

32 – HIV Drug Resistance

Speaker: Michael Saag, MD

2020 INFECTIOUS DISEASE BOARD REVIEW

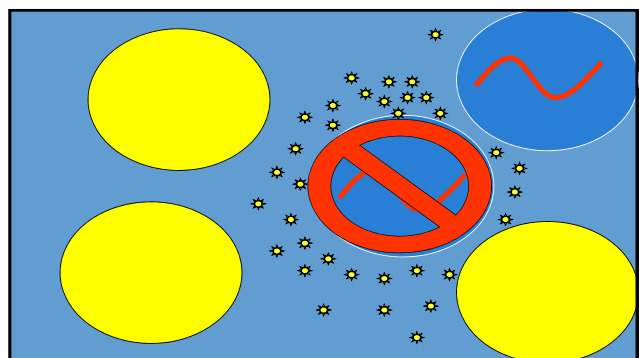
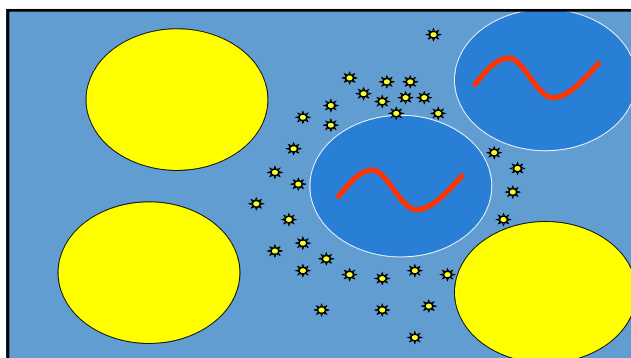
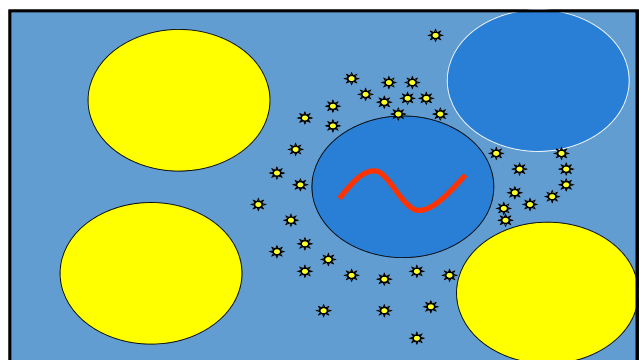
HIV Drug Resistance

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Disclosures of Financial Relationships with Relevant Commercial Interests

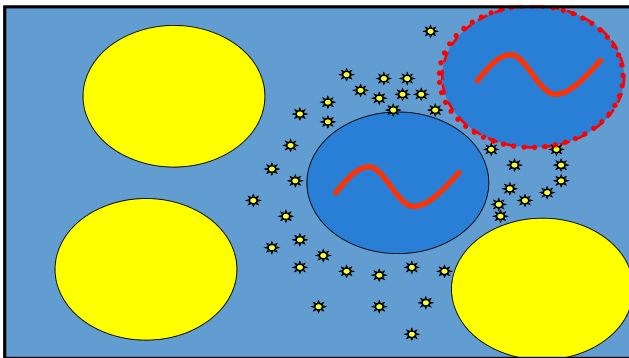
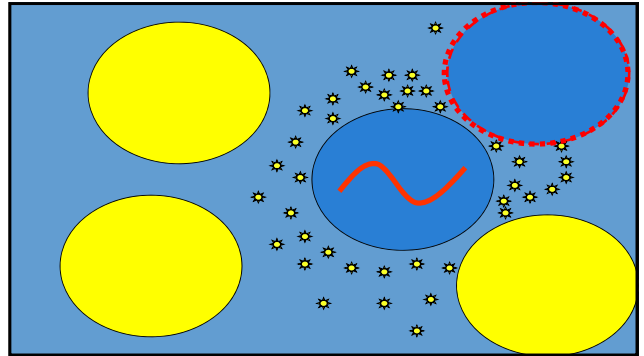
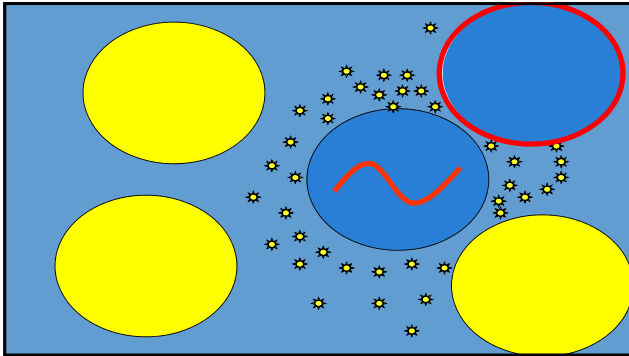
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How does resistance happen?



