insufficient
 - e.g., suppressed patient without records

Part 2: Mechanisms and outcomes of resistance

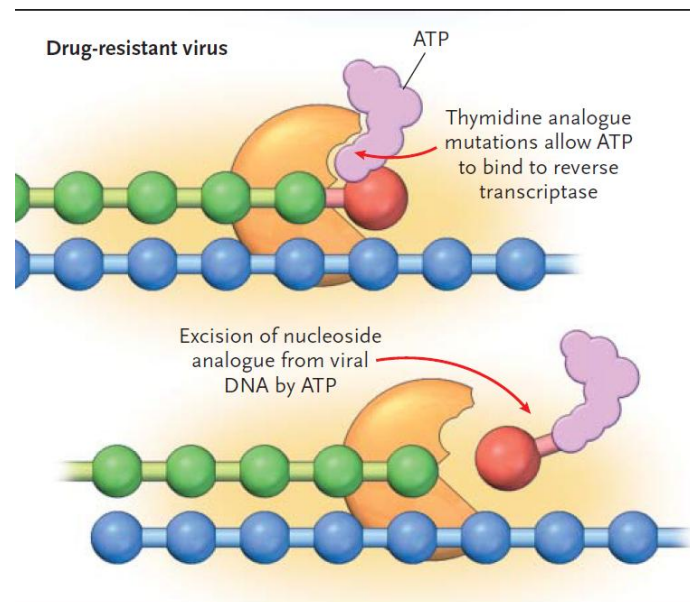
NRTI Mechanisms of Resistance

- Genetic barrier to resistance
 - Varies based on agent
- Impaired incorporation of NRTI into DNA
 - **M184V**, K65R, Q151M complex
 - Mutations change the binding site on the RT



NRTI Mechanisms of Resistance

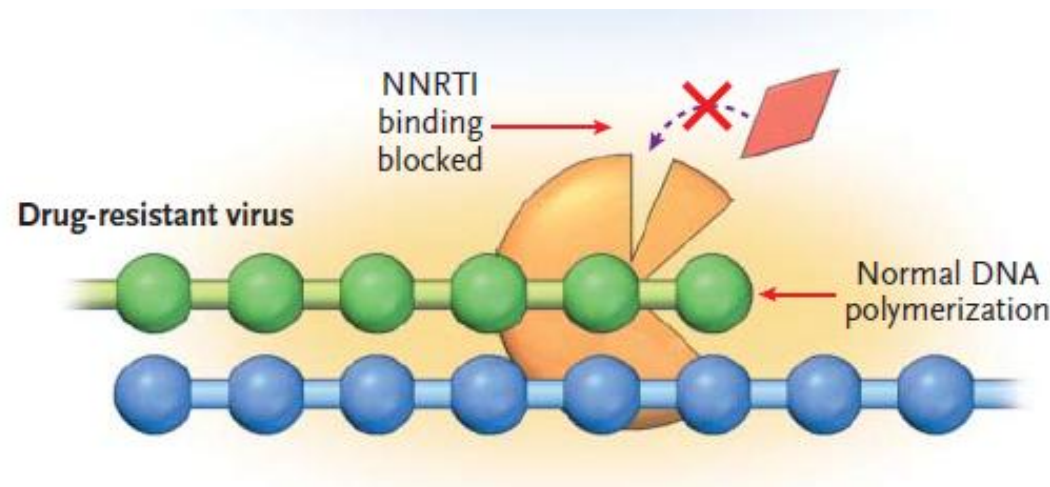
- Removal of the NRTI from the prematurely terminated DNA chain
 - Thymidine analogue mutations (TAMs)
 - “Primer rescue”
 - Decreased in the presence of M184V



Clavel F and Hance AJ. NEJM 2004 DOI:10.1056/NEJMra025195

NNRTI Mechanism of Resistance

- Mutations in the NNRTI-binding pocket
- Low barrier to resistance
- Single point mutations can confer cross-resistance among class
 - Examples: K103N, Y181C/I/V, E138K



