Virologic Failure: Resistance is Not Futile!

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- I have no financial disclosures

Objectives

- Identify factors that influence drug resistance.
- Understand the methods available for measuring HIV drug resistance.
- Identify strategies for responding to detection of moderate to high levels of drug resistant HIV.

So You've Started Someone on Antiretroviral Therapy

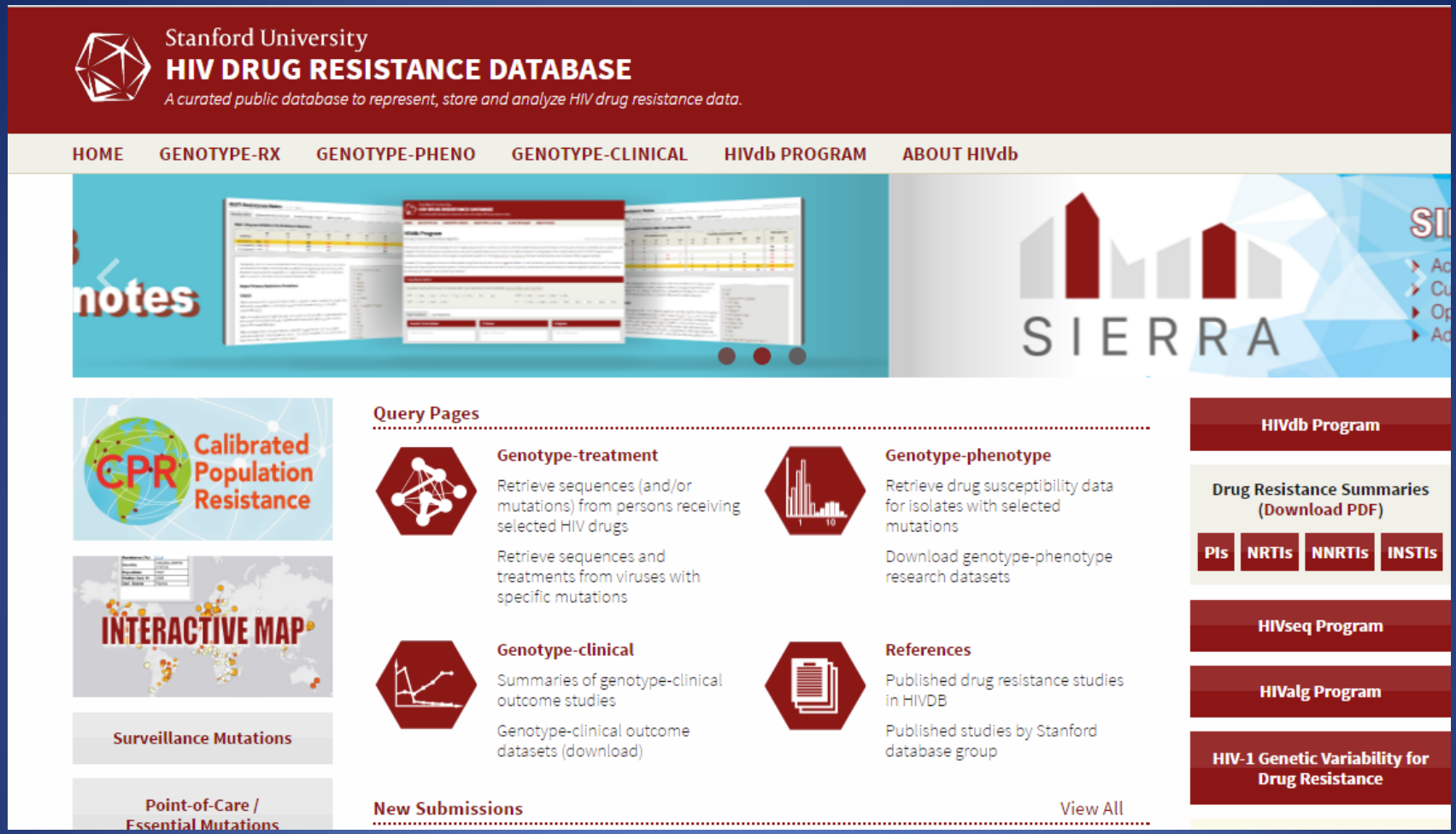
- Can be intimidating
- Is it working? How do you know?
- If it is not working, what can you do about it?

What is antiretroviral therapy (ART) resistance?

