Epidemiological study of Doravirine associated resistance mutations in HIV-1-infected antiretroviral-experienced patients from two large databases in France and Italy

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Abstract # 9
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Conflit of interest declarations

- **AG Marcelin** has no commercial interests.

- **AG Marcelin** has received travel grants, honoraria, and study grants from various pharmaceutical companies including Gilead Sciences, Merck-Sharp & Dohme-Chibret, Jansen and ViiV Healthcare.

- **AG Marcelin** prepared the content of this presentation using his own material with no commercial input.

- **AG Marcelin** may discuss cases and circumstance when drugs are used off label; this is his own personal clinical experience. For the proper use of medications, please review the Product Monographs.
Intensive scale-up of antiretrovirals worldwide for HIV has led to a dramatic decrease in HIV-1 related morbidity and mortality.

Despite these successes, the expansion of treatment has been accompanied by a significant increase in the prevalence of both acquired and transmitted HIV drug resistance.

The increasing prevalence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs):

- Could be due to their large prescription until recently as a third recommended agent combined to a low genetic barrier
- Especially true in sub-Saharan Africa as a result of the extensive use of efavirenz and nevirapine.
Background (2)

- Doravirine (DOR) is a novel HIV-1 NNRTI that has been recently approved.

- DOR has an *in vitro* resistance profile that is distinct from other NNRTIs retaining activity against viruses containing the most frequently transmitted NNRTI mutations, K103N, E138K, Y181C and G190A.¹

- DOR selects for distinct mutations *in vitro*, including mutations at positions 106, 108, 221 and 227 with multiple mutations required for significant levels of resistance.²

¹ Feng et al. AAC 2016 Mar 25;60(4):2241-7
² Feng et al. AAC 2015 Jan;59(1):590-8
Background (3)

- It has been recently shown that DOR in combination therapy has non-inferior efficacy to darunavir/r (800/100 mg) or efavirenz in treatment-naïve patients (DRIVE-FORWARD and DRIVE-AHEAD). ¹, ²

- Switch to DOR/3TC/TDF maintains virological suppression through 48 weeks (DRIVE-SHIFT trial). ³

- There has been limited investigation of the prevalence of mutations associated with resistance to DOR in NNRTI-experienced patients.

¹ Molina et al., Lancet HIV. 2018 May;5(5):e211-e220.
³ Kumar, IDweek 2018, October 3-7, San Francisco, USA
Objectives

The aims of this study were:

• To examine the prevalence of DOR resistance associated mutations in HIV-1-infected ARV-treated patients in France and Italy,

• To compare this prevalence to those known for other NNRTIs (Efavirenz, Rilpivirine, Nevirapine and Etravirine),

• To compare the predicted genotypic resistance within this class of antiretrovirals.
Methods (1)

• Resistance genotypic tests were performed at five reference laboratories:
  
  • 2 in Paris, France (Pitié-Salpêtrière and Bichat Claude Bernard hospitals),
  • 3 in Italy (University of Rome Tor Vergata, INMI Spallanzani-IRCCS, Modena Hospital).

• A total a 9199 reverse transcriptase sequences obtained between 2012 and 2017 from HIV-1 ARV-treated patients in routine clinical care were analyzed:
  
  ➢ NNRTI-failing, n=381
    ➢ Efavirenz, n=189
    ➢ Etravirine, n=32
    ➢ Nevirapine, n=66
    ➢ Rilpivirine, n=94
Methods (2)

• DOR resistance associated mutations used to define DOR resistance in this study were: RT V106A/M, V108I, Y188L, G190S, F227C/L/V, M230I/L, L234I, P236L, K103N+Y181C, K103N+P225H, K103N+L100I.

• The NNRTIs mutations associated with resistance to Efavirenz (EFV), Rilpivirine (RPV), Nevirapine (NVP) and Etravirine (ETV) are those listed in the ANRS algorithm (www.hivfrenchresistance.org), Stanford algorithm (https://hivdb.stanford.edu/), and in the IAS list of mutations (www.iasusa.org).

