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

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**Background:** Doravirine (DOR) is a novel HIV-1 non-nucleoside reverse transcriptase (NNRTI) that is currently in clinical development. It has been recently shown that DOR in combination therapy has non-inferior efficacy to darunavir/r (800/100 mg) in treatment-naive patients. 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, Y181C and G190A. 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. The aim of this study was to examine the prevalence of DOR-associated mutations in HIV-1-infected treatment-naive patients in Europe.

**Materials & Methods:** Resistance genotypic tests were performed at five reference laboratories, 2 in Paris (Pitié-Salpêtrière and Bichat Claude Bernard hospitals) and 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-naive patients in routine clinical care were analyzed. DOR-associated mutations identified in vitro considered were: V106A, V106M, V108I, H221Y, F227L, F227C, F227V, M230I, L234I, P236L, Y318F.

**Results:** Among the 7004 sequences, 3355 were performed between 2010-2012 and 3649 between 2013-2016. The distribution of subtypes was: 53.7% B, 18% CRF02, 4.1% A1, 3.8% C, 3.3% F1 and 17% other various non-B. There was an increase of non-B subtypes between 2010-2012 and 2013-2016 (41% versus 48%, p < 0.001). 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). Among the DOR-associated mutations, the most frequent mutations were V106A/M 0.1% (7), V108I 0.6% (45), H221Y 0.2% (16), F227C/L/V 0.1% (7), M230I 0.05% (3), L234I 0.01% (1), P236L 0% and Y318F 0.3% (22). There was there no significant increase over time and no relationship with any HIV-1 subtype for any of these mutations. In comparison, the prevalences of common NNRTI mutations K103N/S, E138A/G/K/Q/R, Y188C/H/L and G190A/E/S were 2.4% (171), 5.3% (369), 0.3% (20) and 0.6% (41), respectively. 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).

**Conclusions:** These results suggest that the prevalence of DOR-associated mutations in HIV-1-infected treatment-naïve patients is very low and significantly lower than EFV or RPV-associated mutations. In addition, the prevalence of DOR-associated mutations in this population of patients was stable over time and there was no relationship between the presence of DOR-associated mutation and HIV-1 subtype.