



HIV Drug Resistance

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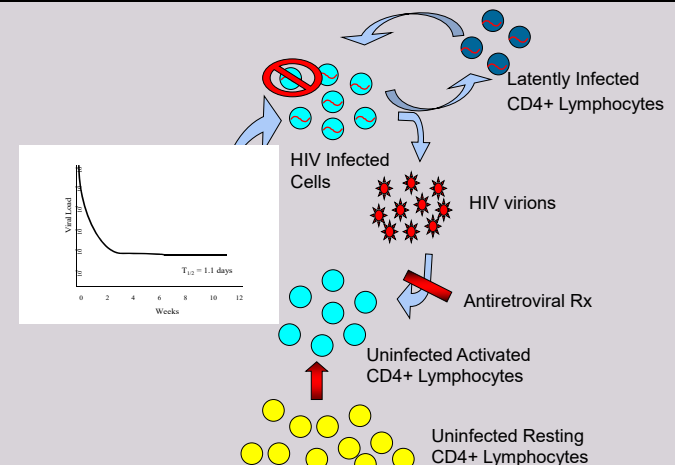
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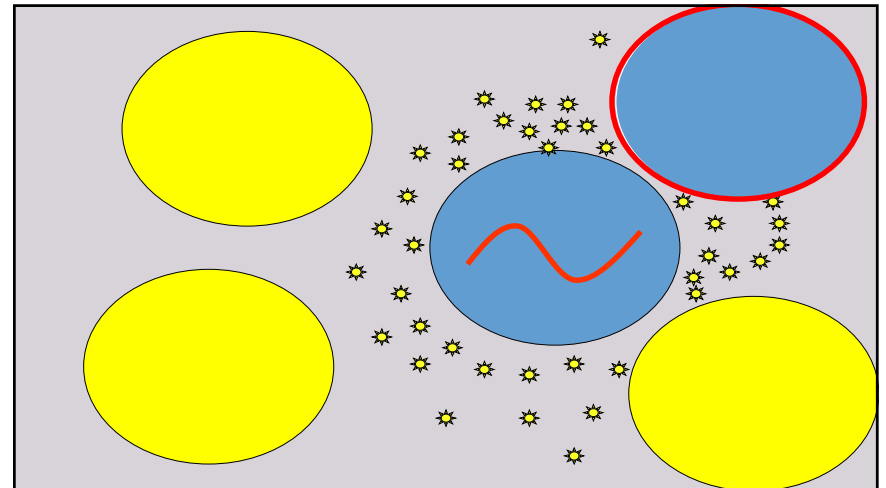
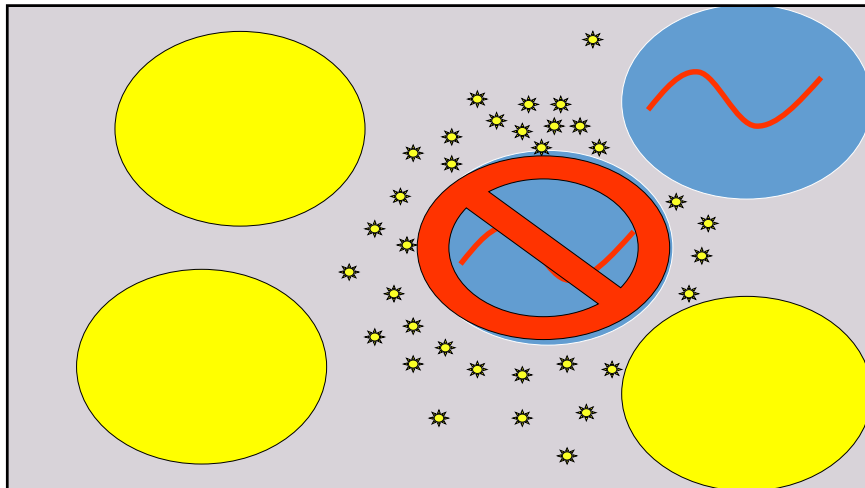
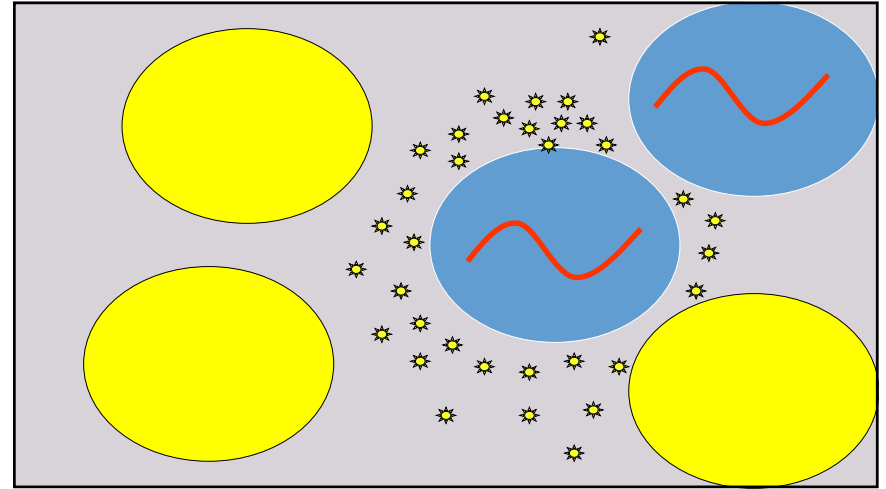
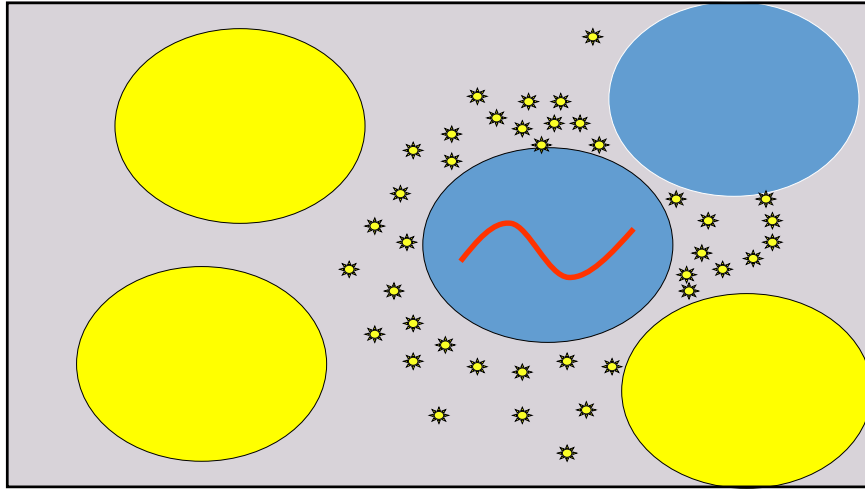


