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Rare occurrence of doravirine resistance-associated mutations in HIV-1-infected treatment-naive patients

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1 **Rare occurrence of doravirine resistance associated mutations in HIV-1-infected**
2 **treatment-naïve patients**

3
4 **Running title:** Primary doravirine HIV-1 resistance

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32 **Word count:** 1500.

33

34 **ABSTRACT**

35

36 **Background:** Doravirine is a novel HIV-1 NNRTIs recently shown to be non-inferior both to
37 darunavir/ritonavir and efavirenz in combination therapy with two nucleoside reverse
38 transcriptase inhibitor in treatment-naïve patients. Doravirine has an *in vitro* resistance profile
39 that is distinct from other NNRTIs and retains activity against viruses containing the most
40 frequently transmitted NNRTIs mutations. The aim of this study was to examine the
41 prevalence of doravirine associated mutations in HIV-1-infected treatment-naïve patients in
42 Europe.

43 **Patients and methods:** From 2010 to 2016, 9764 treatment-naïve patients were tested for
44 NNRTIs antiretroviral drug resistance by bulk sequencing in Greece, Italy and France. We
45 studied the prevalence of doravirine resistance associated mutations previously identified *in*
46 *vitro*: V106A/M, V108I, Y188L, V190S, H221Y, F227C/L/V, M230I/L, L234I, P236L,
47 Y318F and K103N/Y181C.

48 **Results:** Among 9764 sequences, 53.0% and 47.0% of patients had B and non-B subtypes,
49 respectively. Overall, the presence of at least one doravirine resistance associated mutation
50 (n=137; 1.4%) or the K103N/Y181C mutations (n=5; 0.05%) was very rare. The most
51 prevalent mutations were V108I (n=62; 0.6%), Y188L (n=18; 0.2%), H221Y (n=18; 0.2%)
52 and Y318F (n=23; 0.2%). The frequency of doravirine resistance mutations was similar
53 between B and non-B subtypes. In comparison, the prevalence of rilpivirine, etravirine,
54 nevirapine and efavirenz resistance was higher whatever the used algorithm (ANRS: 8.5%,
55 8.1%, 8.3% and 3.9%; Stanford: 9.9%, 10.0%, 7.5%, and 9.4%, respectively).

56 **Conclusions:** The prevalence of doravirine resistance mutations is very low in antiretroviral-
57 naïve patients. These results are very reassuring for doravirine use in naïve patients.

58 **INTRODUCTION**

59

60 Intensive scale-up of antiretrovirals worldwide has led to a dramatic decrease in HIV-1 related
61 morbidity and mortality. Despite this success, the expansion of treatment has been
62 accompanied by a significant increase in the prevalence of acquired and transmitted HIV drug
63 resistance (TDR), mostly driven by NNRTIs.¹

64 Doravirine is a novel HIV-1 NNRTI in phase III clinical development with *in vitro* resistance
65 profile that is distinct from other NNRTIs, retaining activity against viruses containing the
66 most frequently transmitted NNRTIs mutations, such as K103N, E138K, Y181C and G190A.

67 ² Doravirine selects for distinct mutations *in vitro*, including mutations at positions 106, 108,
68 227 and 234 with multiple mutations required for significant levels of resistance.³ Only few
69 single mutations were associated with >10-fold reduced susceptibility to doravirine, including
70 V106A, Y188L and M230L.⁴ Furthermore, the double and triple mutants V106A/F227L,
71 V106/L234I, V106A/F227L/L234I or V106A/G190A/F227L all showed substantial resistance
72 to doravirine.³⁻⁵

73 Recent phase III trials showed that doravirine has non-inferior efficacy when compared to
74 darunavir/r (800/100 mg) or efavirenz in combination with 2 NRTIs in treatment-naïve
75 patients.^{6,7} Data on the occurrence of doravirine-associated mutations in treatment-naïve
76 patients is crucial to inform the further provision of treatment.

77 The aim of this study was to examine the prevalence of doravirine-associated mutations in
78 HIV-1-infected treatment-naïve patients in Europe over time across various subtypes and to
79 compare this prevalence to those known for currently available NNRTIs.