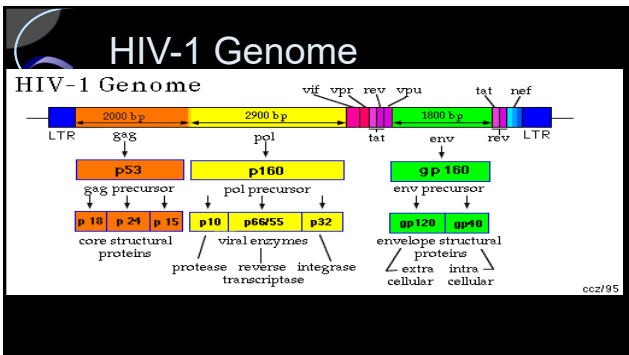
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Resistance Testing

- 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)



Mutation Nomenclature

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

M184V

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Codon (position)
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M184V

Wild-type amino acid (consensus) → M → Mutant amino acid

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

Mutations Selected by NNRTIs

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)^{1,11}

Drug	106	188	190	225	227	230	234
Doravirine ¹²	V	Y	G	P	F	M	L
	A	C	E	H	C	L	I
	I	L	H	K			
	M						
	H						
	I						
Efavirenz	L	K	K	V	V	Y	G
	188	191	193	196	198	199	225
	I	P	N	M	I	C	L
	S						S
							A
							H
Etravirine ¹³	V	A	L	E	V	E	V
	90	98	100	101	106	138	179
	I	G	I	E	I	A	D
	H					C	S
	P					G	F
						K	I
						T	V
						G	A
						D	
Nevirapine	L	K	K	V	V	Y	G
	100	101	103	106	108	181	188
	I	P	N	A	I	C	L
	S	M				I	C
							A
							L
							H
Rilpivirine ¹⁴	L	K	E	V	Y	Y	G
	100	101	138	179	181	188	221
	I	E	A	L	C	L	227
	P		G	L	C	L	230
			K	I	V		234
			K				H
			D				F
							M
							L

Key Issues in HIV Resistance

Easily Tested

- Specific Mutations
- Cross – resistance
- Prevalence of resistance at baseline

Tough to Test

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

HIV Drug Resistance Testing

- Current guidelines recommend an **HIV genotype** as part of screening BEFORE ART is started.
- Following failure of 1st or 2nd regimens, **HIV genotype** is recommended to use with the history to choose the optimal next regimen.
- 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 geno 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

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
65R	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)

CASE 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

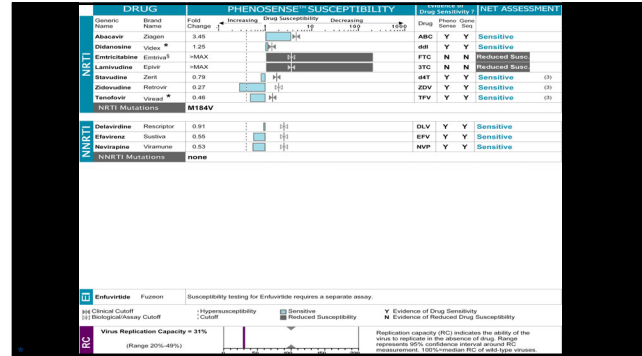
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Question #1

A baseline genotype is ordered that shows an M184V mutation. Which of the following drugs will have reduced susceptibility with this mutation?

- A. Efavirenz
- B. Zidovudine
- C. Tenofovir
- D. Etravirenz
- E. Emtricitabine



CASE 2

- 34 yo 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 M184V and K65R mutations. Which nRTI drugs would you include?

