Resistance to Integrase Strand Transfer Inhibitors

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Raltegravir Resistance
Virologic Failure on Raltegravir

• A patient on tenofovir-emtricitabine (*Truvada*) and Raltegravir (*Isentress*) develops virologic failure with an HIV RNA level of 1,644 copies/ml 18 months after starting this regimen. A baseline genotype showed no mutations and 4 months prior he had an undetectable HIV RNA.

• **What type of resistance test should you order?**
Commercial Integrase Resistance Testing

• Integrase **Genotype**
  - Quest Diagnostics
  - Lab Corp (Monogram Biosciences)
  - Virco Lab

• Integrase **Phenotype**
  - Lab Corp (Monogram Biosciences)
  - Virco
HIV Genotypic Resistance Testing that Includes Integrase

LabCorp (Monogram Biosciences)

*GenoSure PRLme*™

**HIV Drug Resistance Assay**

- PR
- RT
- IN

A Comprehensive Resistance Profile in a Single Test

List Price $890 (as of October 30, 2012)
A patient on tenofovir-emtricitabine (Truvada) and Raltegravir (Isentress) develops virologic failure with an HIV RNA level of 1,644 copies/ml 18 months after starting this regimen. A baseline genotype showed no mutations and 4 months prior he had an undetectable HIV RNA.

**Genotype Result**

RT: M184V
Integrase: N155H
Protease: No mutations
Genotypic Resistance to Raltegravir

- **Primary Mutations**
  - N155H
  - Q148H/K/R
  - Y143R/H/C

Major Pathways of Resistance with Raltegravir

**Raltegravir Resistance Pathways**

**Primary Mutations**
- **N155H**
- **Q148H/K/R**
- **Y143R/H/C**

**Secondary Mutations**
- **L74M, E92Q, T97A, V151I, G163R**
- **L74M, G140A/S, E138K**
- **E92Q, T97A**

Major Pathways of Resistance with Raltegravir

- **Early**
  - N155H

- **Delayed**
  - Q148H/K/R
  - Secondary Mutations (L74M, G140A/S, E138K)

- Secondary Mutations (L74M, E92Q, T97A, V151I, G163R)

Evolution of Integrase Resistance During INSTI Failure
SCOPE Study

A patient on tenofovir-emtricitabine (Truvada) and Raltegravir (Isentress) develops virologic failure with an HIV RNA level of 1,644 copies/ml 18 months after starting this regimen. A baseline genotype showed no mutations and 4 months prior he had an undetectable HIV RNA.

- **Genotype Result**
  - RT: M184V
  - Integrase: N155H
  - Protease: No mutations

- Do you think the patient would respond to Elvitegravir?
Raltegravir and Elvitegravir: Cross Resistance

Graphical Representation of Mean log10 Fold Change Values for Different Genotype

NPM = no primary mutation

Raltegravir and Elvitegravir: Cross Resistance

Graphical Representation of Mean log10 Fold Change Values for Different Genotype

ANRS 138-Easier Trial
Low Level Viremia and Raltegravir Resistance

• **Background**
  - Analysis of INSTI resistance in 49 patients with HIV RNA 50–500 copies/ml after switch from enfuvirtide to raltegravir

• **Results**
  - Significant INSTI resistance mutations in 8%
  - N155H in two and P145S in one
  - Mutations not present on baseline proviral DNA analysis

• **Conclusion**
  - INSTI resistance mutations can emerge during episodes of low level viremia in patients receiving raltegravir-containing regimens

Elvitegravir Resistance
Virologic Failure on Elvitegravir

- A patient on elvitegravir-cobicistat-tenofovir-emtricitabine (Stribild) develops virologic failure with an HIV RNA level of 3,288 copies/ml 9 months after starting this regimen? A genotype (including integrase) is performed and resistance is identified.

- **What resistance pattern would you expect to see?**
  
  A. M184V, K103N  
  B. M184V, E92Q  
  C. K65R, N155H  
  D. K65R, K103N
Virologic Failure on Elvitegravir

• A patient on elvitegravir-cobicistat-tenofovir-emtricitabine (*Stribild*) develops virologic failure with an HIV RNA level of 3,288 copies/ml 9 months after starting this regimen? A genotype (including integrase) is performed and resistance is identified.