80

81 MATERIALS AND METHODS

82

83 All bulk HIV resistance genotypes performed for routine clinical routine for drug-naïve HIV
84 patients care performed between 2010 and 2016 were retrieved at 6 reference laboratories: 2
85 in France (Pitié-Salpêtrière and Bichat Claude Bernard hospitals, n=2941), 3 in Italy
86 (University of Rome “Tor Vergata”, INMI Spallanzani-IRCCS, Modena Hospital, n=4063)
87 and 1 in Greece (Department of Hygiene Epidemiology and Medical Statistics, Medical
88 School, National and Kapodistrian University of Athens, n=1230). In addition, sequences data
89 from drug-naïve patients were provided by a number of centers included in the ARCA
90 database (www.dbarca.net, n=1530) in Italy. Doravirine-associated mutations identified *in*
91 *vitro* and used to define doravirine resistance in this study were: V106A/M, V108I, Y188L,
92 V190S, H221Y, F227C/L/V, M230I/L, L234I, P236L, Y318F and K103N/Y181C.²⁻⁵ HIV-1
93 with at least one of these mutations was considered as resistant to doravirine.

94 NRTIs (zidovudine, emtricitabine/lamivudine, abacavir, tenofovir) and NNRTIs (efavirenz,
95 rilpivirine, nevirapine and etravirine) mutations associated with resistance were those listed in
96 the ANRS algorithm (table of rules 2017; www.hivfrenchresistance.org), in the IAS list 2017
97 (www.iasusa.org) and in the Stanford HIV drug resistance database (HIVdbversion 8.5;
98 <https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/>).

99 Resistance interpretation was made using the Smartgene® Integrated Database Network
100 System (SmartGene, Switzerland; <http://www.smartgene.com>) according to the Stanford
101 University (<https://hivdb.stanford.edu>) or the ANRS Algorithm
102 (<http://www.hivfrenchresistance.org>).

103 HIV-1 subtype was determined on the basis of the reverse transcriptase (RT) and protease
104 coding regions by Smartgene algorithm (Smartgene®, Switzerland) or by phylogenetic

105 analyses, using reference sequences of HIV-1 subtypes and circulating recombinant forms
106 (CRF) from the Los Alamos Database
107 (<https://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html>). Between-group
108 comparisons were carried out with Fisher's exact test using the BiostatTGV web site
109 (<https://biostatgv.sentiweb.fr/?module=tests>).

110

111 RESULTS

112

113 Distribution of HIV-1 subtypes in antiretroviral-naïve patients

114 A total a 9764 RT sequences obtained between 2010 and 2016 for HIV-1 treatment-naïve
115 patients in routine clinical care were analyzed (2010-2012: n=4939; 2013-2016: n=4825). The
116 distribution of subtypes was: 53.0% B subtypes and 47.0% non-B subtypes. Subtypes with
117 prevalence higher than 3.0% included CRF02_AG (14.6%), A (6.3%), C (3.3%) and F
118 (3.2%). There was a significant increase of non-B subtypes in 2013-2016 with respect to
119 2010-2012 (49.4% versus 42.7%, respectively, $p < 0.001$).

120

121 Prevalence of doravirine resistance associated mutations

122 The overall prevalence of sequences with at least 1 doravirine resistance-associated mutation
123 was 1.4% (n = 137). The number of sequences with 1, 2, 3 and 4 doravirine resistance-
124 associated mutations was 127 (1.3%), 8 (0.1%), 1 (0.01%) and 1 (0.01%), respectively. The
125 presence of the double mutant K103N/Y181C was 0.05% (n=5). This prevalence was
126 significantly lower than the prevalence of sequences with at least 1 resistance-associated

127 mutations for other NNRTIs: efavirenz (4.3%, n = 421), nevirapine (4.3%, n = 421),
128 rilpivirine (7.7%, n=755) or etravirine (11.7%, n = 1143) ($p < 0.001$) (Figure 1).

