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].

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) 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 a 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

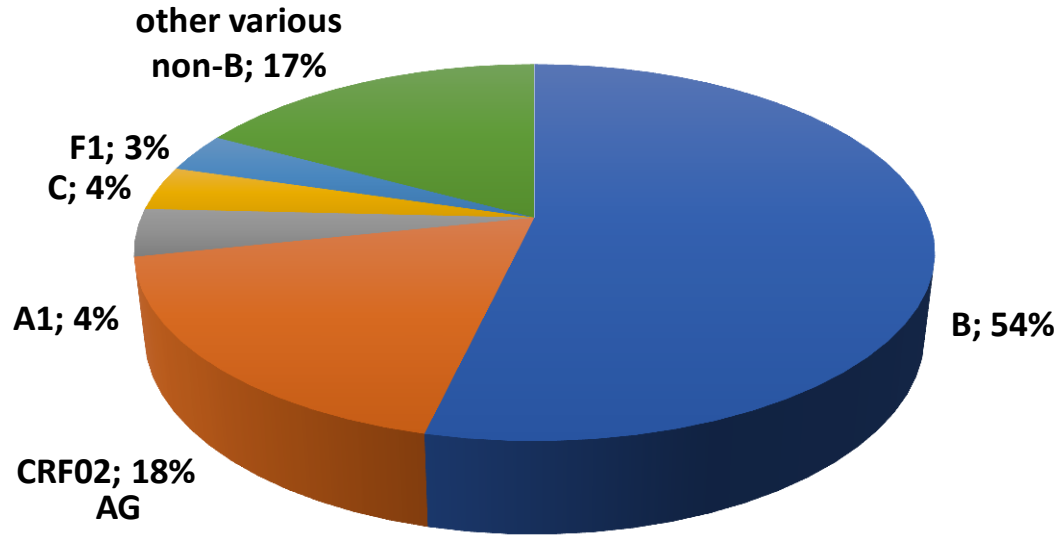
Methods (2)

- 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

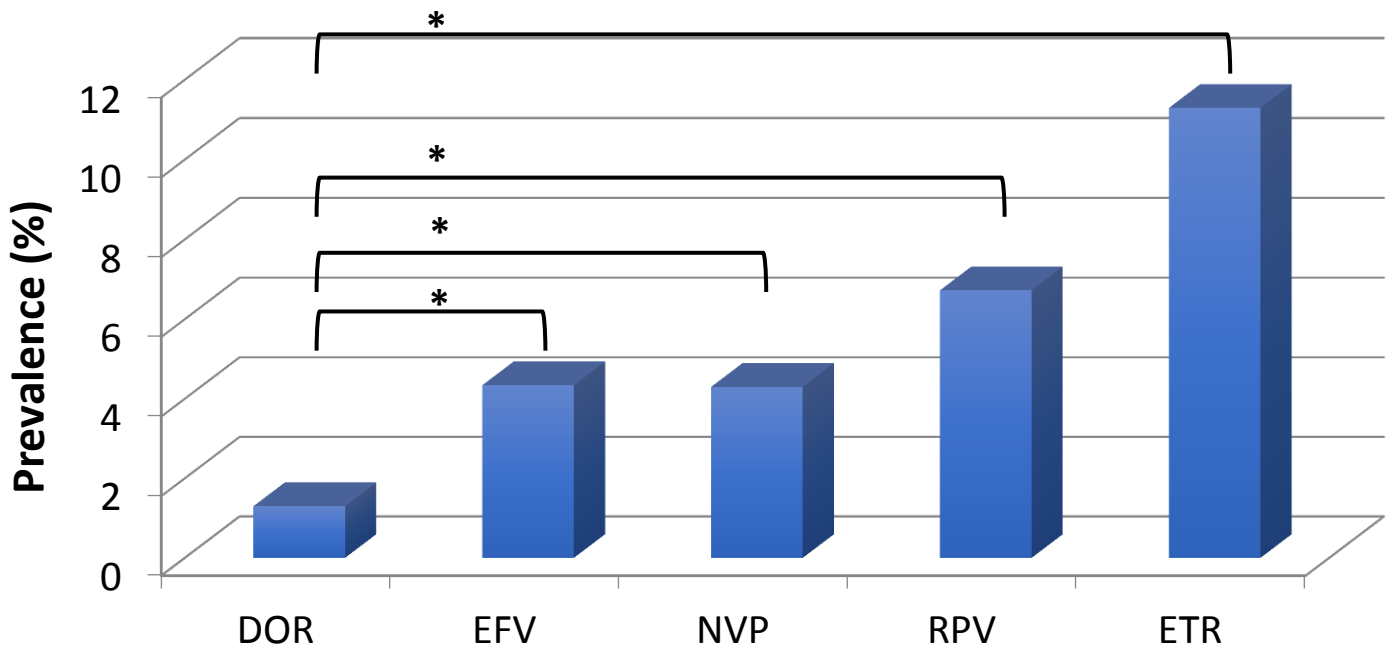
- A total of 7004 sequences were analyzed
  - 3355 were performed between 2010-2012 and 3649 between 2013-2016.
- The distribution of subtypes was: 53.7% B and 46.3% non B