Protease inhibitor resistance

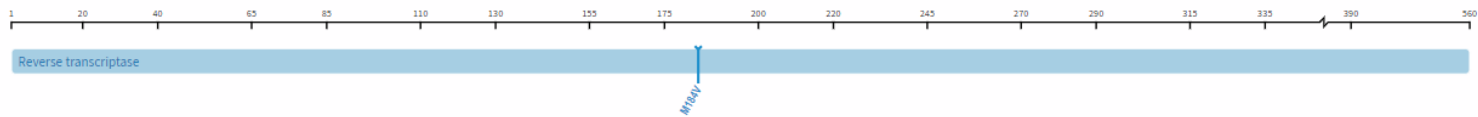
- Higher genetic barrier to resistance
- Require multiple mutations to substantially lose antiviral activity
 - Except: Saquinavir and nelfinavir
- Major (primary) mutations limit effectiveness
- Minor (secondary) mutations can improve viral fitness and may precede the emergence of a major mutation!

INSTI Resistance

- Point mutations in integrase enzyme
- Can confer cross resistance

Dolutegravir ^{bb}					F 121 Y	E 138 A K	G 140 S A		Q 148 H	
Elvitegravir ^{cc}	T 66 I A K	E 92 Q G	T 97 A	F 121 Y				S 147 G	Q 148 R H K	N 155 H
Raltegravir ^{dd}		L 74 M	E 92 Q	T 97 A	F 121 Y	E 138 A K	G 140 S	Y 143 R H C	Q 148 H K R	N 155 H

Mixed properties of mutations



There are no known mutation quality issues.

Drug resistance interpretation: RT HIVDB 9.4.1 (2023-06-11)

NRTI Mutations: **M184V**
NNRTI Mutations: None
RT Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors		Non-nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	Low-Level Resistance	doravirine (DOR)	Susceptible
zidovudine (AZT)	Susceptible	efavirenz (EFV)	Susceptible
emtricitabine (FTC)	High-Level Resistance	etravirine (ETR)	Susceptible
lamivudine (3TC)	High-Level Resistance	nevirapine (NVP)	Susceptible
tenofovir (TDF)	Susceptible	rilpivirine (RPV)	Susceptible

RT comments

NRTI

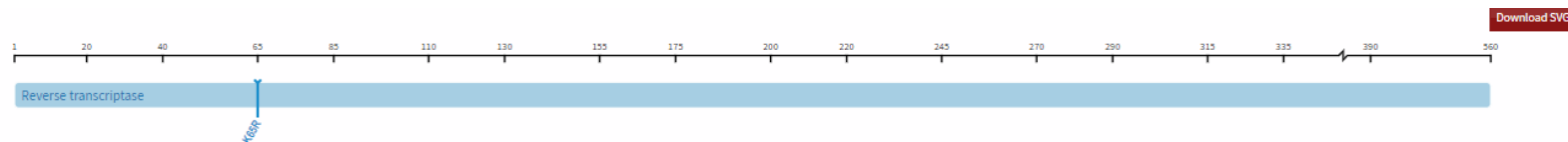
- M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.

Mutation scoring: RT HIVDB 9.4.1 (2023-06-11)

Drug resistance mutation scores of NRTI: Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
M184V	15	-10	60	60	-10

Mixed properties of mutations



There are no known mutation quality issues.

Drug resistance interpretation: RT

HIVDB 9.4.1 (2023-06-11)

NRTI Mutations: **K65R**
 NNRTI Mutations: None
 RT Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	Intermediate Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Intermediate Resistance
lamivudine (3TC)	Intermediate Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT comments

NRTI

- **K65R** confers intermediate reductions in susceptibility to TDF, ABC, and 3TC/FTC. It increases AZT susceptibility. In NRTI-experienced, INSTI-naïve patients with **K65R**, TDF+3TC+DTG is usually highly effective and more effective than AZT/3TC/DTG. However, in patients receiving TDF+3TC+DTG, there is a risk of emergent DTG resistance that does not arise in NRTI-naïve patients receiving TDF+3TC+DTG.

