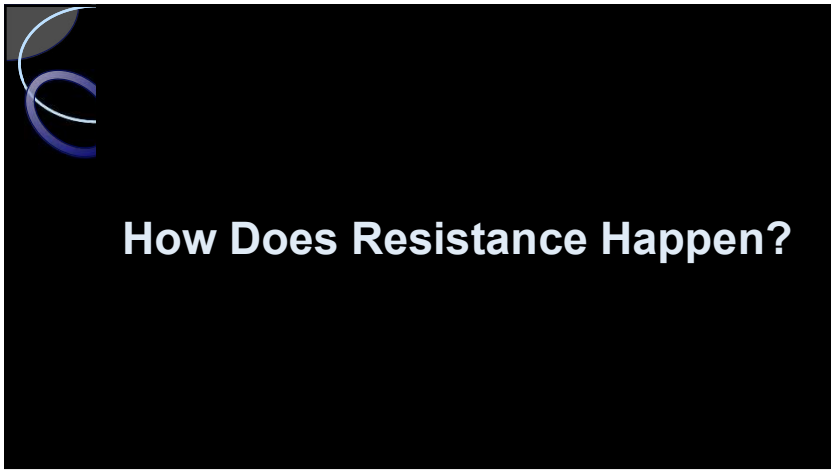
37 HIV Drug Resistance

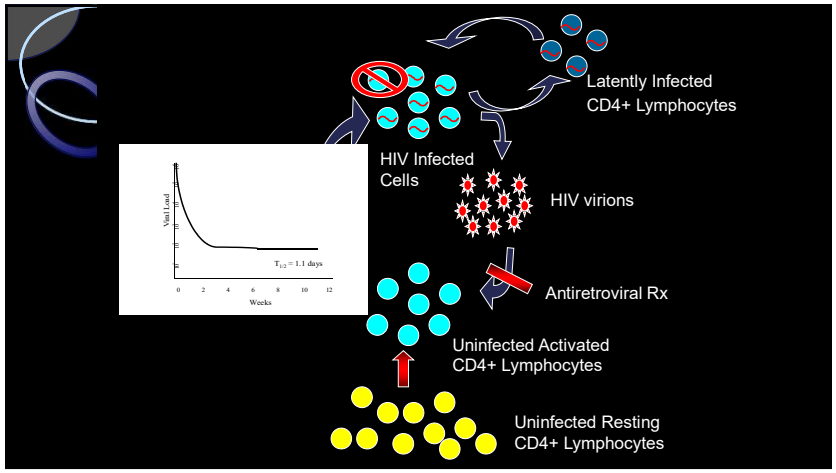
Speaker: Michael Saag, MD

1

2

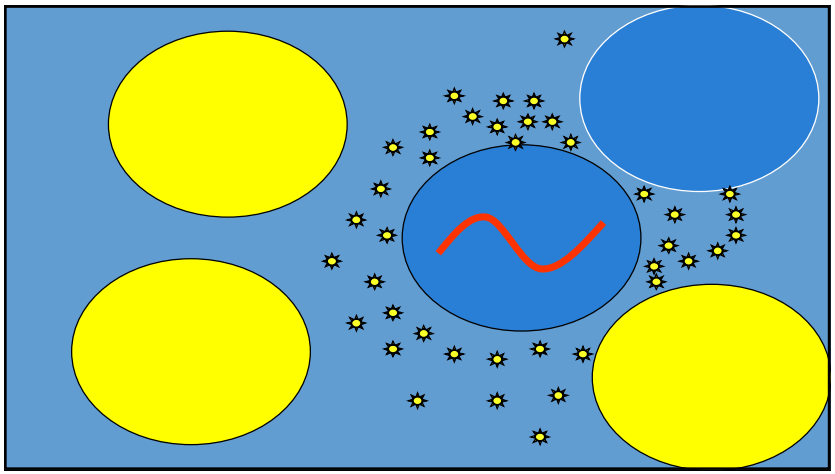