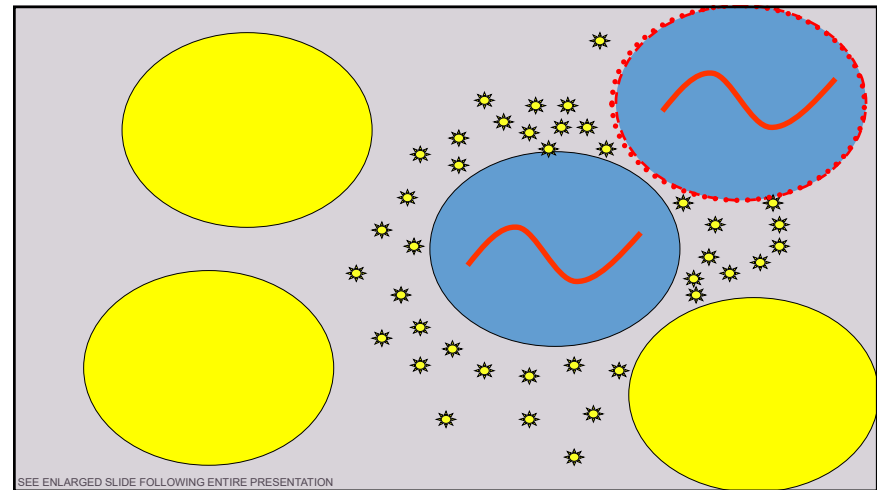
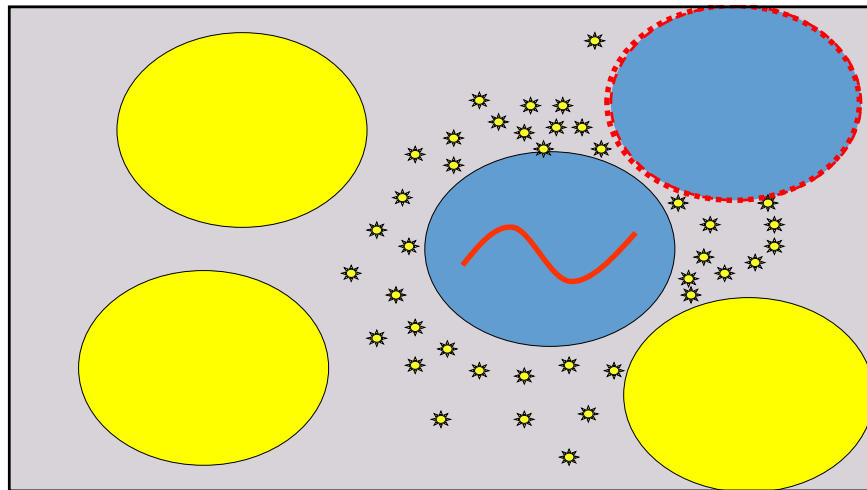
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