Mutation scoring: RT

HIVDB 9.4.1 (2023-06-11)

Drug resistance mutation scores of NRTI:

Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
K65R	45	-10	30	30	50

Mixed properties of mutations

Drug resistance interpretation: RT

HIVDB 9.4.1 (2023-06-11)

NRTI Mutations: **K65R** • **M184V**
 NNRTI Mutations: None
 RT Other Mutations: None

Nucleoside Reverse Transcriptase Inhibitors	
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	High-Level Resistance
lamivudine (3TC)	High-Level Resistance
tenofovir (TDF)	Intermediate Resistance

Non-nucleoside Reverse Transcriptase Inhibitors	
doravirine (DOR)	Susceptible
efavirenz (EFV)	Susceptible
etravirine (ETR)	Susceptible
nevirapine (NVP)	Susceptible
rilpivirine (RPV)	Susceptible

RT comments

NRTI

- **K65R** confers intermediate reductions in susceptibility to TDF, ABC, and 3TC/FTC. It increases AZT susceptibility. In NRTI-experienced, INSTI-naïve patients with **K65R**, TDF+3TC+DTG is usually highly effective and more effective than AZT/3TC/DTG. However, in patients receiving TDF+3TC+DTG, there is a risk of emergent DTG resistance that does not arise in NRTI-naïve patients receiving TDF+3TC+DTG.
- **M184V/I** cause high-level in vitro resistance to 3TC and FTC and low/intermediate resistance to ABC (3-fold reduced susceptibility). **M184V/I** are not contraindications to continued treatment with 3TC or FTC because they increase susceptibility to AZT and TDF and are associated with clinically significant reductions in HIV-1 replication.

Mutation scoring: RT

HIVDB 9.4.1 (2023-06-11)

Drug resistance mutation scores of NRTI:

Copy to clipboard

Rule	ABC	AZT	FTC	3TC	TDF
K65R	45	-10	30	30	50
M184V	15	-10	60	60	-10
Total	60	-20	90	90	40

Part 3: Constructing a regimen: How? With what?

Management of ART Failure: beyond the 2nd line

Susceptible to DTG and PI

- DTG + 2 NRTIs
- Boosted PI + 2 NRTIs
- Boosted PI + Active INSTI

Susceptible to PI only

- Boosted PI + 2 NRTIs
- If boosted PI not used, 2 (preferably 3) active drugs

Susceptible to DTG only

- DTG + 2 NRTIs
- If DTG not used, 2 (preferably 3) active drugs

Susceptible to neither

- 2 (preferably 3) active drugs

The role of the cytosine analogues: 3TC and FTC

- Low genetic barrier (development of M184V mutation)
- May still play role in HTE regimen development to reduce viral fitness
 - These agents should not be considered active if the M184V is present!
- Presence of M184V will delay the appearance of Thymidine analogue mutations

Other NRTIs and NNRTIs

- Tenofovir alafenamide (TAF)
 - Limited in-vitro data suggests *partial* activity of TAF in TAM expressing virus; may be considered where treatment options are heavily limited
- Etravirine (ETR)
 - High genetic barrier to resistance with more than one mutation required for failure
 - ETR resistance scoring system summarized known mutations; A combined score of 3 or 4 denotes significantly decreased efficacy
- Doravirine (DOR)
 - Retains activity among patients with common NNRTI mutations (K103N, Y181C, G190A)
 - Improved drug-drug interaction profile over ETR

Protease Inhibitors

- Darunavir (DRV)
 - Proves a cornerstone of HTE patient regimens
 - Twice daily dosing among viruses expressing a DRV-associated mutation
 - Higher binding affinity to active site than earlier agents within the class

