NNRTI Resistance

- Efavirenz
- Nevirapine
- Rilpivirine
- Etravirine
Interactive map displaying HIV-1 drug resistance in ARV-naive population

Studies of ARV-naive population by region, year and subtype.  » Interactive map
### Reverse Transcriptase

- **Enter Mutation List:**
  - k103n

- **Use The Pulldown Menus:**
  - 41 44 62 65
  - 67 69 70 74
  - 75 77 90 98
  - 100 101 103 106
  - 108 115 116 118
  - 138 151 179 181
  - 184 188 190 210
  - 215 219 221 225
  - 227 230 234 236
  - 238 318 333 348

### Protease

- **Enter Mutation List:**
  - 10 11 13 16
  - 20 23 24 30
  - 32 33 35 36
  - 43 46 47 48
  - 50 53 54 58
  - 60 62 63 71
  - 73 74 76 77
  - 82 83 84 85
  - 88 89 90 93

### Integrase

- **Enter Mutation List:**
  - 51 54 66 68
  - 74 92 95 97
  - 114 121 125 128
  - 138 140 143 145
  - 146 147 148 151
  - 153 154 155 157
  - 163 203 230 263
## Drug Resistance Interpretation: RT

<table>
<thead>
<tr>
<th>NRTI Resistance Mutations:</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI Resistance Mutations:</td>
<td>K103N</td>
</tr>
<tr>
<td>Other Mutations:</td>
<td>None</td>
</tr>
</tbody>
</table>

### Nucleoside RTI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamivudine (3TC)</td>
<td></td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td></td>
</tr>
<tr>
<td>zidovudine (AZT)</td>
<td></td>
</tr>
<tr>
<td>stavudine (D4T)</td>
<td></td>
</tr>
<tr>
<td>didanosine (DDI)</td>
<td></td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td></td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td></td>
</tr>
</tbody>
</table>

### Non-Nucleoside RTI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>efavirenz (EFV)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>etravirine (ETR)</td>
<td>Susceptible</td>
</tr>
<tr>
<td>nevirapine (NVP)</td>
<td>High-level resistance</td>
</tr>
<tr>
<td>rilpivirine (RPV)</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>

### RT Comments

- **NNRTI**
  - K103N causes high-level resistance to NVP, and EFV. It has no effect on ETR or RPV susceptibility.

### Mutation Scoring

<table>
<thead>
<tr>
<th>RT</th>
<th>3TC</th>
<th>ABC</th>
<th>AZT</th>
<th>D4T</th>
<th>DDI</th>
<th>FTC</th>
<th>TDF</th>
<th>EFV</th>
<th>ETR</th>
<th>NVP</th>
<th>RPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>K103N</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>0</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

| Total: | 0   | 0   | 0   | 0   | 0   | 0   | 60  | 0   | 60  | 0   | 0   |

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**Stanford Database**
A 32-year-old man presents after several missed visits. He reports imperfect adherence to tenofovir-emtricitabine-efavirenz (Atripla). HIV RNA level (viral load) has increased from undetectable to 3,410 copies/mL.

Genotype resistance assay shows: K103N

Are other NNRTI’s an option for this patient?
Efavirenz Resistance

• Most common mutation: **K103N**
• May be followed by: G190A/S, Y188L/H/C, K101E, L100I, accessory mutations
• *Efavirenz has long half-life and low barrier to resistance, so K103N often the first mutation with *Atripla* failure*

Libre JM, Schapiro JM, Clotet B. CID. 2010;(50),872-881.
**Key points:**
- K103N knocks out efavirenz and nevirapine
- Rilpivirine remains active *in vitro*; clinical data limited
- Etravirine still works unless additional mutations present

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>Rilpivirine</th>
<th>Etravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>K103N</td>
<td>60</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Penalty score**
- >60: high-level resistance
- 30-60: intermediate-level resistance
- 10-30: low-level resistance
- Less than 0: hypersusceptible
Case #2

• A 55-year-old man has had poor adherence to tenofovir-emtricitabine (*Truvada*) and nevirapine (*Viramune*). HIV RNA level has risen to 1,250 copies/mL.
• What is the most likely nevirapine-associated resistance mutation?
Nevirapine Resistance

- Most common: **Y181C**
- Also possible: Y181I/V, G190A/S/E/Q, Y188L/H/C, K103N/S/T, K101E, A98G, accessory mutations

Libre JM, Schapiro JM, Clotet B. CID. 2010;(50),872-881.
**Y181C**

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>Rilpivirine</th>
<th>Etravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y181C</td>
<td>30</td>
<td>60</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

*Key point: the most common nevirapine mutation affects all NNRTI’s, including etravirine*

Penalty score
- ≥60: high-level resistance
- 30-60: intermediate-level resistance
- 10-30: low-level resistance
- Less than 0: hypersusceptible
Case #3

• A 35-year-old woman has imperfect adherence to tenofovir-emtricitabine-rilpivirine (Complera). HIV RNA level is 4,950 copies/mL.

