PREVALENCE OF RESISTANCE MUTATIONS TO INTEGRASE INHIBITORS IN INI-NAÏVE AND INI-EXPERIENCED HIV-1 INFECTED PATIENTS IN A LARGE ITALIAN COHORT

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Disclosure

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INI-containing regimens

✓ Good safety and efficacy
✓ RAL, EVG: lower genetic barrier than DTG
✓ Extensive (elvitegravir) or partial (dolutegravir) cross-resistance following raltegravir failure
✓ Evidence that frequency of mutations at raltegravir failure influenced by viral load [Armenia 2015] and viral subtype: non-B lower frequency of Q148H/R/K+G140S/A [Doyle 2015]
Objectives

✔ To analyze the prevalence of at least a low-level genotypic resistance to raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG) in ART naïve patients and in INI-experienced patients

✔ To identify determinants of INI resistance
Methods

- IN genotyped ART naïve and INI-experienced patients from the ARCA database (2007-2014)
- At least a low-level resistance (>LLR) to RAL, EVG or DTG predicted by Stanford 7.0 algorithm
- Decreased susceptibility to DTG also defined as detection of Q148H/K/R + ≥1 of G140S/A or E138K
- Viral subtype by Rega 2.0; unresolved classifications were decided by the first BLAST match upon a LANL HIV-1 subtype reference set
- Differences in the prevalence of resistance were assessed by χ-square test
## Characteristics of population (n=1,385)

<table>
<thead>
<tr>
<th>ART-naïve patients (n=297)</th>
<th>INI-experienced patients (n=1,088)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong>*</td>
<td>36 (IQR 29-45)</td>
</tr>
<tr>
<td><strong>Male gender, n (%)</strong></td>
<td>238 (80)</td>
</tr>
<tr>
<td><strong>Viral subtype, %</strong></td>
<td>B 60; CRF31BC 10; CRF02AG 6; CRF28BF 4; other 20</td>
</tr>
<tr>
<td><strong>Years since HIV diagnosis</strong>*</td>
<td>0.06 (0.03-1.2)</td>
</tr>
<tr>
<td><strong>Calendar year of genotype</strong>*</td>
<td>2011 (2009-2012)</td>
</tr>
<tr>
<td><strong>CD4 count (cell/μL)</strong>*</td>
<td>339 (132-490)</td>
</tr>
<tr>
<td><strong>Nadir CD4 count (cell/μL)</strong>*</td>
<td>337 (131-489)</td>
</tr>
<tr>
<td><strong>HIV-1 RNA (copies/mL) on 271 available</strong></td>
<td>46,000 (11,000-180,000)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) except for the * median (IQR)
Frequency of INI resistance mutations (n=1,385)

- Q148H/K/R plus G140S/A or E138K (DTG resistance) detected in 0 ART-naïve patients and in 61 (5.6%) INI-experienced patients
- Any predicted resistance (≥LLR) to INI in 1 (0.3%) ART-naïve patient and in 196 (18%) INI-experienced patients: 17.5% RAL, 15.3% EVG, 7% DTG
- Resistance at RAL failure with any of Y143R/C/H (n=40), Q148H/R/K (n=76), N155H (n=88) was observed in 18%
Predicted resistance (≥LLR) to any INI according to viral subtype in INI-experienced patients.

Chi square p value = n.s.

Viral subtype B: 18.4%  n/N: 143/776
Viral subtype non B: 17%  n/N: 53/312
Predicted decreased susceptibility to DTG according to viral subtype in INI-experienced patients

- Q148HKR + ≥1 of G140S or E138K
  - Viral subtype B: 6.4%
  - Viral subtype non B: 6.7%
  - Chi square p value = n.s.

- Q148HKR + G140S
  - Viral subtype B: 6.3%
  - Viral subtype non B: 6.4%
  - Chi square p value = n.s.

n/N: 50/776, 21/312 for Q148HKR + ≥1 of G140S or E138K
n/N: 49/776, 20/312 for Q148HKR + G140S
Predicted resistance (≥LLR) to any INI according to HIV-RNA levels in INI-experienced patients

<table>
<thead>
<tr>
<th>Virus Load Range</th>
<th>Predicted Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;200 cps/mL</td>
<td>19%</td>
</tr>
<tr>
<td>VL 200-500 cps/mL</td>
<td>22%</td>
</tr>
<tr>
<td>VL 501-1,000 cps/mL</td>
<td>60%</td>
</tr>
<tr>
<td>VL 1,001-10,000 cps/mL</td>
<td>43%</td>
</tr>
<tr>
<td>VL 10,001-100,000 cps/mL</td>
<td>44%</td>
</tr>
<tr>
<td>VL &gt;100,000 cps/mL</td>
<td>30%</td>
</tr>
</tbody>
</table>

n/N: 11/57  6/27  12/20  30/70  23/52  11/36
Primary raltegravir resistance mutations according to HIV-RNA levels in INI-experienced patients

<table>
<thead>
<tr>
<th>HIV-RNA Level (cps/mL)</th>
<th>Y143C/H/R</th>
<th>Q148H/K/R</th>
<th>N155H</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt; 200</td>
<td>4/57</td>
<td>2/27</td>
<td>5/57</td>
</tr>
<tr>
<td>VL 200 - 500</td>
<td>2/27</td>
<td>4/20</td>
<td>2/27</td>
</tr>
<tr>
<td>VL 501 - 1,000</td>
<td>2/20</td>
<td>14/70</td>
<td>6/20</td>
</tr>
<tr>
<td>VL 1,001 - 10,000</td>
<td>6/70</td>
<td>11/52</td>
<td>12/70</td>
</tr>
<tr>
<td>VL 10,001 - 100,000</td>
<td>5/52</td>
<td>5/36</td>
<td>8/52</td>
</tr>
<tr>
<td>VL &gt; 100,000</td>
<td>6/36</td>
<td>2/36</td>
<td>2/36</td>
</tr>
</tbody>
</table>

% of patients with specific resistance mutations across different HIV-RNA levels.
Predicted decreased susceptibility to DTG according to HIV-RNA levels in INI-experienced patients

- VL <200 cps/mL: 0/57 (0%)
- VL 200-500 cps/mL: 2/27 (7%)
- VL 501-1,000 cps/mL: 3/20 (15%)
- VL 1,001-10,000 cps/mL: 10/70 (14%)
- VL 10,001-100,000 cps/mL: 11/52 (21%)
- VL >100,000 cps/mL: 5/36 (13%)
Conclusions

✓ Transmitted INI resistance uncommon in Italy
✓ Modest accumulation of resistance at RAL failure (82% without any mutation at codons 143, 148, 155)
✓ Limited predicted resistance to dolutegravir
✓ In this cohort, resistance to INI is independent from viral subtype but related to VL at failure
✓ Differences with previous studies: earlier failures? Different subtypes?
✓ Need of accurate VL monitoring in RAL treated individuals in order to detect early failure at low VL and avoid resistance accumulation
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