Integrase inhibitors

- Dolutegravir (DTG)
 - Additional cornerstone of HTE patient regimens
 - Twice daily dosing among viruses expressing an INSTI-based mutation OR in patients with concurrent CYP450 inductive medications

Part 4: “Recently approved” antiretrovirals

Inhibitors of Viral Entry

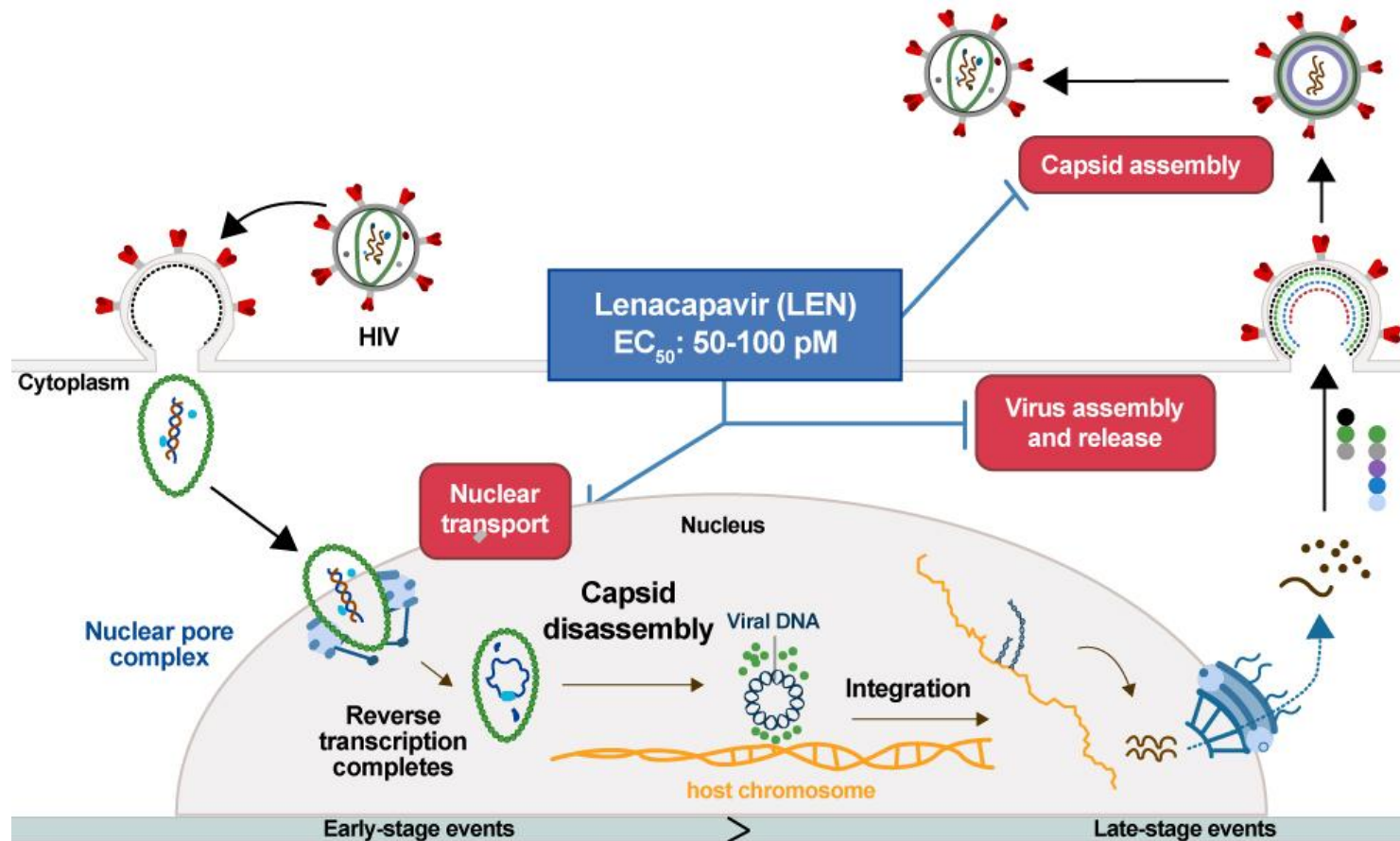
Ibalizumab

- HIV Post-attachment inhibitor binding to domain 2 of the CD4 cell
- Q2week infusion
- Minimal Drug-Drug Interactions – degraded by internalization of bound receptors
- Trial of note: TMB-301
- US FDA approved - 2018