- Reduced susceptibility of Human Immunodeficiency Virus (HIV) to a specific antiviral drug
  - Drug less effective in replication blockade
  - > 200 copies/mL of blood (DHHS guidelines, 2016)
- Caused by mutations in viral genome
- May be:
  - Agent specific
  - Cross-resistance (multiple drugs)
- Magnitude of resistance variable by mutation and number

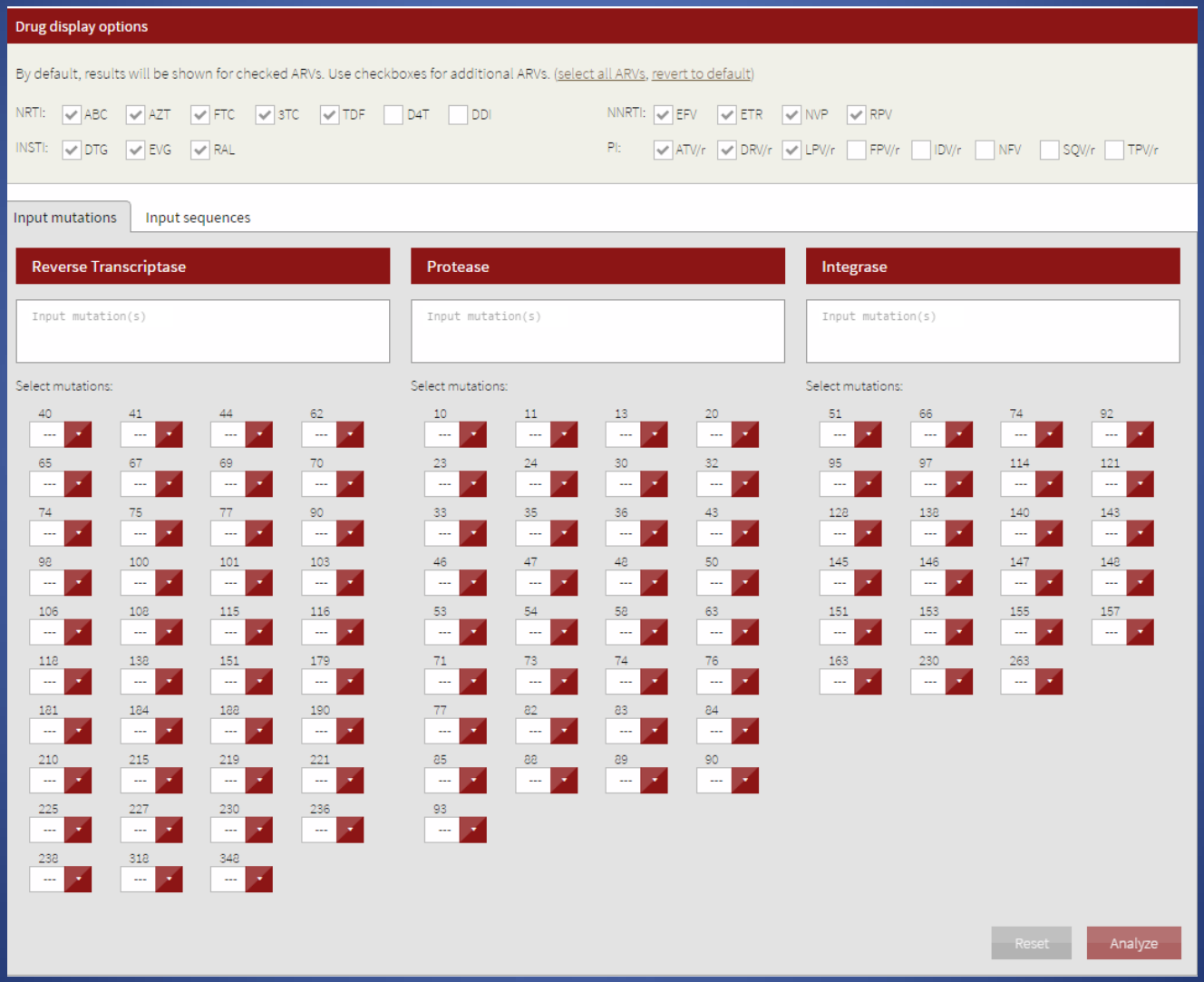
Approach to Potential Resistance

- Is it really resistance?
- Selecting a resistance test
- Considering the entire library of resistance
- Address root cause
- Use resources:
  - Colleagues
  - Resistance Databases (Stanford)
  - National Clinical Consultation Center



https://hivdb.stanford.edu/

Making a “Master” Genotype



hivdb.stanford.edu/hivdb/by-mutations

34-yo-male with HIV initiated on antiretroviral therapy 3 years ago with consistently suppressed virus presents for follow up. Previous CD4 1100 cells/mm^3 6 months ago. Labs today: CD4 1264 cells/mm^3 and viral load 65 copies/mL.

What is going on here?

What is our next step?

Just A Little Bit of Virus?