3

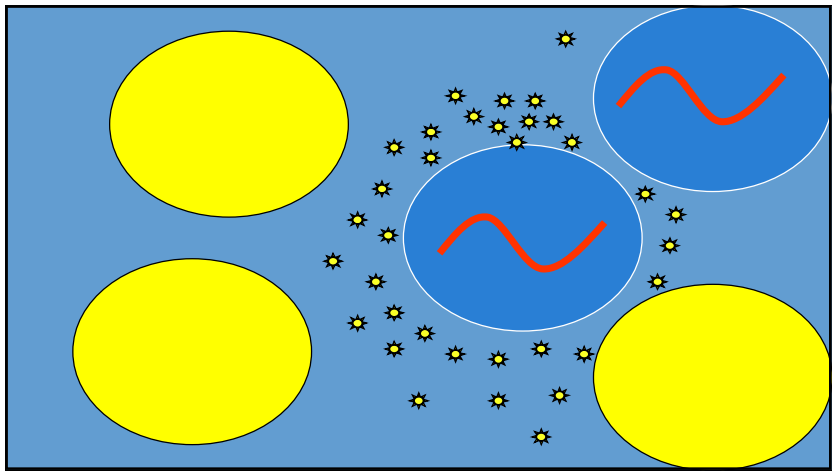


4

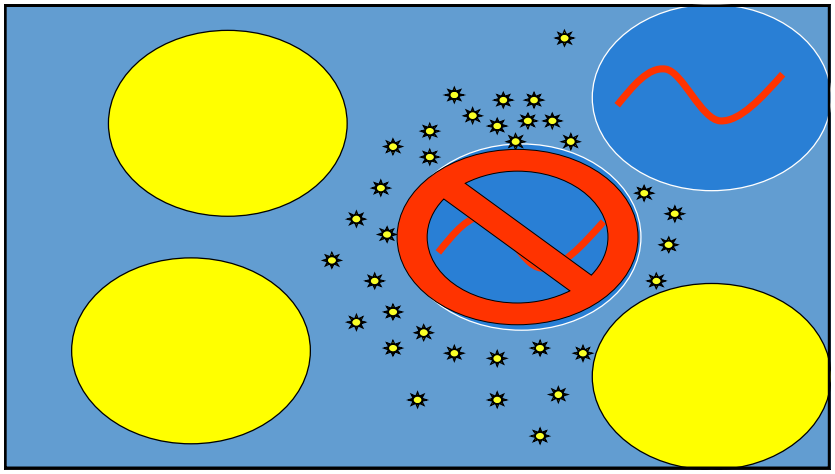
37 HIV Drug Resistance
Speaker: Michael Saag, MD



