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

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Abstract #8
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Background (1)

• 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 (TDR).

• TDR may impact response to therapy, leading to virologic failure and the evolution of further drug resistance.

• The increasing prevalence of TDR has been driven in particular by an increase in resistance to NNRTI. This is 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 non-nucleoside reverse transcriptase (NNRTI) that is currently in clinical development.

• 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\(^2\).

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1 Feng et al. AAC 2016 Mar;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) in treatment-naïve patients\(^1\).

• Data relating to DOR-associated mutations in treatment-naïve patients is crucial to inform the further provision of treatment.

\(^1\) Molina et al. CROI 2017. Abstract 45LB
Objectives

• The aim of this study was to examine the prevalence of DOR-associated mutations in HIV-1-infected treatment-naïve patients in Europe
  • over time (2010-2016)
  • across various subtypes

• To compare this prevalence to those known for other NNRTIs (Efavirenz, Rilpivirine, Nevirapine and Etravirine)
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 of 7004 reverse transcriptase sequences obtained between 2010 and 2016 from HIV-1 treatment-naïve patients in routine clinical care were analyzed

• DOR-associated mutations identified in vitro and used to define DOR resistance in this study were: V106A, V106M, V108I, H221Y, F227L, F227C, F227V, M230I, L234I, P236L, Y318F
Methods (2)

- The NNRTI mutations associated with resistance to Efavirenz, Rilpivirine, Nevirapine and Etravirine are those listed in the ANRS algorithm (www.hivfrenchresistance.org) and in the IAS list of mutations (www.iasusa.org).

- Resistance interpretation was made using the Smartgene® Integrated Database Network System.
Results: subtypes

• A total of 7004 sequences were analyzed
  • 3355 were performed between 2010-2012 and 3649 between 2013-2016.

• The distribution of subtypes was: **53.7% B and 46.3% non B**

  - B: 54%
  - CRF02: 18%
  - A1: 4%
  - C: 4%
  - F1: 3%
  - Other various non-B: 17%

• There was an increase of non-B subtypes between 2010-2012 and 2013-2016 (41% versus 48%, p < 0.001)
Results: DOR associated mutations (1)

- The overall prevalence of sequences with at least 1 DOR-associated mutation was 1.3% (n = 91).
  - This was significantly lower than the prevalence of sequences with at least 1 EFV-associated mutation (4.3%, n = 304) or with at least 1 RPV-associated mutation (6.7%, n = 472), (p < 0.001).
Results: DOR associated mutations (2)

• Among the DOR-associated mutations, the most frequent mutations were V108I 0.6% (45), Y318F 0.3% (22) and H221Y 0.2% (16)

• The other being very rare: V106A/M 0.1% (7), F227C/L/V 0.1% (7), M230I 0.05% (3), L234I 0.01% (1), P236L 0%.
  • There was no significant increase over time and no relationship with any HIV-1 subtype for any of these mutations.
Results: other NNRTIs associated mutations (1)

• In comparison, the prevalence of common NNRTI mutations were K103N/S 2.4% (171), E138A/G/K/Q/R 5.3% (369), Y188C/H/L 0.3% (20) and G190A/E/S 0.6% (41).
Results: other NNRTIs associated mutations (2)

- Between 2010-2012 and 2013-2016, there was a significant increase in K103N/S (1.8% versus 3%, \( p = 0.002 \)) and in G190A/E/S (0.3% versus 0.8%, \( p = 0.003 \))

- There was no relationship between these mutations and any HIV-1 subtype
Results: interpretation of resistance

<table>
<thead>
<tr>
<th></th>
<th>% resistant strains</th>
<th>% susceptible strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOR*</td>
<td>1.3</td>
<td>98.7</td>
</tr>
<tr>
<td>RPV**</td>
<td>7.7</td>
<td>92.3</td>
</tr>
<tr>
<td>EFV</td>
<td>4.0</td>
<td>96.0</td>
</tr>
<tr>
<td>NVP</td>
<td>8.3</td>
<td>91.7</td>
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<tr>
<td>ETR</td>
<td>7.0</td>
<td>93.0</td>
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</table>

** ANRS algorithm (www.hivfrenresistance.org)
Conclusions

• The prevalence of DOR-associated mutations in HIV-1-infected treatment-naïve patients in Italy and France is
  • very low (1.3%)
  • significantly lower than EFV (4.3%) or RPV (6.7%)-associated mutations, NNRTIs currently recommended as first line regimen.
  • stable over time
  • not related to any HIV-1 subtype

• These results are very reassuring in the perspective of the use of DOR in naïve patients
  • able to cover the commonly transmitted EFV and RPV mutations in vitro