• What is the most likely rilpivirine-associated resistance mutation?
Rilpivirine Resistance

- Most common rilpivirine mutation: **E138K**
- With *Complera* failure, most often see: **E138K + M184I**
  - M184I enhances rilpivirine resistance and causes emtricitabine resistance at the cost of viral fitness
- Other mutations: V90I, K101E/P/T, V179I/D/L, Y181C/I/V, V189I, H221Y, F227C/L, M230I/L

http://hivdb.stanford.edu
Kulkarni R et al. JAIDS; 59(1): 47-54.
**E138K**

<table>
<thead>
<tr>
<th></th>
<th>Efavirenz</th>
<th>Nevirapine</th>
<th>Rilpivirine</th>
<th>Etravirine</th>
</tr>
</thead>
<tbody>
<tr>
<td>E138K</td>
<td>10</td>
<td>10</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>

**Key point:** NNRTI cross-resistance is more common with rilpivirine than efavirenz

Penalty score
- >60: high-level resistance
- 30-60: intermediate-level resistance
- 10-30: low-level resistance
- Less than 0: hypersusceptible
Case #4

- A 45-year-old woman presents for an initial visit. She doesn’t recall the names of the ARV’s she was taking most recently and has been off of them for 4 weeks.
- You perform a genotype resistance assay and find the following NNRTI mutations: K103N, Y181I and P225H.
- Is etravirine an option for this patient?

### NNRTI DRUGS

- RESCYPTOR, (delavirdine, DLV)  
- SUSTIVA, (efavirenz, EFV)  
- VIRAMUNE, (nevirapine, NVP)  
- INTELENCE, (etravirine, ETR)

NNRTI associated resistance mutations found: K103N, Y181I, P225H
Etravirine Resistance

- Etravirine may retain activity even if resistance develops to other NNRTI’s
- Depends on # of mutations and which specific mutations
- Most significant: Y181C/I/V
- Best way to determine susceptibility: phenotype
  - Methods to estimate susceptibility:
    - DUET (Tibotec) weighted scoring system
    - Monogram Biosciences weighted scoring system

Libre JM, Schapiro JM, Clotet B. CID. 2010;(50),872-881.
# Etravirine: DUET Score

<table>
<thead>
<tr>
<th>Weight</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Y181I/V</td>
</tr>
<tr>
<td>2.5</td>
<td>L100I, K101P, Y181C, M230L</td>
</tr>
<tr>
<td>1.5</td>
<td>V106I, E138A, V179F, G190S</td>
</tr>
<tr>
<td>1</td>
<td>V90I, A98G, K101E/H, V179D/T, G190A</td>
</tr>
</tbody>
</table>

*Response rates based on total score:*
- 0-2: 74% (highest response)
- 2.5-3.5: 52% (intermediate response)
- >4.0: 38% (progressively reduced response)

**Etravirine: Monogram “Enhanced” Score**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>L100I, K101P, Y181C/I/V</td>
</tr>
<tr>
<td>3</td>
<td>E138A/G, V179E, G190Q, M230L, K238N</td>
</tr>
<tr>
<td>2</td>
<td>K101E, V106A/I, E138K, V179L, Y188L, G190S,</td>
</tr>
<tr>
<td>1</td>
<td>V90I, A98G, K101H, K103R, V106M, E138Q,</td>
</tr>
<tr>
<td></td>
<td>V179D/F/I/M/T, Y181F, V189I, G190A/E/T, H221Y,</td>
</tr>
<tr>
<td></td>
<td>P225H, K238T</td>
</tr>
</tbody>
</table>

Total score $\geq 4$ correlates with fold-change on phenotype that indicates resistance (90% sensitivity, 85% specificity)

Summary of Key Mutations

• Efavirenz: K103N, also knocks out nevirapine
• Nevirapine: Y181C, more etravirine cross-resistance
• Rilpivirine: E138K +/- M184I, more NNRTI cross-resistance
• Etravirine: scoring systems estimate degree of resistance