HIV Drug Resistance

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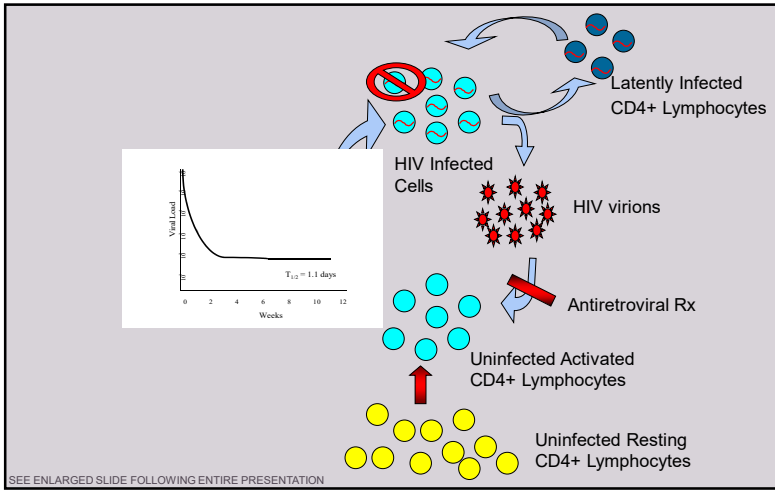
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

How Does Resistance Happen?