How Does Resistance Happen?







Resistance Testing

- Genotypic resistance test
 - Perform test that gives mutations in viral genes
- Phenotypic resistance test
 - Perform test that describes growth of virus in the presence of anti-HIV drugs
- Limitations:
 - Cannot detect minority species (< 10% of viral population)

Key Issues in HIV Resistance

Easily Tested

- Specific Mutations
- Cross – resistance
- Prevalence of resistance at baseline
- Role of archived DNA HIV virions

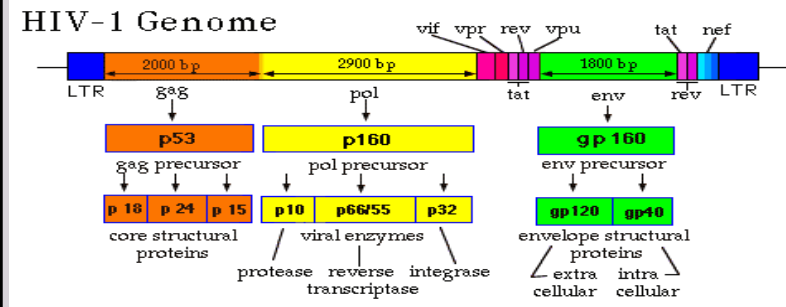
Tough to Test

- Definition of Phenotypes
- Complex resistance patterns
- Genetic Barrier
- Nuances of Resistance
- Relationship between Pk and Pd

HIV Drug Resistance Testing

- [HIV genotype](#) as part of screening BEFORE ART is started AND
- Following failure of 1st or 2nd regimens
- Following failure of 3rd and subsequent regimens, both [HIV genotype](#) AND [HIV phenotype](#) should be sent.
- If there is discordance between genotype and phenotype results, use the genotype result (more sensitive).
- NOTE WELL: Resistance mutations accrued from an earlier regimen MAY NOT be detected by tests obtained at the time of the current failing regimen

HIV-1 Genome



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Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

Mutation Nomenclature

Codon (position)
PR = 1-99 amino acids
RT = 1-560 amino acids

M184V

Wild-type
amino acid
(consensus)

Mutant
amino acid

Table 1. Amino acids and their abbreviations.