The Blip

- An episode of low-level viremia that is proceeded and followed by suppression below the quantification limit of an assay WITHOUT a change in therapy
- Less than 200 copies/ML
- Often unclear cause
- Repeat viral load

Persistent Low Level Viremia (PLLV)

- A viral load <200 copies/mL but not “undetectable”
- Action controversial
- Follow closely
- Consider Archive Genotype*

* We’ll come back to this

Antimicrob Agents Chemother. 2014 Jul; 58(7): 3585–3598

56-yo-male with HIV diagnosed 7 years ago. He has been on antiretroviral therapy for >5 years consistently with a viral load < 20 copies/mL. He has recently signed up for your health system patient access portal. He calls you to discuss the following result:

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SPECIMEN DESCRIPTION:          (PURPLE TOP) EDTA WHOLE BLOOD/PLASMA
HIV QUANTITATIVE VIRAL LOAD RESULT:   HIV-1 RNA Detected
Log base ten value = <1.3
Copies RNA per mL = <20
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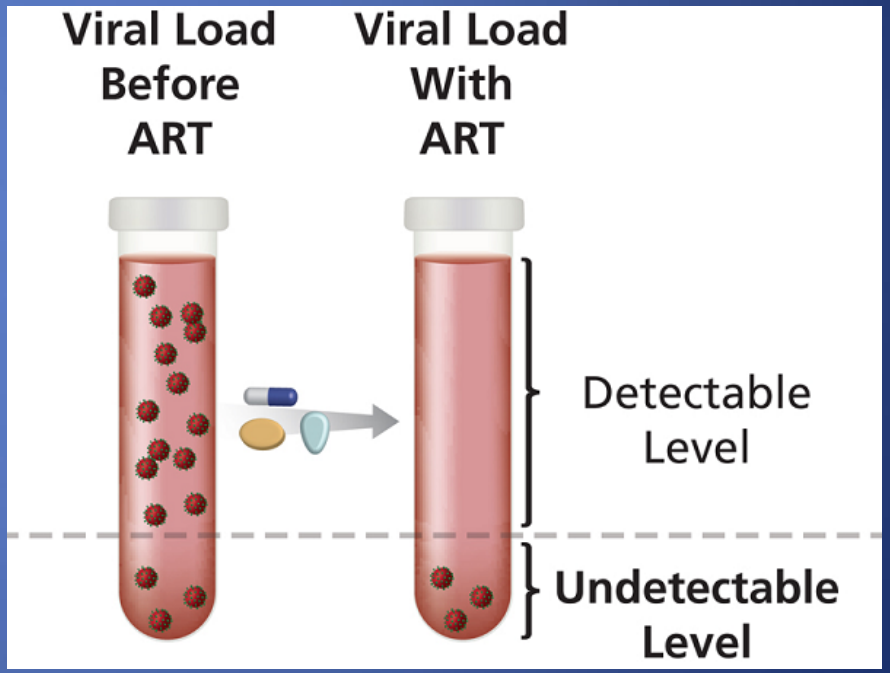
How should we address his concerns?

“Detectable but not Quantifiable”

- Usually viral load of <20-50 copies/mL
- Moving target
- Most would not change therapy
- Future standards?



http://www.medifee.com/

Resistance or Not?

- Baseline resistance testing
- Repeat an abnormal result (ie. viral load) prior to making therapy changes

- If established that resistance present, try to determine cause:
  - Adherence
  - Absorption
  - Drug interactions

Testing for Resistance

- When
  - Entrance to care
  - Initiation of therapy
  - In virologic failure:
    - Failure with HIV RNA >1000 copies/mL
    - Failure with HIV RNA 500 -1000 copies/mL
      - Testing should be attempted but may not be successful
    - Suboptimal viral load reduction
    - On therapy if able

DHHS Guidelines for Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, 2016

Resistance Testing: Genotype vs. Phenotype

Genotype

- Advantages
  - Availability
  - Less technically demanding
  - Mutations likely precede phenotypic resistance
  - Less expensive

Phenotype

- Advantages
  - Direct measure of susceptibility
  - More familiar reporting results

Genotype vs. Phenotype Limitations

Genotype

- Limitations
  - Indirect measure
  - May not correlate to phenotype
  - Expert interpretation required
  - Insensitive for minor mutations
  - Relies upon known mutations
  - May need separate test for integrase inhibitor panel

Phenotype

- Limitations
  - Limited availability
  - Technically demanding
  - Insensitive for detecting minor mutations
  - Clinically significant breakpoints not defined
  - Costly

Archive Genotype

- Introduced 2014
- Designed to measure resistance in virologically suppressed patients
- Facilitate therapy switch in otherwise suppressed patients.