- A. ZDV
- B. TDF
- C. ddI
- D. ABC

DRUG	GENOTYPIC SUSCEPTIBILITY	NET ASSESSMENT
Abacavir	Reduced Susceptibility	Y Y Sensitive
Didanosine	Reduced Susceptibility	Y Y Sensitive
Emtricitabine	Reduced Susceptibility	Y Y Sensitive
Lamivudine	Reduced Susceptibility	Y Y Sensitive
Zidovudine	Reduced Susceptibility	Y Y Sensitive



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CASE 3

- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- A Genotype was ordered.

Question #3

- Which of the following mutations indicate high level resistance to efavirenz ?
- A. M184V
 - B. K65R
 - C. K219Q
 - D. K67N
 - E. K103N

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.

HIV Resistance – Protease inhibitors (PI)

- In general, currently used protease inhibitors require multiple mutations for resistance (i.e. have a high genetic barrier).
 - Exception: **I50L** alone confers resistance to atazanavir (ATV).
- Patients experiencing failure on a 2 NRTI + boosted PI regimen most often have **NO** PI mutations.
- With significant prior protease inhibitor use, because of multiple mutations, a phenotype is

CASE 4

- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

Question #4

- 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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InSTI Resistance Mutations

Drug	118	138	140	146	155	156	188	203
Bictegravir™	G	E	G	G				
Cabotegravir™	T	G	E	G	S	N		
Dolutegravir™								
Elvitegravir™								
Raltegravir™								

CASE 5

- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- A Tropism test was ordered.

Question #5

Which of the following results would indicate the highest likelihood of maraviroc activity in the regimen?

- Pure R5 virus
- Pure X4 virus
- Mixture of R5 and X4 viruses
- Dual Tropic (R5/X4) virus

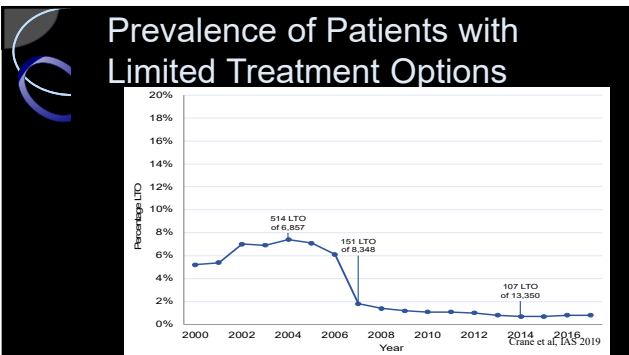
CASE 6

- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
 - CD4 82 cells/uL
 - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #6

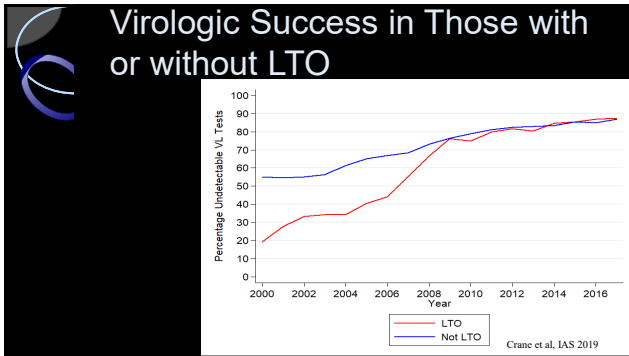
What is the likelihood she has high level resistance (< 2 active drugs available) ?

- < 1 %
- 1 - 5 %
- 5 -10%
- 10 - 20%
- > 20%



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Common Mutations To Memorize

• M184V/I	3TC and FTC
• M41L, D67N, K70R, L210W, T215Y, K219Q	"TAMS"
4 or more thymidine-analog mutations (TAMS) affect <u>all</u> approved nucleosides	
• K65R	tenofovir
• Q151M, 69SSS	multi-NRTI
• K103N	EFV (and NVP)
retains susceptibility to etravirine	
• Y181C	NVP and other NNRTI
• E138K, K101E	RPV and other NNRTI
• I50L	ATV
• N155H, Q148H/R/K	RAL and EVG
• Y143C	RAL
• R263K	DTG

- ### 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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