Fostemsavir

- HIV attachment inhibitor binding to GP120, thereby preventing an open confirmation
- 600mg ER tablet BID
- CYP450 substrate
- Trial of note: BRIGHT
- US FDA approved 2020

Capsid Inhibitor - Lenacapavir



Part 5: Clinician resources

IAS-USA resistance listings

Special Contribution

2022 Update of the Drug Resistance Mutations in HIV-1

Annemarie M. Wensing, MD, PhD; Vincent Calvez, MD, PhD; Francesca Ceccherini-Silberstein, PhD; Charlotte Charpentier, PharmD, PhD; Huldrych F. Günthard, MD; Roger Paredes, MD, PhD; Robert W. Shafer, MD; Douglas D. Richman, MD

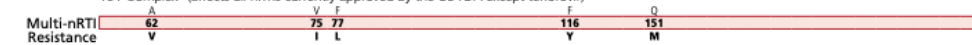
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)¹

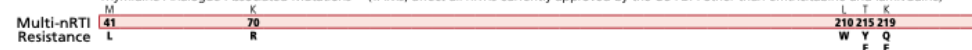
69 Insertion Complex² (affects all nRTIs currently approved by the US FDA)



151 Complex³ (affects all nRTIs currently approved by the US FDA except tenofovir)



Thymidine Analogue-Associated Mutations^{4,5} (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)



Complete reference

- Full listings of all known resistant mutations to all agents
- Comments available per ARV to assist in interpretation
- Will not reflect additive / mixed effects of mutations

- <https://www.iasusa.org/resources/hiv-drug-resistance-mutations/>

HIV Drug Resistance database

- Comprehensive resource of resistance mutations
- Proprietary algorithm of individual mutation effects
 - Predicts combined effects for comprehensive analysis
- Able to receive input from multiple genotypes

hivdb.stanford.edu

Stanford University
HIV DRUG RESISTANCE DATABASE
A curated public database to represent, store and analyze HIV drug resistance data.

Reverse Transcriptase
Enter/paste mutations

Protease
Enter/paste mutations

Integrase
Enter/paste mutations

40 41 44 62
65 67 69 69
70 74 75 77
90 98 100 101
103 106 108 115
116 118 118 151
119 181 184 188
130 210 215 219
221 225 227 230
234 236 238 318
348

10 11 13 20
22 24 30 32
33 35 36 43
46 47 48 50
53 54 58 63
71 73 74 76
77 82 83 84
85 88 89 90
93

51 66 74 92
95 97 114 118
121 128 138 140
143 145 146 147
148 149 151 153
155 157 163 230
232 263

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- Case consultation service
- Submit cases electronically or by phone
- May reflect US-based practice / medication availability which may not be available locally!

nccc.ucsf.edu

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- New drugs and diagnostic techniques
- Drug interactions and toxicity
- Adherence
- Co-infection management
- Initiating HIV care
- Primary care of persons with AIDS
- Pediatric HIV care

Related Information

How are we responding to the COVID-19 pandemic?

The NCCC is pleased to support ongoing efforts to prevent, prepare for, and respond to COVID-19 as it relates to HIV, hepatitis prevention and treatment.

CLINICIAN SUPPORT

In the U.S., nearly **1.2 MILLION** people have **HIV**,
and **1 in 5** don't know it.



Questions?

Thank You For Your Time!