• Resistance interpretation was made using the Smartgene® Integrated Database Network System.
Results (1): HIV-1 subtypes

• A total of 9199 RT sequences were analyzed.

• The distribution of subtypes was: 45.3% B and 54.7% non B.
Results (2): DOR resistance associated mutations

• The overall prevalence of RT sequences with at least 1 DOR-associated mutation was 12.2% (n = 1119).

• Among the DOR-associated mutations, the most frequent mutations were (> 1,5% up to 3,9%):
  V108I (n=307), M230I/L (n=256), K103N+Y181C (n=361), K103N+P225H (n=264) and K103N+100I (n=156).

• The other were very rare (< 1,5%):
  V106A/M (n=77), Y188L (n=107), G190S (n=24), F227C/L/V (n=49), L234I (n=13), P236L (n=0).
Results (3): other NNRTIs resistance associated mutations

- In comparison, the most frequent common NNRTIs resistance mutations were:
  V90I (n=580), K103N/S (n=934), E138A/G/K/Q/R (n=1001), Y181C/H/L (n=521) and G190A/E/S (n=258).
Among the DOR-associated mutations, the most frequent mutations were:

- V106A/M (n=10), V108I (n=35), Y188L (n=10),
- G190S (n=8), K103N+Y181C (n=15),
- K103N+P225H (n=18) and K103N+100I (n=15).

The other were very rare:

- F227C/L/V (n=7), M230I/L (n=0), L234I (n=2),
- P236L (n=0).

In comparison, the most frequent common NNRTIs mutations were:

- V90I (n=34), K103N/S (n=109),
- E138A/G/K/Q/R (n=48), Y181C/H/L (n=54) and
- G190A/E/S (n=34).

### Results (4): NNRTI-failing group (n=381)

<table>
<thead>
<tr>
<th>Mutation</th>
<th>DOR Prevalence (%)</th>
<th>Common NNRTIs Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V106A/M</td>
<td>2.6</td>
<td>9.2</td>
</tr>
<tr>
<td>V108I</td>
<td>2.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Y188L</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Y181C</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>G190S</td>
<td>3.9</td>
<td>4.7</td>
</tr>
<tr>
<td>K103N</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>K103N+Y181C</td>
<td>28.6</td>
<td>12.6</td>
</tr>
<tr>
<td>K103N+P225H</td>
<td>8.9</td>
<td>14.2</td>
</tr>
<tr>
<td>K103N+100I</td>
<td>8.9</td>
<td>8.9</td>
</tr>
</tbody>
</table>

- **DOR**
- **common NNRTIs**
Results (5): genotypic interpretation of resistance

- The DOR resistance was lower than other NNRTIs resistance (p<0.001)

- The DOR resistance was lower than
  - EFV, NVP and RPV with ANRS algorithm (p<0.001),
  - EFV and NVP with Stanford algorithm (p<0.001).

ANRS algorithm (www.hivfenresistance.org); Stanford algorithm (https://hivdb.stanford.edu)
Conclusions

• The prevalence of DOR resistance associated mutations in HIV-1-infected ARV-treated patients in Italy and France was low (12.2%).

• The prevalence of DOR resistance was significantly lower than:
  - the other NNRTIs in this whole set of sequences,
  - the first generation NNRTIs in the subgroup of NNRTI-failing patients and also RPV according to the ANRS algorithm.

• These results support potential DOR use even in NNRTI-experienced patients as the prevalence of mutations conferring resistance to DOR remains low in patients presenting mutations against the NNRTIs currently in use.

• Previous EFV and ETR experience has been associated with a higher risk of DOR resistance

• However, the role of DOR in vivo must be confirmed by clinical observations in such patients

• Clinical studies are warranted to better define the resistance patterns of DOR

1 Sterrantino et al. IJAA 2019
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