Alanine	A
Cysteine	C
Aspartate	D
Glutamate	E
Phenylalanine	F
Glycine	G
Histidine	H
Isoleucine	I
Lysine	K
Leucine	L
Methionine	M
Asparagine	N
Proline	P
Glutamine	Q
Arginine	R
Serine	S
Threonine	T
Valine	V
Tryptophan	W
Tyrosine	Y

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Everything You Need to Know About Nucleoside Analog Resistance in One Slide!

Mutation	Selected By	Effects on Other NRTIs
M184V	3TC, FTC	- Loss of susceptibility to 3TC, FTC - ↓ susceptibility to ABC, ddI (clinically insignificant) - Delayed TAMS and ↑ susceptibility to AZT, d4T, TDF
TAMs	AZT, d4T	- ↓ susceptibility to all NRTIs based on number of TAMs - More resistance with 41/210/215 than 67/70/219 pathway
451M, 69ins	AZT/ddI, ddI/d4T	- Resistance to all NRTIs - T69ins: TDF resistance
K65R	TDF, ABC, ddI	- Variable ↓ susceptibility to TDF, ABC, ddI (and 3TC, FTC) - ↑ susceptibility to AZT
74V	ABC, ddI	- ↓ susceptibility to ABC, ddI - ↑ susceptibility to AZT, TDF
44D, 118I	AZT, d4T	- Increase NRTI resistance (with 41/210/215 pathway)

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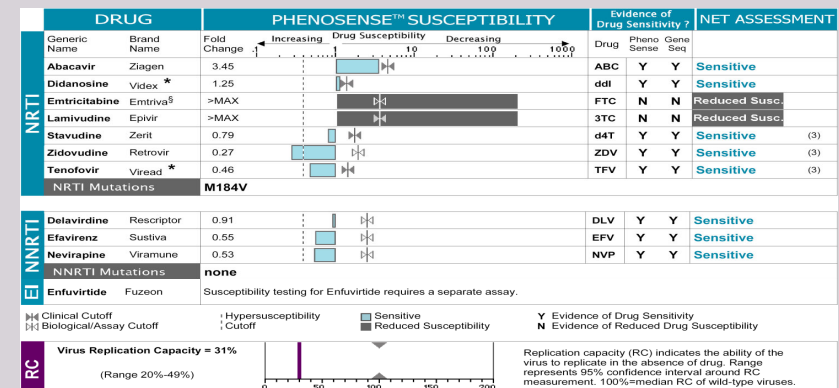
Question #1

- 25-year-old man presents with newly diagnosed HIV
- Had an episode c/w acute seroconversion syndrome 4 months ago
- Initial HIV RNA 40,000; CD4 443 cells/uI
- He wants to start ARV therapy
- A baseline genotype is ordered that shows an M184V mutation

Question #1

Which of the following drugs will have reduced susceptibility with this mutation?

- Efavirenz
- Zidovudine
- Tenofovir
- Etravirine
- Emtricitabine



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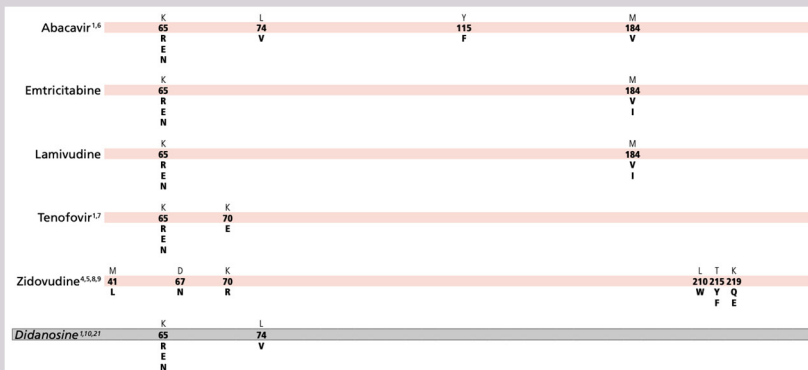
Question #2

- 34-year-old woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

Question #2

The genotype shows an a K65R mutation.
Which RTI drugs would you include?