  - 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)

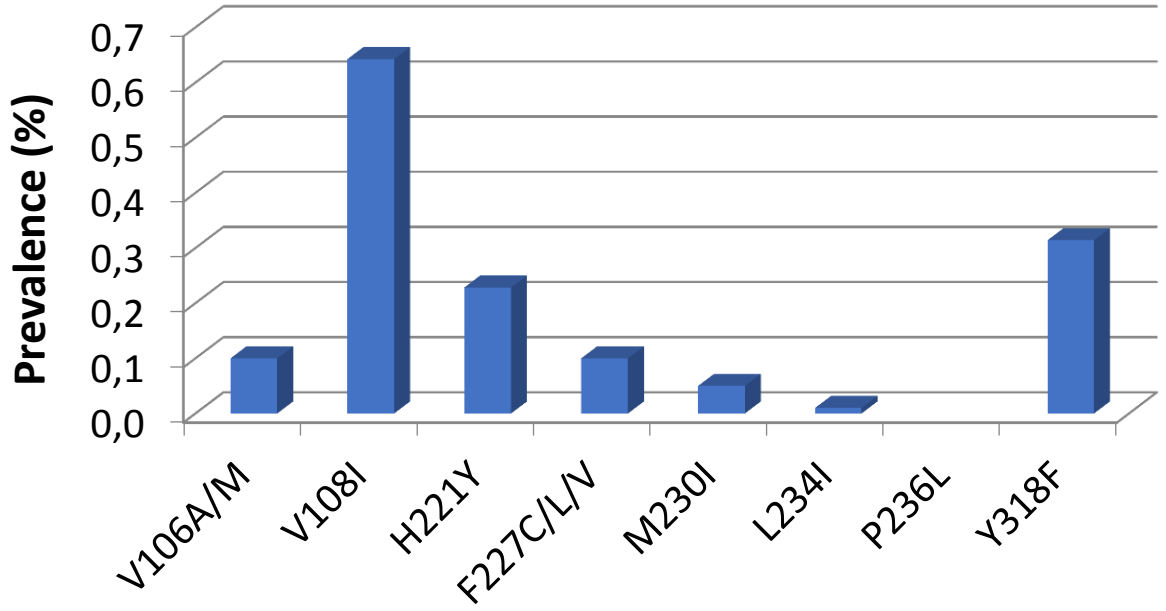
- The overall prevalence of sequences with at least 1 DOR-associated mutation was 1.3% (n = 91).
  - This was significantly lower than the prevalence of sequences with at least 1 EFV-associated mutation (4.3%, n = 304) or with at least 1 RPV-associated mutation (6.7%, n = 472), ($p < 0.001$).