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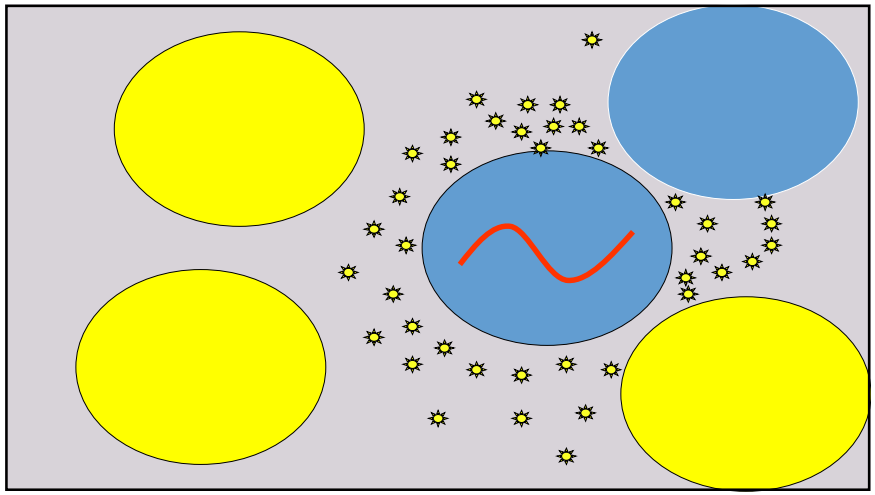
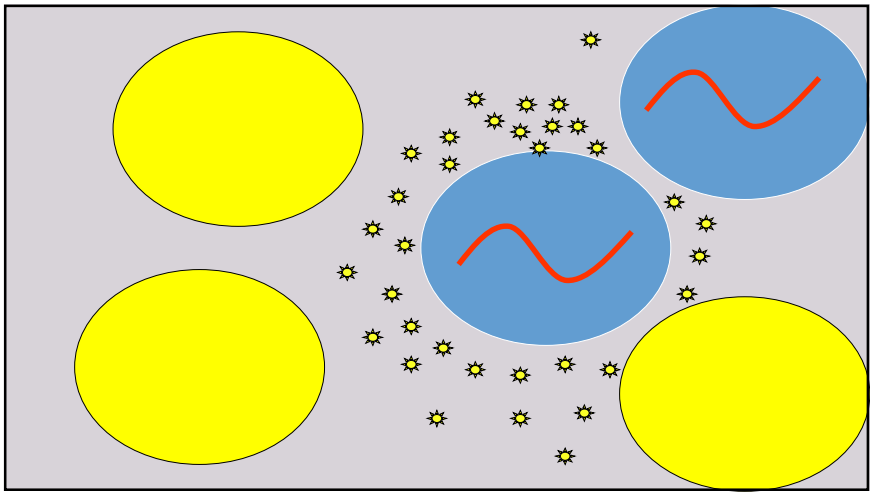
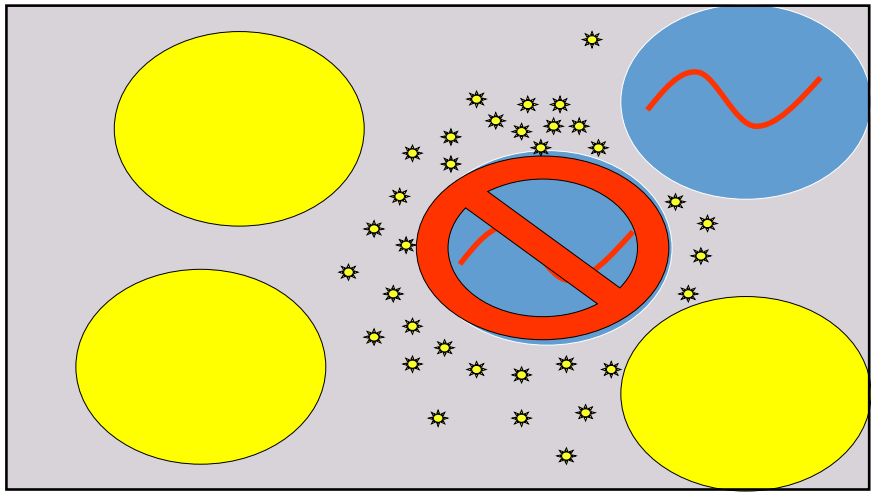
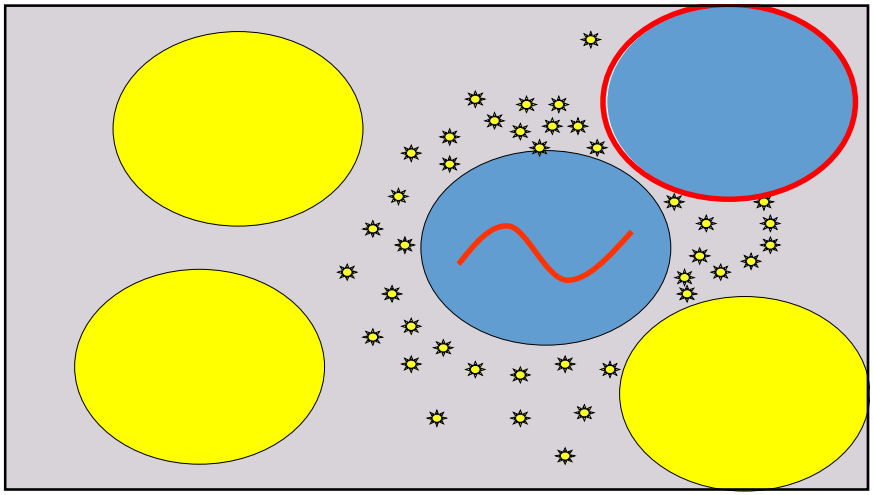


