47 – HIV Drug Resistance

Speaker: Michael Saag, MD

INFECTIOUS DISEASE BOARD REVIEW
TWENTY TWENTY-ONE
IDBR 2021

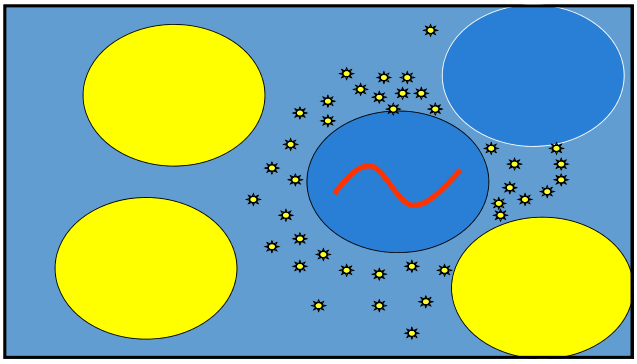
HIV Drug Resistance

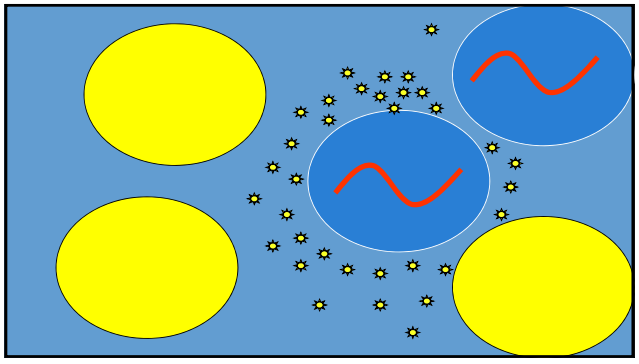
Michael S. Saag, MD
Director, Center for AIDS Research, University of Alabama at Birmingham
Professor of Medicine, Director of UAB CFAR, Jim Straley Chair in AIDS Research, University of Alabama at Birmingham

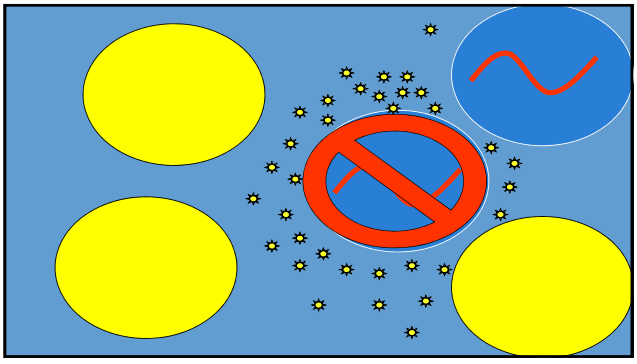
Disclosures of Financial Relationships with Relevant Commercial Interests

- None

How does resistance happen?







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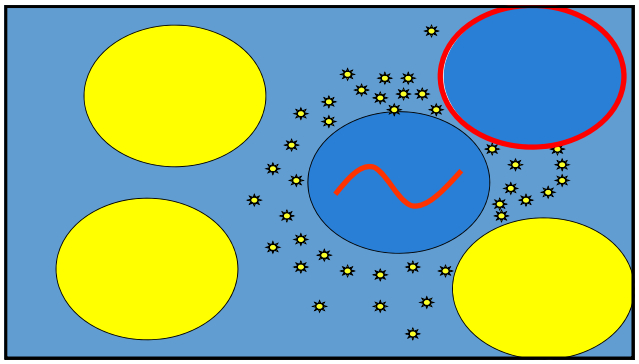
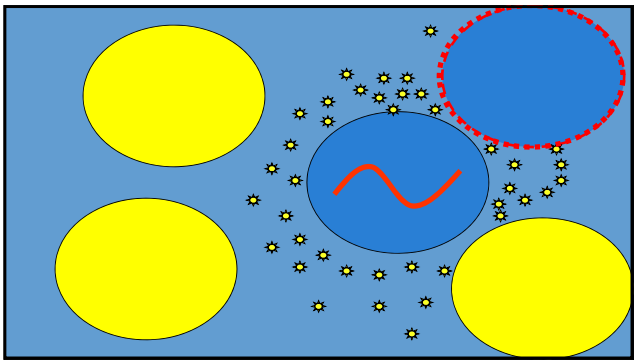
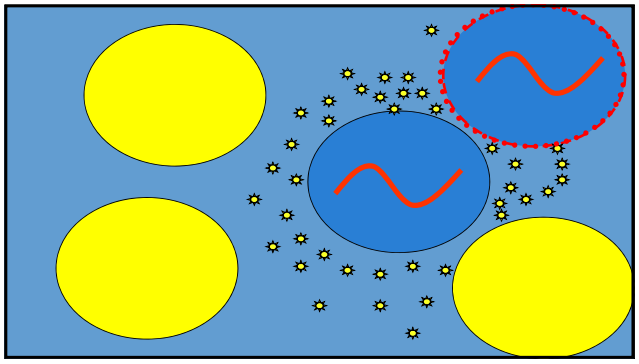