* : p < 0,001

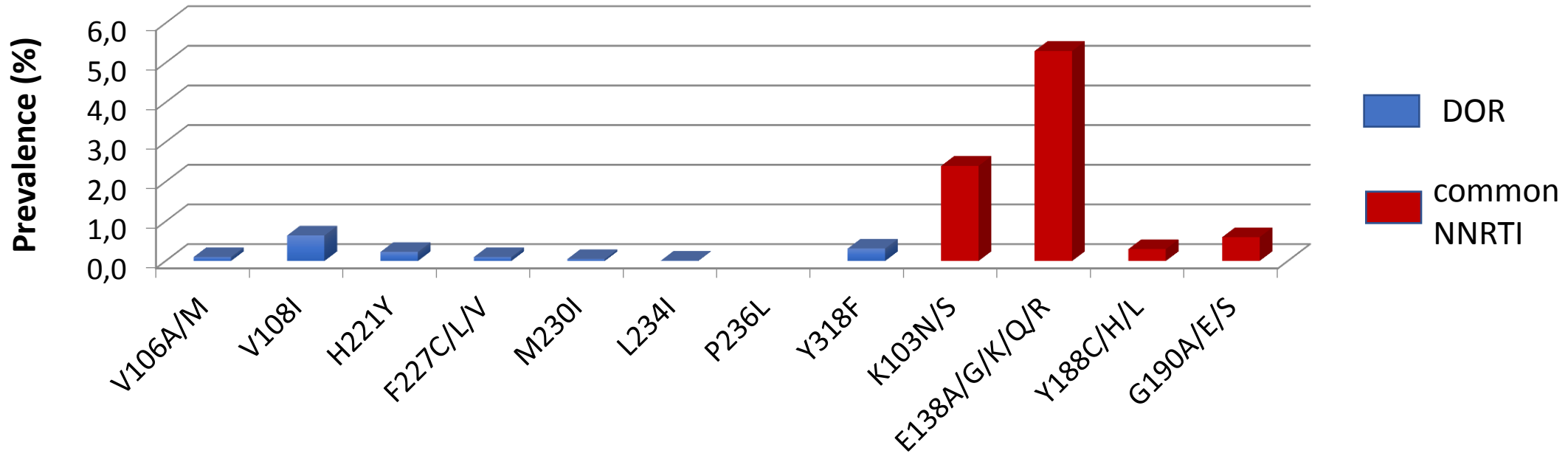
Results: DOR associated mutations (2)

- 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.



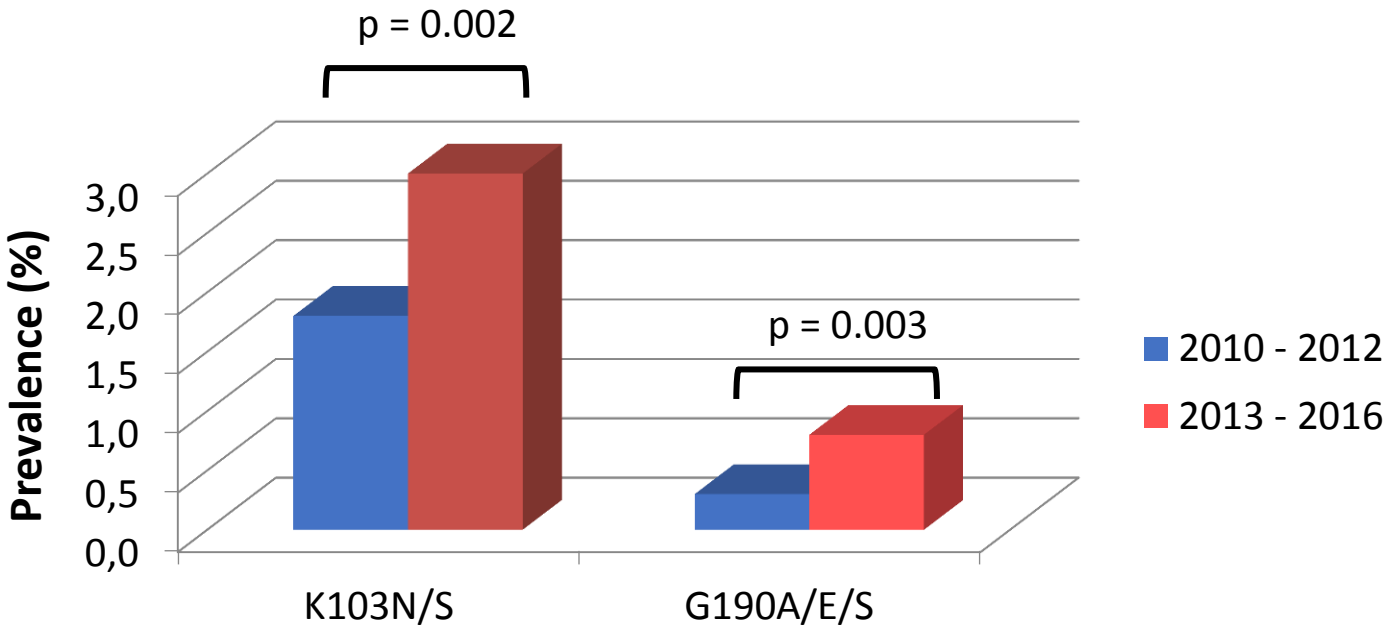
Results: other NNRTIs associated mutations (1)

- 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

	% resistant strains	% susceptible strains
DOR*	1.3	98.7
RPV**	7.7	92.3
EFV	4.0	96.0
NVP	8.3	91.7
ETR	7.0	93.0

* DOR-associated mutations list: V106A, V106M, V108I, H221Y, F227L, F227C, F227V, M230I, L234I, P236L, Y318F
** 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*

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