129 Among the doravirine resistance-associated mutations, the most frequent mutations were
130 V108I (0.6%; n=62), Y188L (0.2%; n=18), H221Y (0.2%; n=18) and Y318F (0.2%; n=23)
131 (Figure 2). The other doravirine resistance-associated mutations were very rare: V106A/M
132 (0.1%; n=8), G190S (0.1%; n=5), F227C/L/V (0.1%; n=12), M230I/L (0.04%; n=4), L234I
133 (0.01%; (n=1), P236L (0.03%; n=3), K103N/Y181C (0.05%, n=5). In comparison, the
134 prevalence of common NNRTIs mutations were K103N/S (2.1%; n=208), E138A/G/K/Q/R
135 (6.5%; n=637), Y188C/H/L (0.2%; n=22) and G190A/E/S (0.5%; n=51) (Figure 2). Between
136 2010-2012 and 2013-2016, there was only a significant increase for K103N/S (2.0% versus
137 3.0%, $p = 0.003$) and in G190A/E/S (0.3% versus 0.7%, $p = 0.003$).

138

139 **Interpretation of resistance to doravirine, NRTIs and other NNRTIs**

140 The presence of at least one doravirine-associated mutation was interpreted as resistance to
141 doravirine, thus 1.4% (n=142) of sequences were considered resistant to doravirine in
142 comparison with 8.5% (n=833) to rilpivirine, 8.1% (n=788) to etravirine, 8.3% (n=809) to
143 nevirapine and 3.9% (n=348) to efavirenz according to the 2017 ANRS algorithm. Then,
144 0.8%, 0.5%, 0.9%, 0.9%, of the sequences were both resistant to doravirine and rilpivirine or
145 etravirine or nevirapine or efavirenz, respectively. The results were slightly different
146 according to the Stanford algorithm: 9.9% (n=967) for rilpivirine, 10.0% (n=979) for
147 etravirine, 7.5% (n=730) for nevirapine and 9.4% (n=828) for efavirenz, and 1.0%, 1.0%,
148 0.6% and 0.6% of the sequences both resistant to doravirine and efavirenz or nevirapine or
149 etravirine or rilpivirine, respectively.

150 For NRTIs, 3.5%, 1.6%, 1.0% and 0.2% of sequences were resistant to zidovudine,
151 lamivudine/emtricitabine, abacavir and tenofovir with both resistance algorithms,
152 respectively. Few samples were considered resistant to doravirine and also to zidovudine or
153 lamivudine/emtricitabine or abacavir or tenofovir in 0.4%, 0.4%, 0.09% and 0.02% of cases,
154 respectively.

155

156 **NNRTI resistance according to the subtype**

157 There was no relationship between subtypes and the presence of doravirine-associated
158 mutations (1.6% and 1.3% in B versus non-B subtypes, respectively; $p=0.168$). In contrast,
159 according to both ANRS and Stanford algorithms, the prevalence of resistance was
160 statistically higher for B than non-B subtypes for nevirapine (11.2% versus 5.12%, $p<0.001$
161 and 8.0% versus 6.8%, $p=0.025$, respectively) and rilpivirine (9.3% versus 7.7%, $p=0.006$ and
162 10.7% versus 8.9%, $p=0.003$, respectively). The resistance to etravirine was also statistically
163 higher for B subtype only with the Stanford algorithm (10.9% versus 9.0%, $p=0.002$).

164

165 **DISCUSSION**

166 This is the first study showing that the prevalence of doravirine resistance-associated
167 mutations in HIV-1-infected treatment-naïve patients is very low in a large European
168 database, significantly lower than other NNRTIs resistance-associated mutations,
169 antiretrovirals potentially recommended as first line regimen.⁸⁻¹⁰ This occurrence was stable
170 over time and not related to any HIV-1 subtype.

171 The proportion of non-B subtypes was higher in our study (47.0%) compared to the
172 continuous HIV drug resistance surveillance program (SPREAD) taking place in 27 countries

173 in Europe from 2002 to 2007 (32.7%), or to the last studies in France or in Italy (30.8%).¹¹⁻¹³
174 However, this higher prevalence of non-B subtypes is consistent with their continuous
175 increase in Europe or their high prevalence observed recently in Greece.¹³⁻¹⁵ Thus, our study
176 provides a representative view of HIV subtypes circulating in Western Europe and shows that
177 resistance to NNRTIs was higher for B than non-B subtypes, except for doravirine.