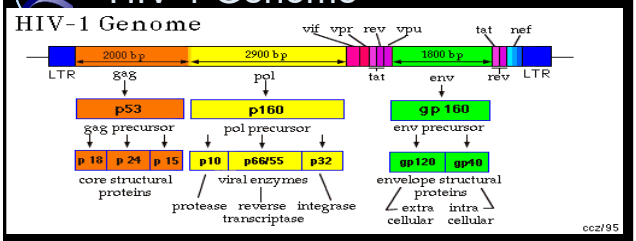




Resistance Testing

- 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)

HIV-1 Genome



Mutation Nomenclature

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

M184V

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M184V

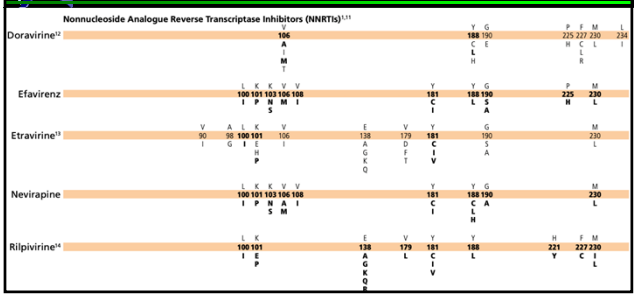
Wild-type amino acid (consensus)

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

Mutations Selected by NNRTIs



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

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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. Etravirene
E. Emtricitabine

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Answer #1

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

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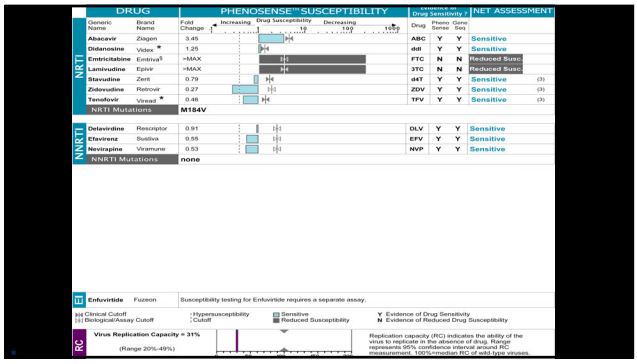


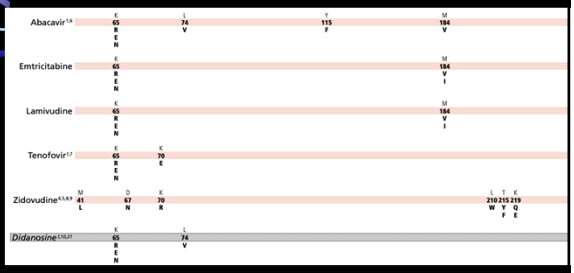
CASE 2

- 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



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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

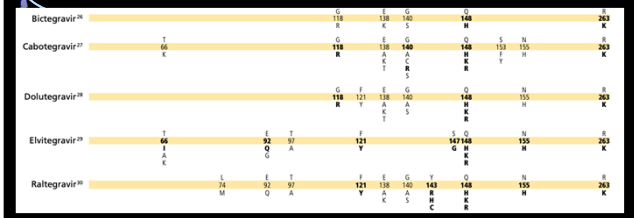
- 34 yo woman diagnosed with HIV three years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- She was treated with TDF / FTC / ELV/ Cobi (FDC)
- The regimen failed after 12 months

Question #4

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

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

InSTI Resistance Mutations



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?

A. Pure R5 virus
B. Pure X4 virus
C. Mixture of R5 and X4 viruses
D. Dual Tropic (R5/X4) virus

CASE 6

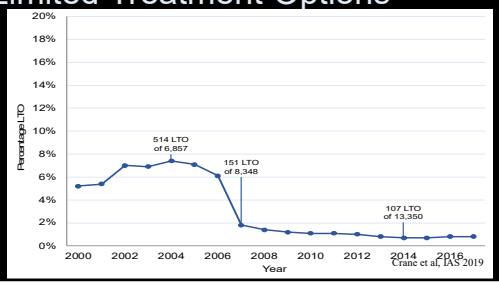
- 34 yo woman diagnosed with HIV 22 years ago
- Initially presented with PJP
- Initial Lab values
  - CD4 82 cells/uL
  - VL 106,000 c/mL
- Has been on multiple regimens over the years

Question #6

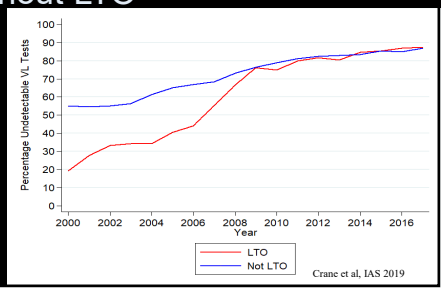
What is the likelihood she has high level resistance (< 2 active drugs available) ?

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

Prevalence of Patients with Limited Treatment Options



Virologic Success in Those with or without LTO



Common Mutations To Memorize

- M184V/I — 3TC and FTC
- M41L, D67N, K70R,L210W, T215Y, K219Q — "TAMS"
  - 4 or more thymidine-analog mutations (TAMS) affect all 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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