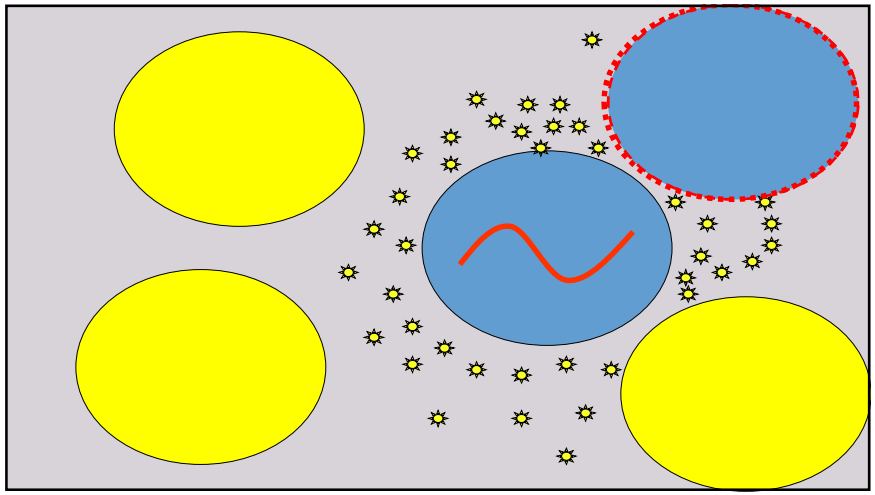


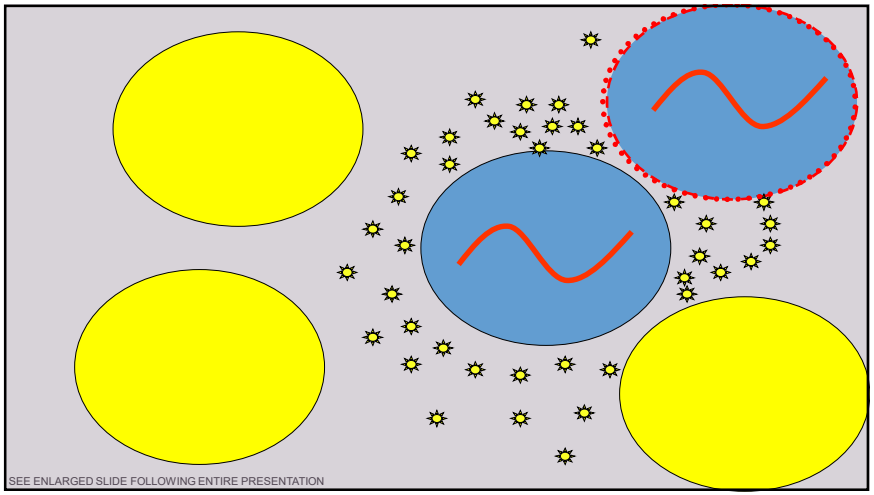




36 HIV Drug Resistance

Speaker: Michael Saag, MD





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

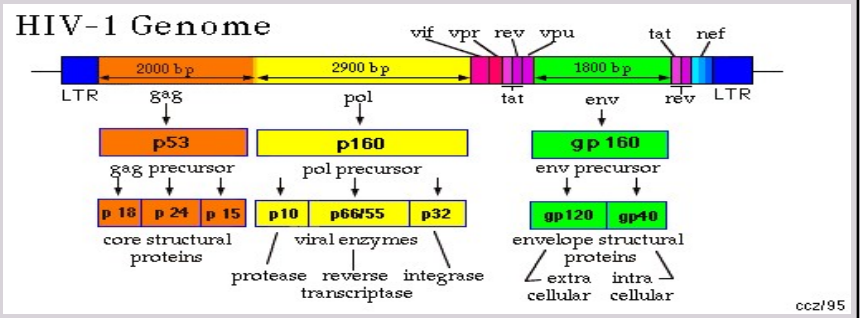
- Definition of Phenotypes
- Complex resistance patterns
- Genetic Barrier
- Nuances of Resistance
- Relationship between Pk and Pd

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

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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
Tryosine	Y

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

Mutation	Selected By	Effects on Other NRTIs
184V	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
~~151M, 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/ul
- 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?