• **What resistance pattern would you expect to see?**

  A. M184V, K103N
  ✔B. M184V, E92Q
  C. K65R, N155H
  D. K65R, K103N
## Resistance Data from Studies 102 and 103

### Subjects with Virologic Failure (N = 13)

<table>
<thead>
<tr>
<th>NRTI Resistance: Genotype Data</th>
<th>N = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>A62A/V</td>
<td>2 (17%)</td>
</tr>
<tr>
<td>K65R</td>
<td>4 (33%)</td>
</tr>
<tr>
<td>M184V</td>
<td>12 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ISTI Resistance Genotype Data: 1° Mutations</th>
<th>N = 11</th>
</tr>
</thead>
<tbody>
<tr>
<td>T66I</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>E92Q</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Q148R</td>
<td>3 (27%)</td>
</tr>
<tr>
<td>N155H</td>
<td>3 (27%)</td>
</tr>
</tbody>
</table>

### Resistance Data with EVG-Cobi-TDF-FTC Virologic Failures

#### Genotypic Data from Studies 102 and 103

<table>
<thead>
<tr>
<th>Patient</th>
<th>Genotype Data from Patients with Virologic Failure (N = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRTI</td>
</tr>
<tr>
<td>1</td>
<td>A62V</td>
</tr>
<tr>
<td>2</td>
<td>A62V</td>
</tr>
<tr>
<td>3</td>
<td>K65R</td>
</tr>
<tr>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>M184V</td>
</tr>
<tr>
<td>6</td>
<td>M184V</td>
</tr>
<tr>
<td>7</td>
<td>M184V</td>
</tr>
<tr>
<td>8</td>
<td>M184V</td>
</tr>
<tr>
<td>9</td>
<td>M184I</td>
</tr>
<tr>
<td>10</td>
<td>M184V</td>
</tr>
<tr>
<td>11</td>
<td>M184V</td>
</tr>
<tr>
<td>12</td>
<td>K65R</td>
</tr>
<tr>
<td>13</td>
<td>K65R</td>
</tr>
</tbody>
</table>

**Most common pattern of resistance:** M184V and E92Q

Major Pathways of Resistance with Elvitegravir

Elvitegravir Resistance Pathways

Primary Mutations
- N155H
- Q148H/K/R
- E92Q

Secondary Mutations
- ?
- ?
- ?
Virologic Failure on Elvitegravir

- The genotype shows M184V and E92Q. You are going to change the patient’s antiretroviral regimen.

- **Do you think the patient will likely respond to raltegravir?**

  A. Yes
  B. No
# Resistance Data with EVG-Cobi-TDF-FTC Virologic Failures

## Phenotypic Data from Studies 102 and 103

<table>
<thead>
<tr>
<th>Patient</th>
<th>Integrase Strand Transfer Inhibitor and Mean Fold Value Change</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elvitegravir (biologic cut-off = 2.5)</td>
<td>Raltegravir (biologic cut-off = 1.5)</td>
</tr>
<tr>
<td>1</td>
<td>&gt;198</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>149</td>
<td>6.2</td>
</tr>
<tr>
<td>3</td>
<td>111</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>6.0</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>3.6</td>
</tr>
<tr>
<td>7</td>
<td>36</td>
<td>3.0</td>
</tr>
<tr>
<td>8</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>3.3</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>8.7</td>
</tr>
<tr>
<td>11</td>
<td>5.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Dolutegravir
Dolutegravir-ABC-3TC versus Efavirenz-TDF-FTC
SINGLE: 48 Week Virologic Result

Dolutegravir-ABC-3TC: No Integrase Resistance with Virologic Failure

Dolutegravir ("572") in Patients with Raltegravir Resistance

VIKING Cohort I: Results

Source: Eron JJ, et al. 18th CROI. 2011:Abstract 151LB.
Dolutegravir ("572") in Patients with Raltegravir Resistance
VIKING Cohort I and II: Results

HIV RNA < 400 copies/ml OR > 0.7 log Decrease in HIV RNA

- All Patients
  - Cohort I: 78
  - Cohort II: 96

- Patients with Q148 + Secondary Mutations
  - Cohort I: 33
  - Cohort II: 100

- Patients with Other Mutations
  - Cohort I: 100
  - Cohort II: 92

Source: Eron JJ, et al. 18th CROI. 2011:Abstract 151LB.
## INSTI-Resistance Associated Mutations

### Major (Black) and High-Level Major (Red) Mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amino Acid Positions</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir</td>
<td>66 92 140 147 148 155</td>
<td>I A K Q S A G H R H</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>66 92 140 143 148 155</td>
<td>A Q S A R C H R K H</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>92 140 148 155</td>
<td>Q S A H R K</td>
</tr>
</tbody>
</table>

Source: Stanford Database
Resistance to Integrase Strand Transfer Inhibitors (ISTIs)

Key Concepts

- Raltegravir & elvitegravir have low-medium genetic barrier to resistance
- Dolutegravir has medium-high genetic barrier to resistance
- Genotype is appropriate test to evaluate resistance to ISTIs
- Raltegravir & elvitegravir have major cross-resistance
- Dolutegravir likely effective in early virologic failure with ISTI (RAL or EVG)
- Avoid prolonged failure with raltegravir or elvitegravir
- Dolutegravir requires higher dose when used with prior ISTI failure