Archived vs Plasma Virus

"The PBMC-derived HIV-1 DNA and circulating HIV-1 RNA represent two different viral compartments in the same individual."*

HIV-1 DNA ("Archived")

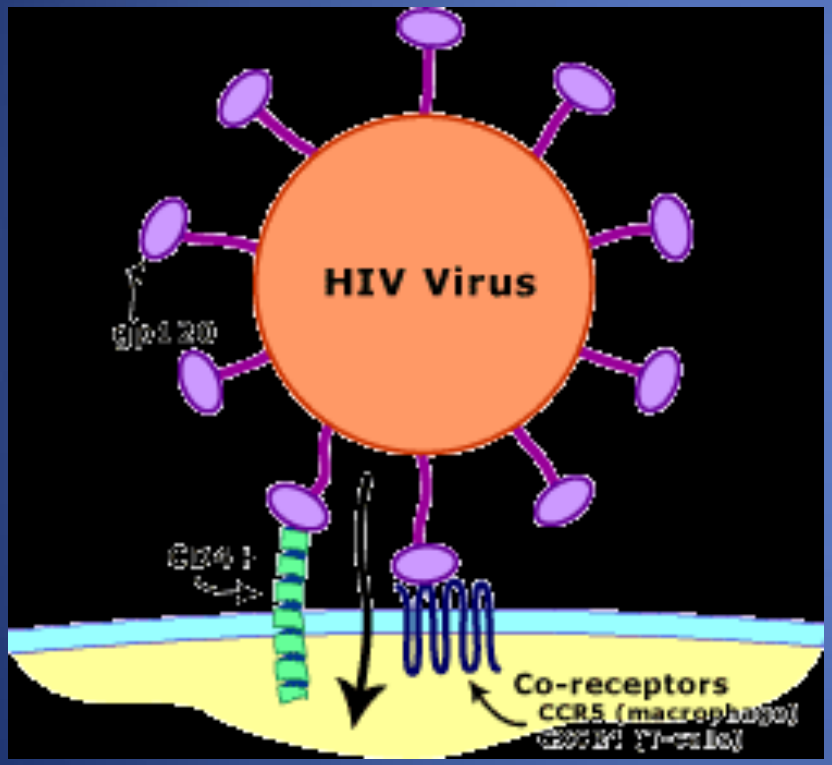
- Virus transmitted and archived at the time of acute infection
- Mutations acquired during the course of the patient's ARV treatment

HIV-1 RNA ("Plasma")

- The actively replicating virus from productively infected cells.
- The most current form of the virus.

* VanDamme AM, et al. *AIDS Rev*. 2011; 13:77-108.

Co-Receptor Tropism Testing



http://genetics.thetech.org

- Perform when:
  - Considering use of CCR5 co-receptor antagonist
  - Virologic failure on CCR5 antagonist

aidsinfo.nih.gov

Mutation Reporting Convention

Wild-type Amino Acid Designation

Substituted Amino Acid Designation

Lysine (K) replaced by asparagine (N)

Mutations Behave Like:

Light Switch

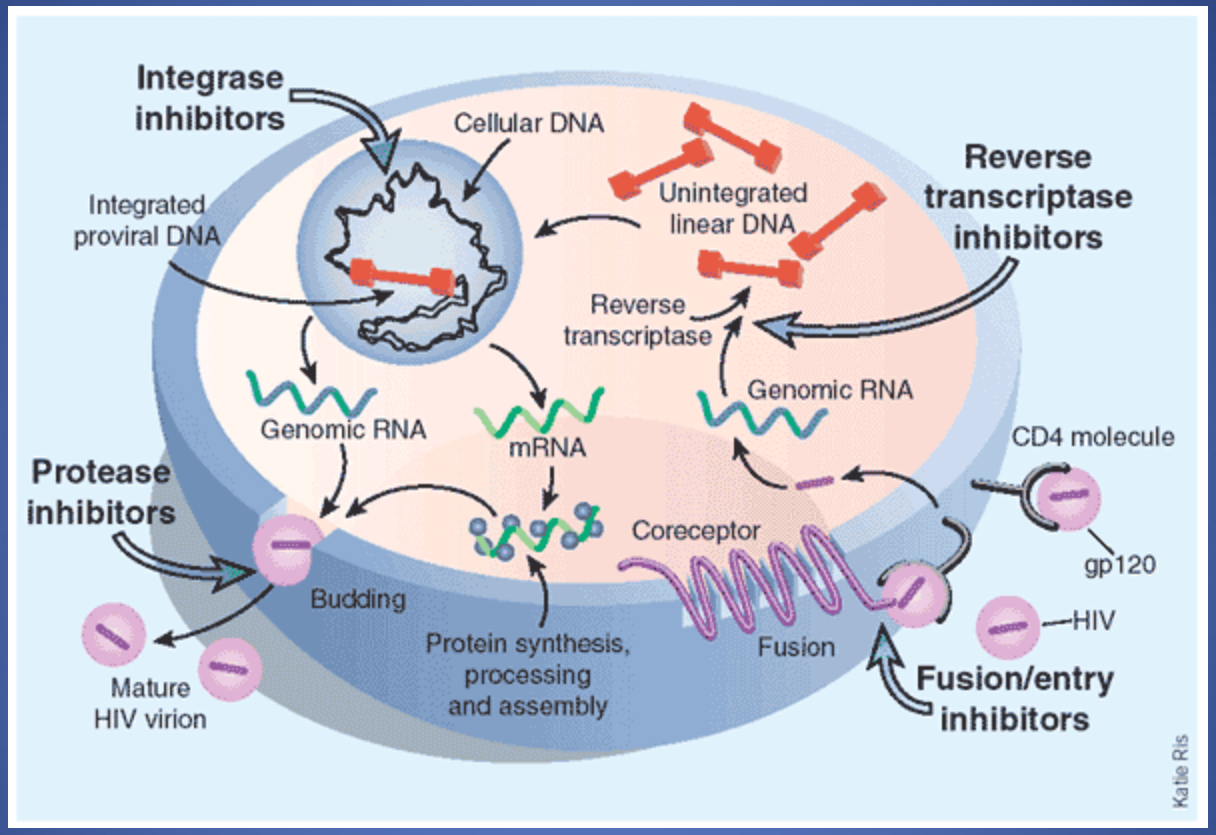
westsidewholesale.com

Dimmer Switch

Adapted from David Spach, MD

Drug Categories

NRTI	NNRTI	Protease Inh	Integrase Inh	Entry Inh
Tenofovir (TDF/TAF)	Efavirenz (EFV)	Darunavir (DRV)	Raltegravir (RAL)	Maraviroc (MVC)
Entricitabine (FTC)	Rilpivirine (RPV)	Atazanavir (ATV)	Elvitegravir (EVG)	Enfuvirtide (ENF)
Abacavir (ABC)	Etravirine (ETR)	Ritonavir (/r)	Dolutegravir (DTG)	
Lamivudine (3TC)	Nevirapine (NVP)	Lopinavir (LPV)		
Zidovudine (AZT)	Delavirdine (DLV)	Fosamprenavir (FPV)		
Stavudine (D4T)		Tipranovir (TPV)		
Didanosine (DDI)		Saquinavir (SQV)		
		Nelfinavir (NFV)		
		Indinavir (IDV)		


Integrase inhibitors
Cellular DNA
Integrated proviral DNA
Unintegrated linear DNA
Reverse transcriptase inhibitors
Reverse transcriptase
Genomic RNA
mRNA
Genomic RNA
CD4 molecule
Protease inhibitors
Coreceptor
gp120
Budding
HIV
Protein synthesis, processing and assembly
Fusion
Mature HIV virion
Fusion/entry inhibitors
Katie Ris

35-yo-female with HIV/AIDS that returns to clinic for follow up. She misses 1 or 2 out of every 3 appointments scheduled. Currently on TDF/FTC/DRV/r. Viral load today is 10,000. HLAB5701 is negative. A genotype reveals the following mutation: M184I

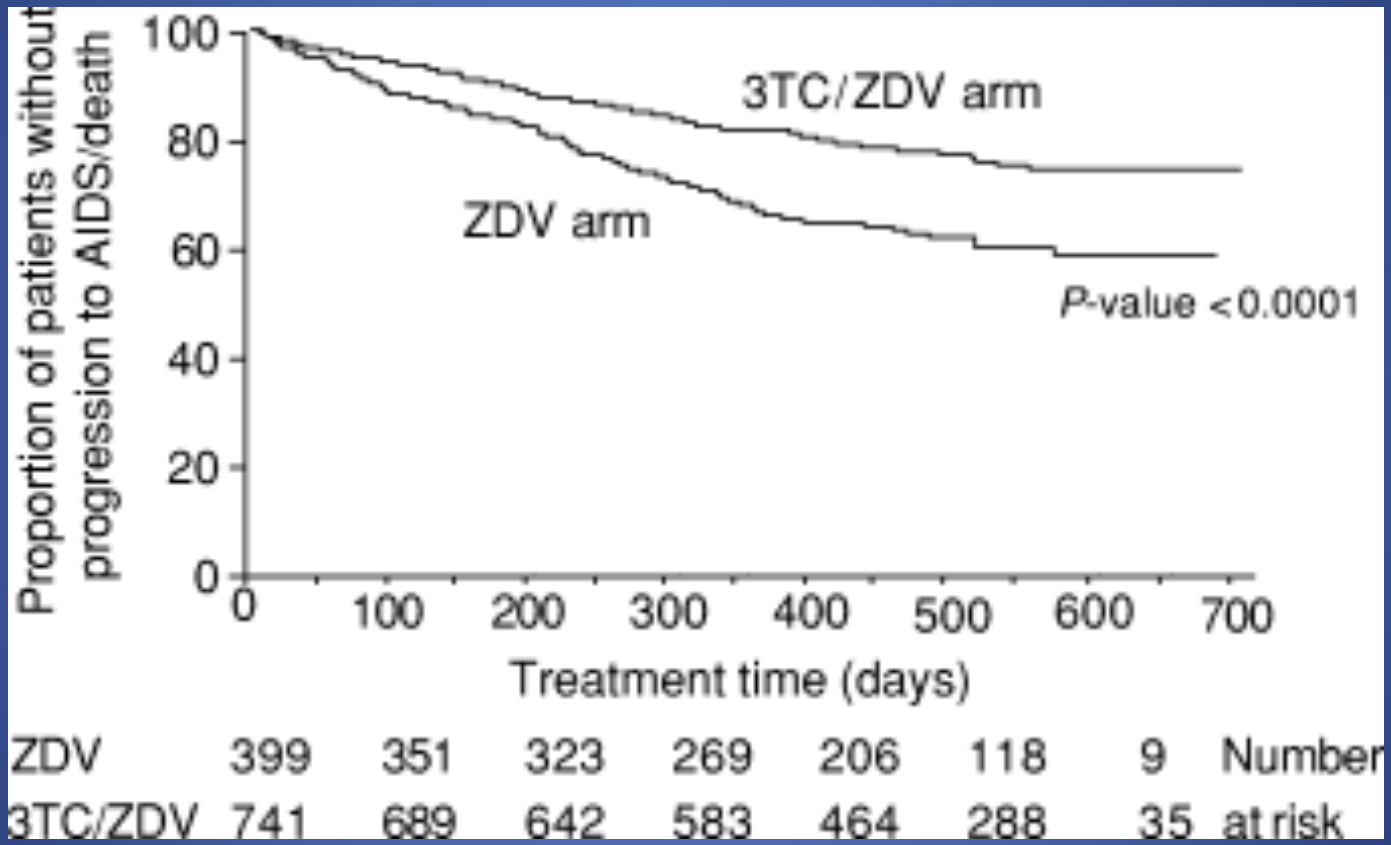
Assuming good adherence to regimen, what changes would you suggest?