A. Efavirenz
B. Zidovudine
C. Tenofovir
D. Etravirine
E. Emtricitabine

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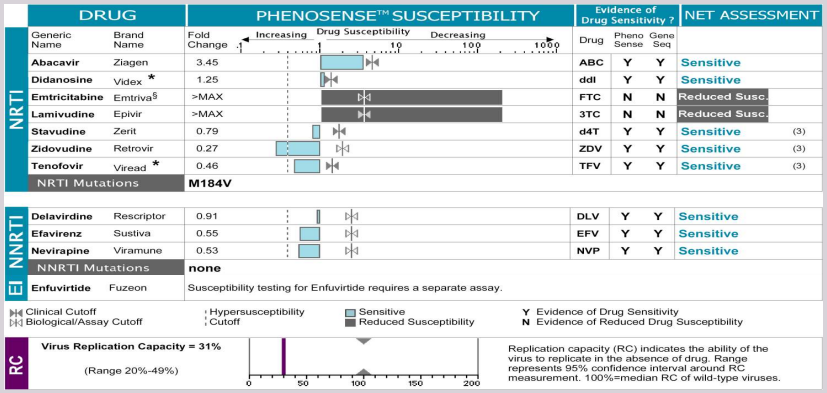

DRUG		PHENOSENSE™ SUSCEPTIBILITY	Evidence of Drug Sensitivity ?			NET ASSESSMENT	
Generic Name	Brand Name	Fold Change (Increasing / Decreasing Drug Susceptibility)	Drug	Pheno Sense	Gene Seq		
NRTI							
Abacavir	Ziagen	3.45	ABC	Y	Y	Sensitive	
Didanosine	Videx *	1.25	ddI	Y	Y	Sensitive	
Emtricitabine	Emtriva§	>MAX	FTC	N	N	Reduced Susc.	
Lamivudine	Epivir	>MAX	3TC	N	N	Reduced Susc.	
Stavudine	Zerit	0.79	d4T	Y	Y	Sensitive	(3)
Zidovudine	Retrovir	0.27	ZDV	Y	Y	Sensitive	(3)
Tenofovir	Viread *	0.46	TFV	Y	Y	Sensitive	(3)
NRTI Mutations		M184V					
NNRTI							
Delavirdine	Rescriptor	0.91	DLV	Y	Y	Sensitive	
Efavirenz	Sustiva	0.55	EFV	Y	Y	Sensitive	
Nevirapine	Viramune	0.53	NVP	Y	Y	Sensitive	
NNRTI Mutations		none					
EI							
Enfuvirtide	Fuzeon	Susceptibility testing for Enfuvirtide requires a separate assay.					

Clinical Cutoff / Biological/Assay Cutoff — Hypersusceptibility Cutoff — Sensitive / Reduced Susceptibility — Y Evidence of Drug Sensitivity / N Evidence of Reduced Drug Susceptibility

RC Virus Replication Capacity = 31% (Range 20%-49%) (0, 50, 100, 150, 200)

Replication capacity (RC) indicates the ability of the virus to replicate in the absence of drug. Range represents 95% confidence interval around RC measurement. 100%=median RC of wild-type viruses.

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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. ddI
D. ABC
E. Islatravir

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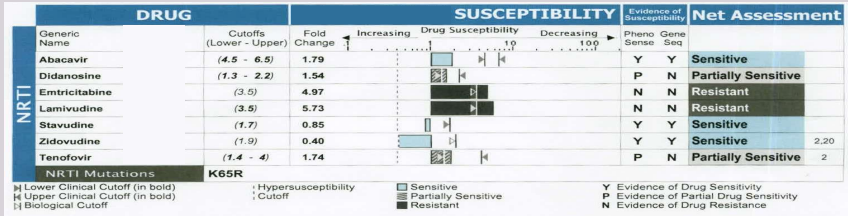

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Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

- 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

Question #3

- 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 #3

Which of the following mutations indicate high level resistance to elvitegravir?

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

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Which of the following mutations indicate high level resistance to elvitegravir?