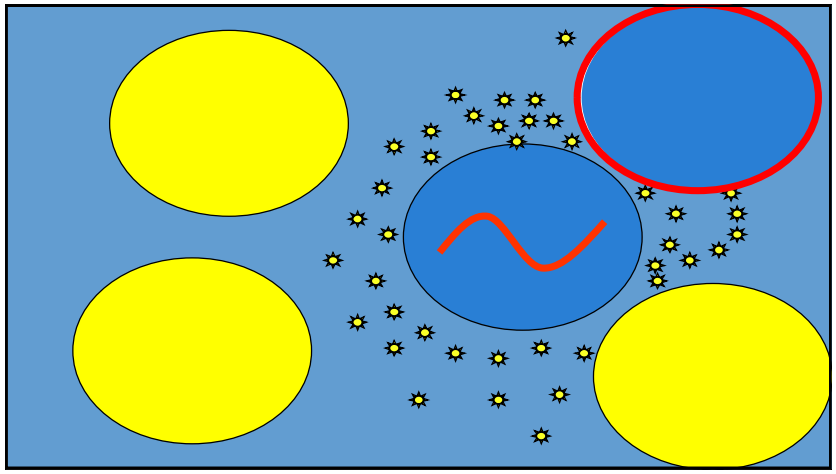
5



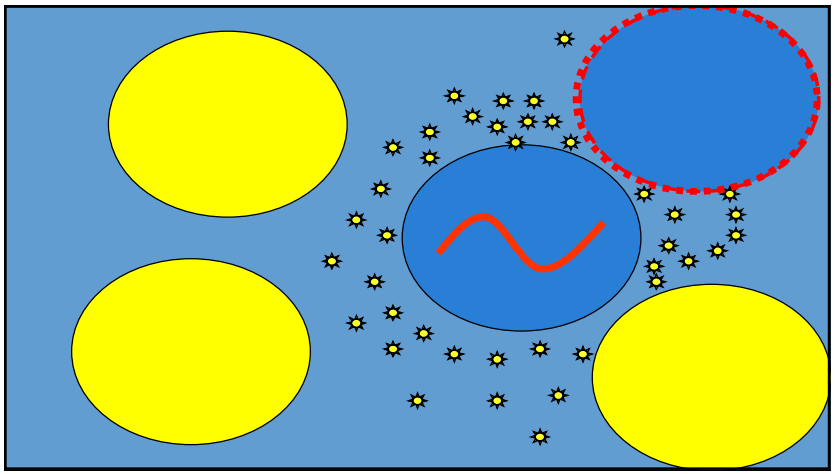
6



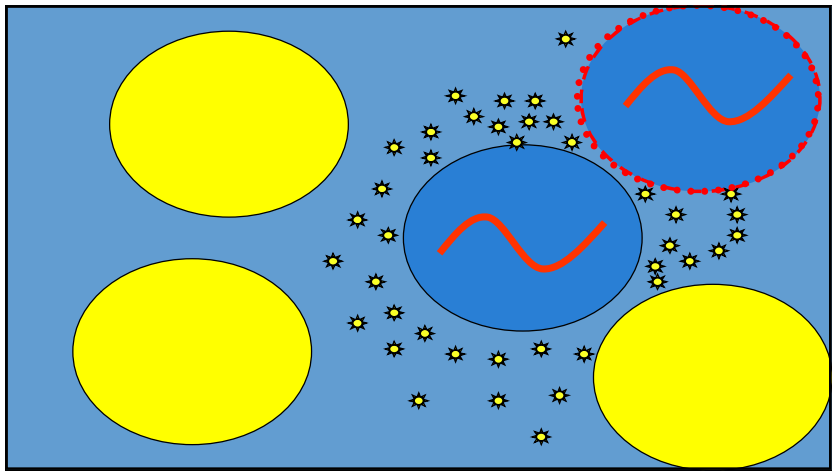
7



8



9



10

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)

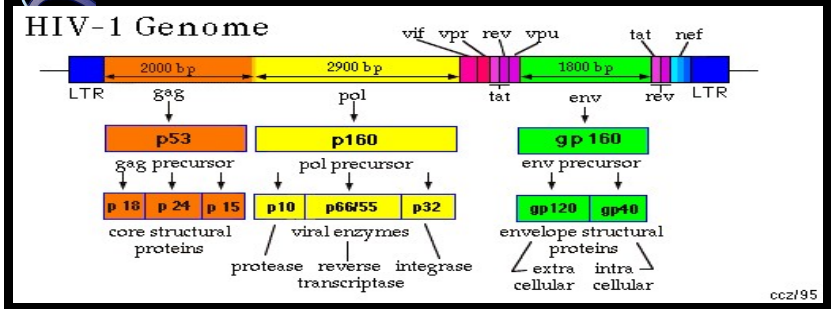
11

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

12

HIV-1 Genome



13

Mutation Nomenclature

Codon (position)

PR = 1-99 amino acids

RT = 1-560 amino acids

M184V

14

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
Tryosine	Y

15

Question #1 PREVIEW QUESTION

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.