184V

- M184V most common nucleoside reverse transcriptase inhibitor (NRTI) mutation
- Selected for by 3TC, FTC
  - Reduces susceptibility to these drugs x100 fold
  - Slight decrease in ABC activity
  - Increased activity: AZT, TDF (probably TAF), d4T
- Decreased viral fitness
  - virus “expends more energy to maintain”
  - Reversion to wild type without “pressure”

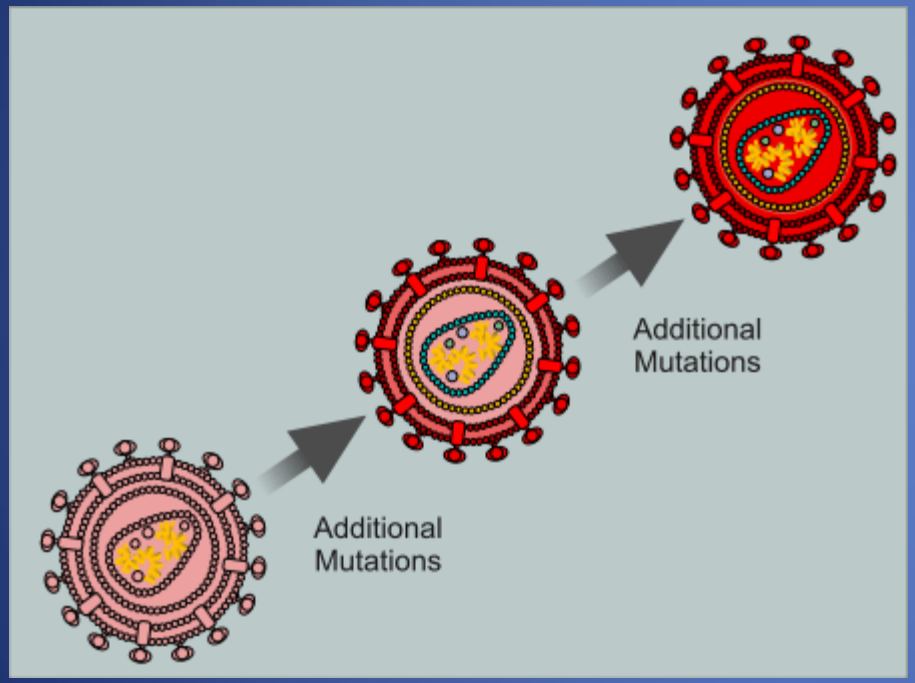
Hivdb.stanford.edu; Bartlett, Medical Management of HIV, 2012

The Impact of the M184V Substitution in HIV-1 Reverse Transcriptase on Treatment Response



HIV Medicine
Volume 3, Issue 2, pages 135-145, 14 MAY 2002 DOI: 10.1046/j.1468-1293.2002.00101.x
http://onlinelibrary.wiley.com/doi/10.1046/j.1468-1293.2002.00101.x/full#f1

M184I



fthmb.tqn.com

- Precursor to 184V
- Same impact
  - Resistance profile
  - Decreased fitness
- 184I +138K-> increased RPV resistance

Hivdb.stanford.edu

35-yo-female with HIV/AIDS that returns to clinic for follow up. She misses 1 or 2 out of every 3 appointments scheduled. Currently on TDF/FTC/DRV/r. Viral load today is 10,000. HLAB5701 is negative. A genotype reveals the following mutation: M184I

What drugs are active? Which are inactive?