- A. ZDV
- B. TDF
- C. ddl
- D. ABC
- E. Islatravir



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	DRUG	SUSCEPTIBILITY			Evidence of Susceptibility		Net Assessment
		Cutoffs (Lower - Upper)	Fold Change	Increasing Drug Susceptibility	Pheno	Gene	
NRTI	Abacavir	(4.5 - 6.5)	1.79		Y	Y	Sensitive
	Didanosine	(1.3 - 2.2)	1.54		P	N	Partially Sensitive
	Emtricitabine	(3.5)	4.97		N	N	Resistant
	Lamivudine	(3.5)	5.73		N	N	Resistant
	Stavudine	(1.7)	0.85		Y	Y	Sensitive
	Zidovudine	(1.9)	0.40		Y	Y	Sensitive
	Tenofovir	(1.4 - 4)	1.74		P	N	Partially Sensitive 2
NRTI Mutations							
K65R							
W Lower Clinical Cutoff (in bold) H Upper Clinical Cutoff (in bold) I Biological Cutoff Y Evidence of Drug Sensitivity P Evidence of Partial Drug Sensitivity N Evidence of Drug Resistance Y Evidence of Drug Sensitivity P Evidence of Partial Drug Sensitivity N Evidence of Drug Resistance Y Evidence of Drug Sensitivity P Evidence of Partial Drug Sensitivity N Evidence of Drug Resistance							

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- **K103N** is the signature mutation for **efavirenz** (EFV)
- **Y181C** is the signature mutation for **nevirapine** (NVP)
- Older NNRTIs, efavirenz and nevirapine, have **low genetic barriers** (require only 1 mutation for resistance) and are **COMPLETELY** cross-resistant to one another
- Newer NNRTIs, etravirine (ETR), rilpivirine (RPV), and doravirine (DOR) have higher barriers to resistance (require >1 mutation for resistance)
- **K103N** has no effect on etravirine susceptibility
- **Rilpivirine** failure is associated with **E138K**, **K101E**, and/or **Y181C** and consequently, resistance to ALL NNRTIs

- 34-year-old woman diagnosed with HIV 10 years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- Started on TDF / FTC / EFV (FDC)
- Did well for a while, then the regimen failed

A. Q148R
B. L68I
C. L68V
D. K67N
E. K65R

Drug	Genotype	118	138	140	148	153	155	263
Bictegravir ²⁶	G	E	G	O	R			
	118 R	138 K	140 S	148 H				263 K
Cabotegravir ²⁷	T	G	E	G	O	S	N	R
	66 K	118 R	138 K	140 A	148 H	153 F	155 Y	263 K
Dolutegravir ²⁸	G	F	E	G	O	N	R	
	118 R	121 Y	138 A	140 S	148 H	155 H		263 K
Elvitegravir ²⁹	T	E	T	F	S	N	R	
	66 I	92 Q	97 G	121 Y	147/148 G	155 H		263 K
Raltegravir ³⁰	L	E	T	F	E	G	Y	Q
	74 M	92 Q	97 A	121 Y	138 K	140 S	143 P	148 H

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Speaker: Michael Saag, MD

Lenacapavir Resistance Mutations

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

Lenacapavir ³¹	L	M	Q	K	N	A	T
	56	66	67	70	74	105	107
	I	I	H	N	D	T	N
				S	S		
				R			

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Question #4

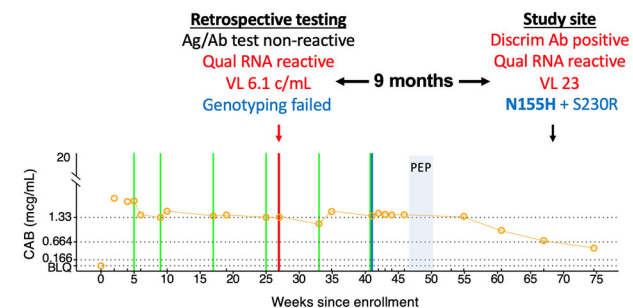
- 34-year-old MSM receiving CAB IM q 2 months for pre-exposure prophylaxis for last 6 months; hasn't missed a dose
- Asymptomatic
- HIV Ag/Ab test Positive
- HIV RNA 766 c/ml

Question #4

Which of the following ARV resistance mutations is most likely in this setting?