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

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

16

Question #1 PREVIEW QUESTION

IDBR INFECTIOUS DISEASE BOARD REVIEW 2025

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

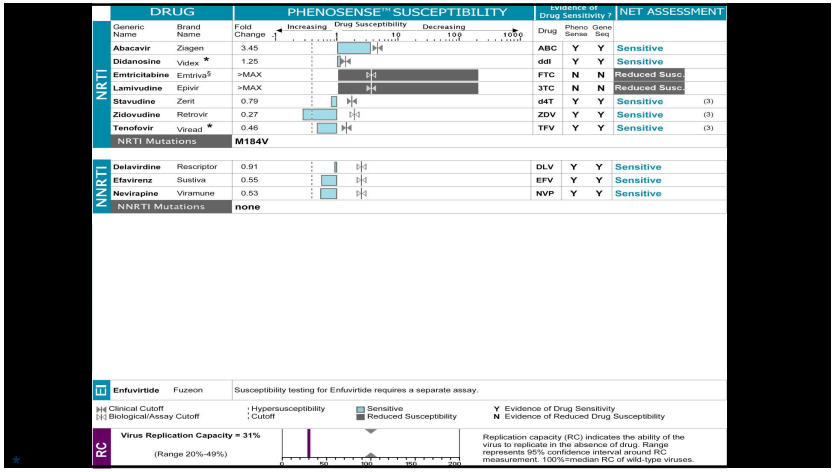
He wants to start ARV therapy

A baseline genotype is ordered that shows an M184V mutation.

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

A. Efavirenz
B. Zidovudine
C. Tenofovir
D. Etravirene
E. **Emtricitabine***

17



18

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

19

Question #2

The genotype shows an M184V and K65R mutations.

Which nRTI drugs would you include?

A. ZDV
B. TDF
C. TAF
D. ABC

20

Question #2

The genotype shows an M184V and K65R mutations.

Which nRTI drugs would you include?

A. **ZDV ***
B. TDF
C. TAF
D. ABC

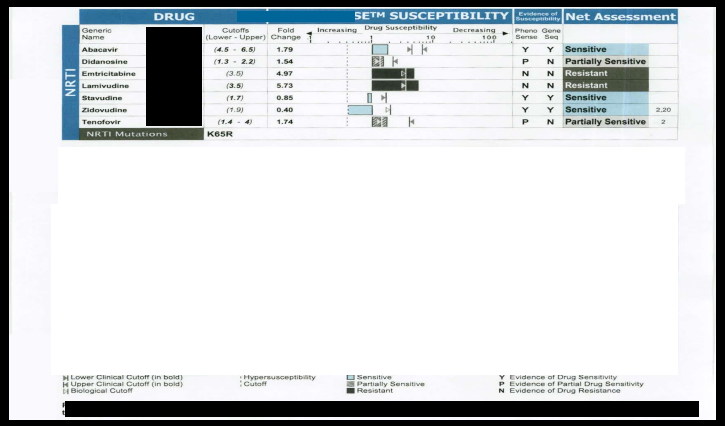
21

The genotype shows a K65R mutation.

Which nRTI drugs would you include?

A. **ZDV: Correct Answer**
B. TDF: TDF won't work well
C. TAF: Won's work well either
D. ABC: Abacavir activity typically reduced with a K65R mutation especially if M184V is also present

22



23

Non-nucleoside Reverse Transcriptase (NNRTI) Mutations

- K103N is the signature mutation for efavirenz (EFV)
- 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

24

Question #3

- 34-year-old 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

25

Question #3

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

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

26

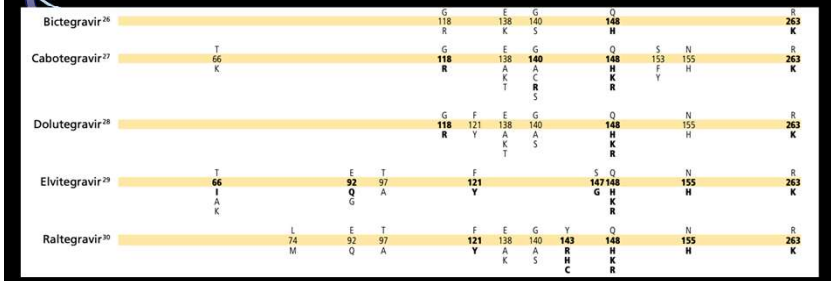
Question #3

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

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

27

InSTI Resistance Mutations



28

Lenacapavir Resistance Mutations

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

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

29

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 negative
- Routine screening: HIV RNA 6.1 c/ml