What changes should we make?

K65R

- Selected for by: TDF, ABC, d4T, ddI, rarely 3TC
- Reduces susceptibility:
  - 2 fold: TDF, ABC, ddI
  - 5-10 fold: 3TC, FTC
  - Can co-exist with 184V/I
- Increases susceptibility:
  - AZT (except in presence of 151M)

A 57-yo-male with HIV/AIDS for 10 years presents to clinic to establish care. He has had a long history of antiretroviral treatment in the past and cannot recall all of his previous medications. He is not currently on antiretroviral therapy. A HIV genotype reveals the following mutations: 41L, 103N, 181C, 215Y, 184V

What therapy should we consider?

Thymidine Analog Mutations (TAMS)

- M41L
- D67N
- K70R
- L210W
- T215Y

- Selected by: AZT, d4T
- “Dimmer switch”
- Cumulative effect
- If multiple TAMS assume M184V!
- Reduced susceptibility: AZT, d4T, ABC, ddI, TDF
- Not all are created equal

Adapted from David Spach, MD

A 57-yo-male with HIV/AIDS for 10 years presents to clinic to establish care. He has had a long history of antiretroviral treatment in the past and cannot recall all of his previous medications. He is not currently on antiretroviral therapy. A HIV genotype reveals the following mutations: 41L, 103N, 181C, 215Y, 184V

What therapy should we consider?

NRTI Resistance to Know

- M184V/I
  - Common
  - May “hide” in a wild type
- TAMS
  - Cumulative
  - “Dimmer switch”
- K65R

50-yo-male recently diagnosed with HIV here to establish care. No prior history of antiretroviral therapy in the past. He is interested in starting medications. On review of genotype you note the following mutations: K103N. Initial viral load 8,000 copies/mL. CD4 >500 cells/mm^3

What drug(s) should we avoid?

What other mutations might be present?

Transmitted Resistance

- "Resistance testing at entry to care regardless of whether antiretroviral therapy (ART) will be initiated immediately."
  - DHHS Treatment Guidelines (2016)
- Frequency of ≥ 1 major resistance mutations in treatment naïve patients (North America): 10-24%
- Durable
- Measure of the dominant species present

Buschacz, JAntChemo 2015; CID 2005 41:233

K103N

- Most common non-nucleoside reverse transcriptase inhibitor (NNRTI) mutation
- “Light Switch”
- Selected by:
  - NVP, EFV
- Reduces susceptibility:
  - NVP (50X), EFV (20x)
- When coexists with M184V:
  - 2/3 patients
  - If keep of EFV can lead to more mutations
  - No set guidelines for regimen in setting; would favor integrase inhibitor

Lancet. 2011 Jul 16;378(9787):229-37

Your new patient sees a drug chart on the wall and is intrigued by the small pill size of TAF/FTC/RPV. After discussing potential side effects, drug-drug interactions, dosing strategy, you both agree to start this medication. He is lost to follow up. He returns to care 9 months later with reported “good” adherence to medications. Labs as follows:

HIV viral RNA: 4500 copies/mL

Genotype: K103N, E138K, M184I

What now?

E138K

- NNRTI mutation selected by RVP
  - Decreased activity of RVP
  - Decreased activity of ETV compared with K103N
- In combination with M184I
  - Can cause failure on RPV-containing regimen
  - Significant activity decrease in ETV

Etravirine (ETV)

- Consider in salvage
- “Dimmer drug”
- Multiple mutations to completely eliminate activity; determined by scoring system
- Use mutation calculator to assist in assessing activity

Adapted from David Spach, MD

Hivdb.stanford.edu;

NNRTI Resistance to Know

- K103N
  - Common
  - May have masked M184V
- E138K
  - RVP and ETV to some extent
  - Enhancement of M184I
- Etravirine scoring

Protease Inhibitor Resistance

- Class typically with high ceiling for resistance
- “Dimmer Switch” mutations
- Complex
- Use resistance data base

45-yo-female with HIV on TDF/FTC, RAL presents for follow up. Previously well-controlled, but admits to only taking 3-4 doses/week since last visit 4 months ago. Current viral load 1644 copies/mL.

Baseline genotype: no mutations.