- S147G
- N155H
- Y143R
- E92Q
- K65R

Case Study: Confirmation of Infection



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InSTI Resistance Mutations

Bictegravir ²⁶				G		E	G		Q			R
				118	138	140			148			263
				R	K	S			H			K
Cabotegravir ²⁷	T			G		E	G		Q	S	N	R
	66			118	138	140			148	153	155	263
	K			R	A	A			H	F	H	K
					K	T			K	R		
Dolutegravir ²⁸				G	F	E	G		Q		N	R
				118	121	138	140		148		155	263
				R	Y	A	A		H		K	K
					T	K	S		K			
Elvitegravir ²⁹	T		E	T		F		S	Q		N	R
	66	92	97	A		121		147	148	155	263	K
	I	Q	G			Y		G	H	H		
	A							K	R			
Raltegravir ³⁰		L	E	T		F	E	G	Y	Q	N	R
		74	92	97		121	138	140	143	148	155	263
		M	Q	A		Y	A	A	R	H	H	K
							K	S	H	K		

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Question #5

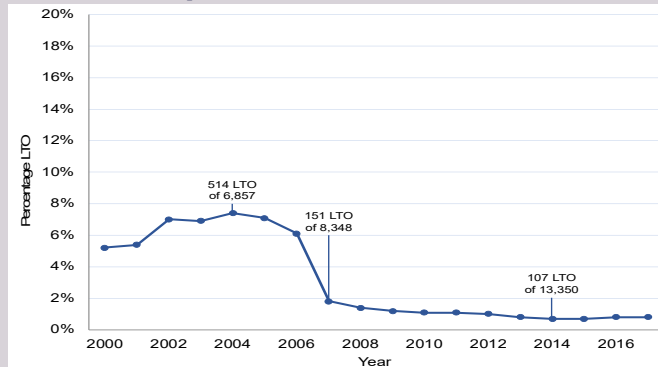
- 34-year-old woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
 - CD 482 cells/uL
 - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #5

What is the likelihood she has high level resistance (< 2 active drugs available)?

- A. < 1 %
- B. 1 - 5 %
- C. 5 -10%
- D. 10 - 20%
- E. > 20%

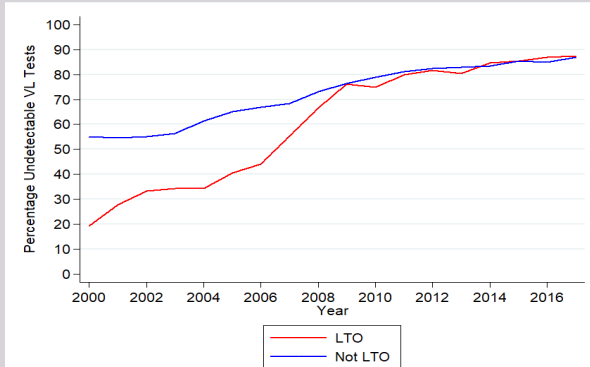
Prevalence of Patients with Limited Treatment Options



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Crane et al. IAS 2019

Virologic Success in Those with or without LTO



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Crane et al. IAS 2019

Common Mutations To Memorize

• M184V/I	3TC and FTC
• M41L, D67N, K70R, L210W, T215Y, K219Q 4 or more thymidine-analog mutations (TAMS) affect all approved nucleosides	"TAMS"
• K65R	Islatravir, Tenofovir
• K103N	EFV (and NVP)
• Y181C	NVP and other NNRTI
• E138K, K101E	RPV and other NNRTI
• I50L	ATV
• N155H, Q148H/R/K	RAL and EVG
• Y143C	RAL
• R263K	DTG

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Summary

- High concern about resistance testing on Board Exams
- Difficult to create test questions that do not require complex interpretation, have a single best answer, or are not 'multiple true-false'
- Knowing common mutations and their role is a good way to prepare for the exam

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