30

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

31

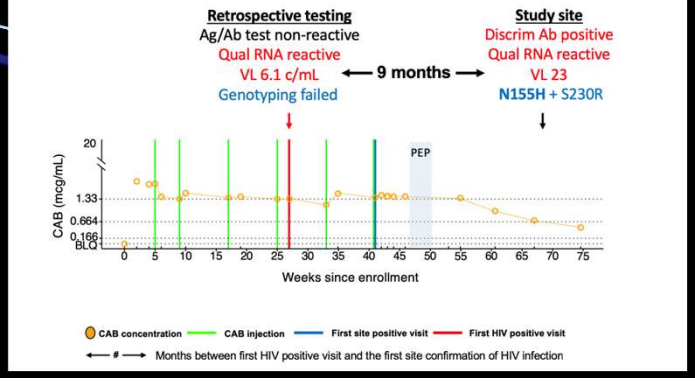
Question #4

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

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

32

Case Study: Confirmation of Infection



33

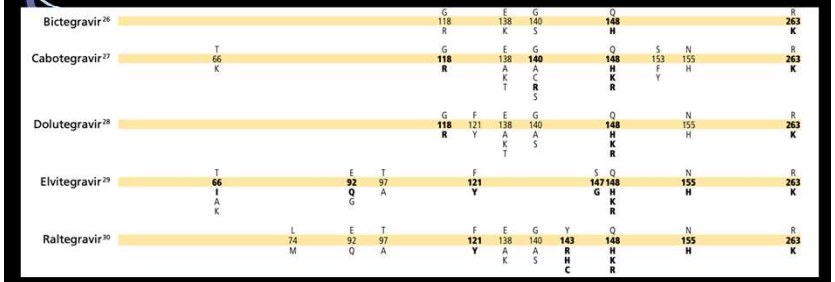
Question #4 (cont.)

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

A. S147G: Elvategravir
B. **N155H: Cabotegravir (and others) ***
C. Y143R: Raltegravir
D. E92Q: Raltegravir / Elvategravir
E. K65R: Tenofovir (!)

34

InSTI Resistance Mutations



35

Question #5

- 34-year-old 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

36

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%

37

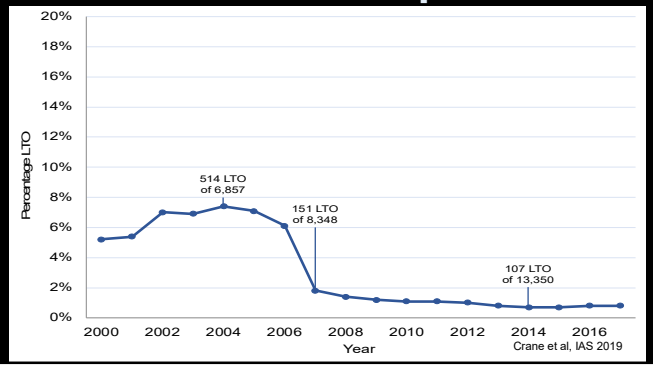
Question #5

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%

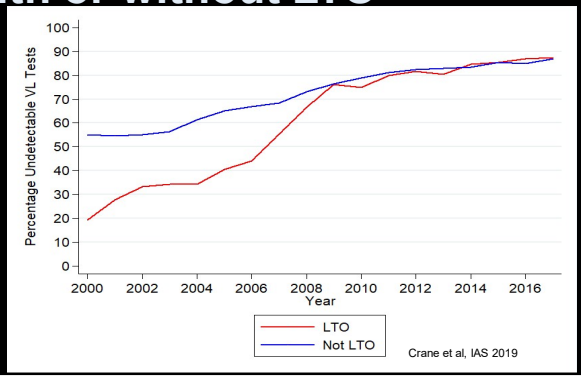
38

Prevalence of Patients with Limited Treatment Options



39

Virologic Success in Those with or without LTO



40

Common Mutations To Memorize

• **M184V/I**	3TC and FTC
• **K65R**	Tenofovir
• **K103N**	EFV retains susceptibility to etravirine
• **Y181C**	Many NNRTIs
• E138K, K101E	RPV and other NNRTI
• I50L	ATV
• **N155H, Q148H/R/K**	RAL and EVG
• **Y143C**	RAL
• **R263K**	DTG

41

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

42

• **Contact me:**
msaag@uabmc.edu

43