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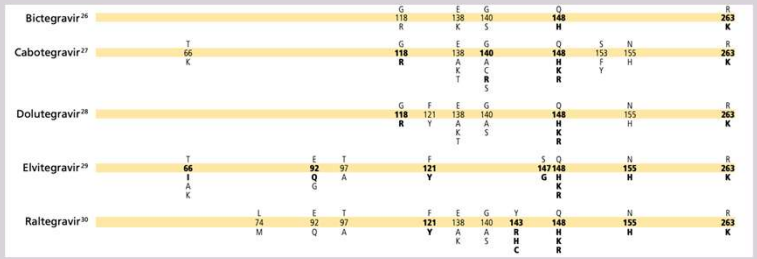
InSTI Resistance Mutations



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Lenacapavir Resistance Mutations

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

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

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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?

A. S147G
B. N155H
C. Y143R
D. E92Q
E. K65R

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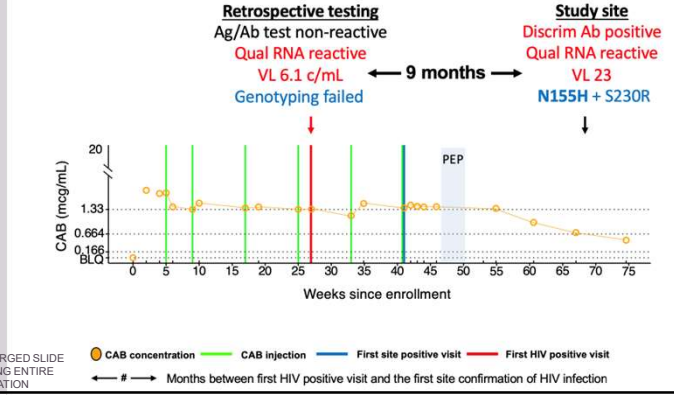
Case Study: Confirmation of Infection



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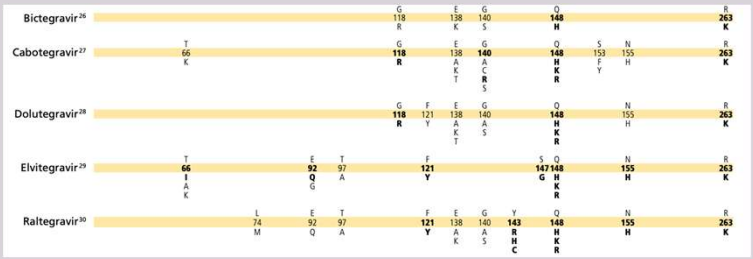

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Question #5

- 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%

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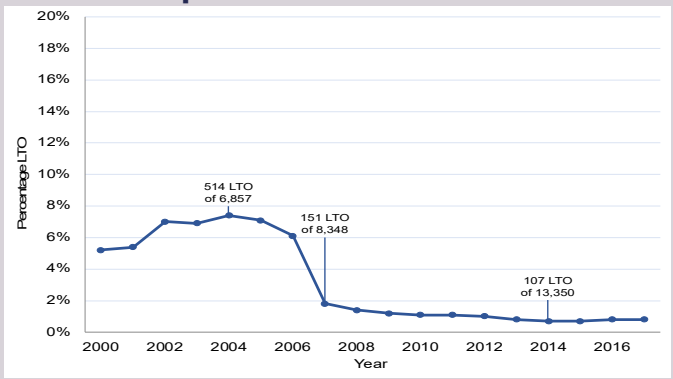
Prevalence of Patients with Limited Treatment Options



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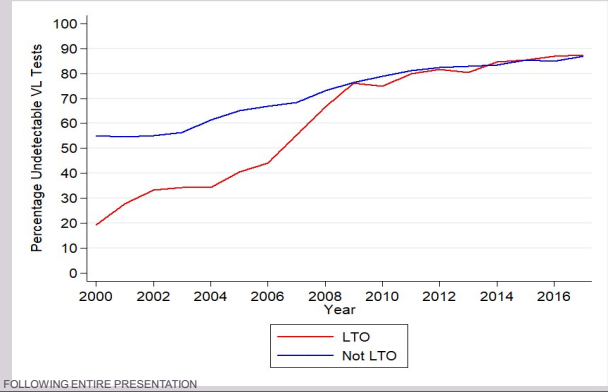
Crane et al, IAS 2019

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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