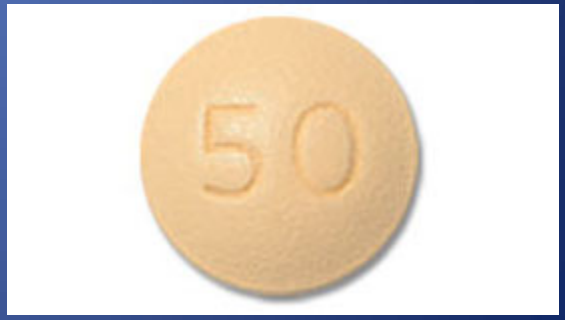
What has happened here?

Integrase Inhibitor Resistance

- Newest class; evolving
- Often not evaluated on standard genotype
- Variable ceiling for resistance

Raltegravir

Elvitegravir

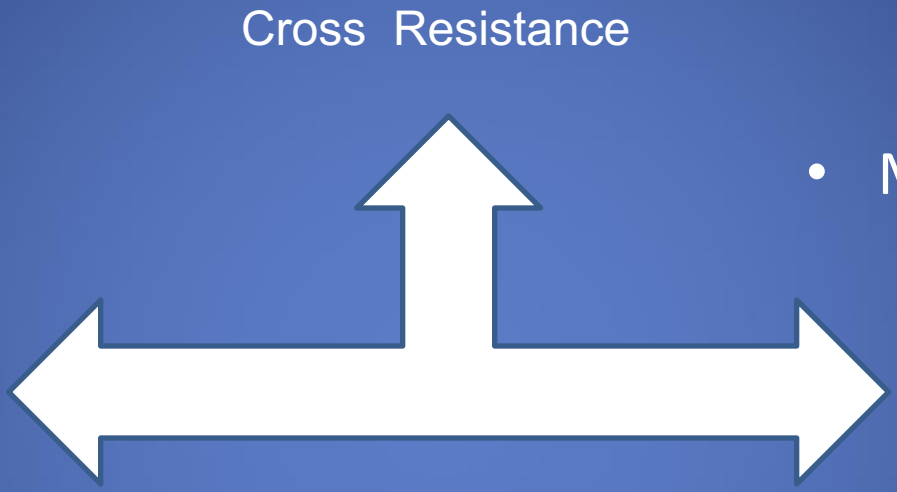


Dolutegravir

Integrase Inhibitor Mutations

Raltegravir

- Low barrier
  - Y143
  - Q148
  - N155



Elvitegravir

- Medium Barrier
  - E92
  - Q148
  - N155

- G140+ G148 = high degree of resistance
- Q148 pathway can lead to DOL resistance
- Avoid prolonged failure!

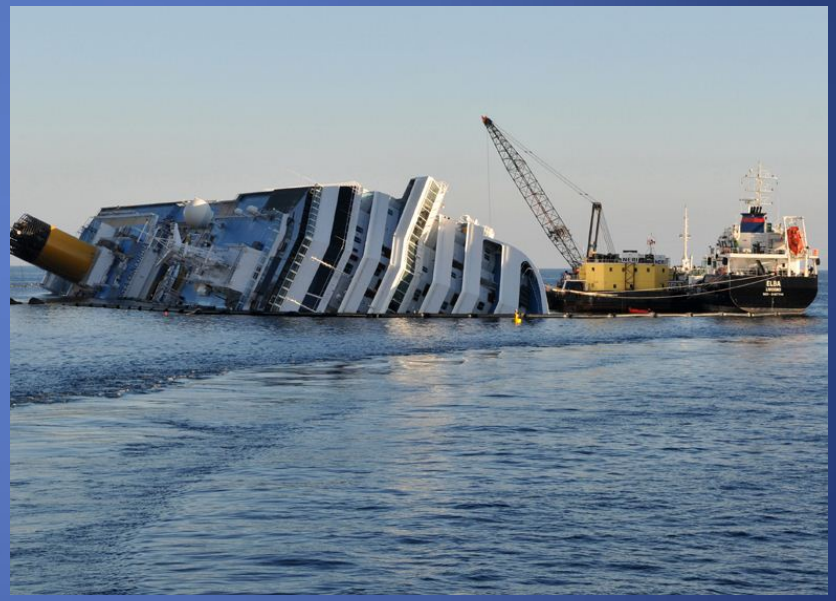
Dolutegravir

- No clear reports of dolutegravir resistance in setting of no prior integrase resistance
- “Dimmer” drug
- Once daily vs. Twice daily dosing
  - If 148 mutation present would use twice daily dosing—not clear in package insert (Viking-3 Study)

Castagna J Inf Dis 2014

Deep Salvage

- Deep salvage = Deep breaths
- Genotypes are additive
- Try to add two potentially active drugs
- Think outside the box!
  - Atypical backbone
  - Experimental drugs
  - Use resources!



wplgroup.com

Resources

- National Clinical Consultation Center/Clinicians' Warmline (CDC
  - M-F 9AM-8PM EST
  - 1-800-933-3413
- HIV Drug Resistance Database
  - Hivdb.stanford.edu