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
Making a “Master” Genotype

**Drug display options**

By default, results will be shown for checked ARVs. Use checkboxes for additional ARVs. (select all ARVs, revert to default)

<table>
<thead>
<tr>
<th>NRTI</th>
<th>ABC</th>
<th>AZT</th>
<th>FTC</th>
<th>ATC</th>
<th>TDF</th>
<th>D4T</th>
<th>DD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSTI</th>
<th>DTG</th>
<th>Efav</th>
<th>RAL</th>
</tr>
</thead>
</table>

**Input mutations**

**Reverse Transcriptase**

**Protease**

**Integrase**

**Select 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

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:

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

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 (i.e., 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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td>• Availability</td>
<td>• Direct measure of susceptibility</td>
</tr>
<tr>
<td>• Less technically demanding</td>
<td>• More familiar reporting results</td>
</tr>
<tr>
<td>• Mutations likely precede phenotypic resistance</td>
<td>• Less expensive</td>
</tr>
</tbody>
</table>
## Genotype vs. Phenotype

### Limitations

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
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</thead>
<tbody>
<tr>
<td><strong>Limitations</strong></td>
<td><strong>Limitations</strong></td>
</tr>
<tr>
<td>Indirect measure</td>
<td>Limited availability</td>
</tr>
<tr>
<td>May not correlate to phenotype</td>
<td>Technically demanding</td>
</tr>
<tr>
<td>Expert interpretation required</td>
<td>Insensitive for detecting minor mutations</td>
</tr>
<tr>
<td>Insensitive for minor mutations</td>
<td>Clinically significant breakpoints not defined</td>
</tr>
<tr>
<td>Relies upon known mutations</td>
<td>Costly</td>
</tr>
<tr>
<td>May need separate test for integrase inhibitor panel</td>
<td></td>
</tr>
</tbody>
</table>
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.”*

<table>
<thead>
<tr>
<th>HIV-1 DNA (&quot;Archived&quot;)</th>
<th>HIV-1 RNA (&quot;Plasma&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Virus transmitted and archived at the time of acute infection</td>
<td>• The actively replicating virus from productively infected cells.</td>
</tr>
<tr>
<td>• Mutations acquired during the course of the patient’s ARV treatment</td>
<td>• The most current form of the virus.</td>
</tr>
</tbody>
</table>

Co-Receptor Tropism Testing

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

http://genetics.thetech.org

aidsinfo.nih.gov
Mutation Reporting Convention

Wild-type Amino Acid Designation

Substituted Amino Acid Designation

K103N

Position of Codon in Genome

Lysine (K) replaced by asparagine (N)
Mutations Behave Like:

Light Switch

Dimmer Switch

westsidewholesale.com

Adapted from David Spach, MD
## Drug Categories

<table>
<thead>
<tr>
<th>NRTI</th>
<th>NNRTI</th>
<th>Protease Inh</th>
<th>Integrase Inh</th>
<th>Entry Inh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir (TDF/TAF)</td>
<td>Efavirenz (EFV)</td>
<td>Darunavir (DRV)</td>
<td>Raltegravir (RAL)</td>
<td>Maraviroc (MVC)</td>
</tr>
<tr>
<td>Entricitabine (FTC)</td>
<td>Rilpivirine (RPV)</td>
<td>Atazanavir (ATV)</td>
<td>Elvitegravir (EVG)</td>
<td>Enfuvirtide (ENF)</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Etravirine (ETR)</td>
<td>Ritonavir (/r)</td>
<td>Dolutegravir (DTG)</td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>Nevirapine (NVP)</td>
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<td></td>
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</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td>Delavirdine (DLV)</td>
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<tr>
<td>Stavudine (D4T)</td>
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<tr>
<td>Didanosine (DDI)</td>
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<tr>
<td>Didanosine (DDI)</td>
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<tr>
<td>Nelfinavir (NFV)</td>
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<tr>
<td>Indinavir (IDV)</td>
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</table>
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

- Graph showing the proportion of patients without progression to AIDS/death over treatment time (days) for ZDV arm and 3TC/ZDV arm.
- Table showing numbers of patients at risk for each arm:
  - ZDV: 399, 351, 323, 269, 206, 118, 9
  - 3TC/ZDV: 741, 689, 642, 583, 464, 288, 35
- P-value < 0.0001
M184I

- Precursor to 184V
- Same impact
  - Resistance profile
  - Decreased fitness
- 184I +138K-> increased RPV resistance
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?
Thymididine 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/mm³

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 $\geq 1$ 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
Integrate Inhibitor Mutations

**Raltegravir**
- Low barrier
  - Y143
  - Q148
  - N155

**Elvitegravir**
- Medium Barrier
  - E92
  - Q148
  - N155

Cross Resistance
- 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