178 In *in vitro* studies, the resistance mutations associated to doravirine with the highest fold
179 change were V106A, Y188L and M230L.⁴ In the DRIVE-FORWARD clinical study,
180 resistance to doravirine emerged in one participant as a multiple mutant (V106I, H221Y and
181 F227C) in the context of non-compliance.⁶ In DRIVE-AHEAD, in the doravirine group, the
182 NNRTI mutations were for 1.6% of patients.⁷ In our study, the prevalence of these resistance
183 mutations was very low (<0.2%) and the double or triple HIV mutants showing the highest
184 level of *in vitro* resistance were virtually absent (<0.001%).³⁻⁵

185 Overall, our results showed that primary resistance is currently less frequent for doravirine
186 than for other second generation NNRTIs such as etravirine and rilpivirine. This difference
187 could be explained by some resistance mutations associated to etravirine or rilpivirine, like
188 V90I, A98G, V106I, V179D/F/T and especially E138A, which are not included in the
189 doravirine resistance-associated mutations list. For example, E138A was present in 4.2% of
190 the sequences in this study. Similarly, the prevalence of the E138A polymorphic substitution
191 which can decrease rilpivirine susceptibility was 3.2% (95% CI 1.9%–4.6%) in 2010/11 in
192 antiretroviral naïve chronically HIV-1 infected patients in France.¹⁶ One limitation of this
193 study is its descriptive aspect. It should be interesting to further study the impact of these
194 studied resistance mutations on doravirine phenotypic susceptibility to and also virological
195 response.

196 These results are very reassuring in the perspective of the use of doravirine in naïve patients
197 since doravirine remains active against the commonly transmitted efavirenz and rilpivirine

198 mutations *in vitro*. However, the role of doravirine *in vivo* remains to be confirmed through
199 clinical observations, particularly because patients harboring NNRTI-resistant virus were
200 deliberately excluded from clinical trials completed so far.

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202

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210

211

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217

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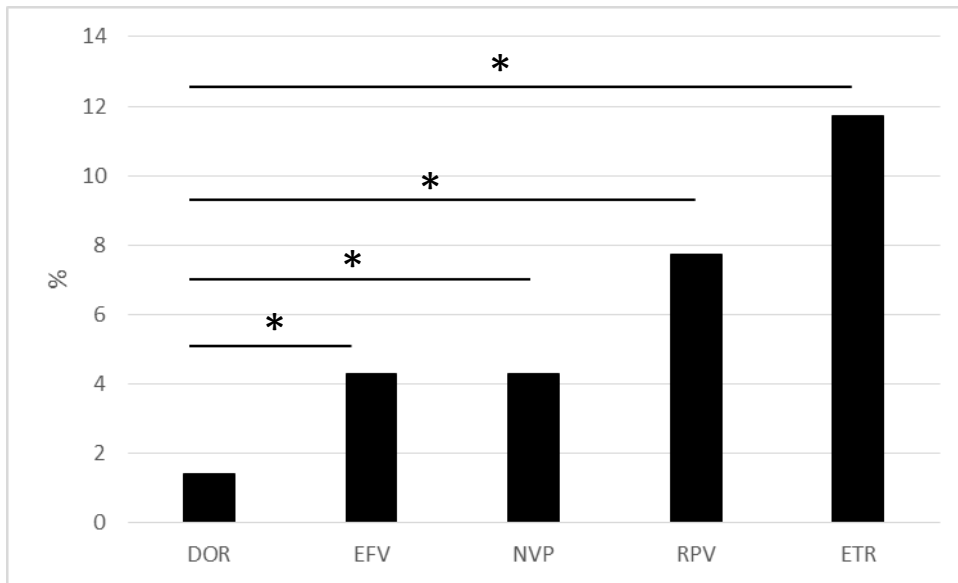
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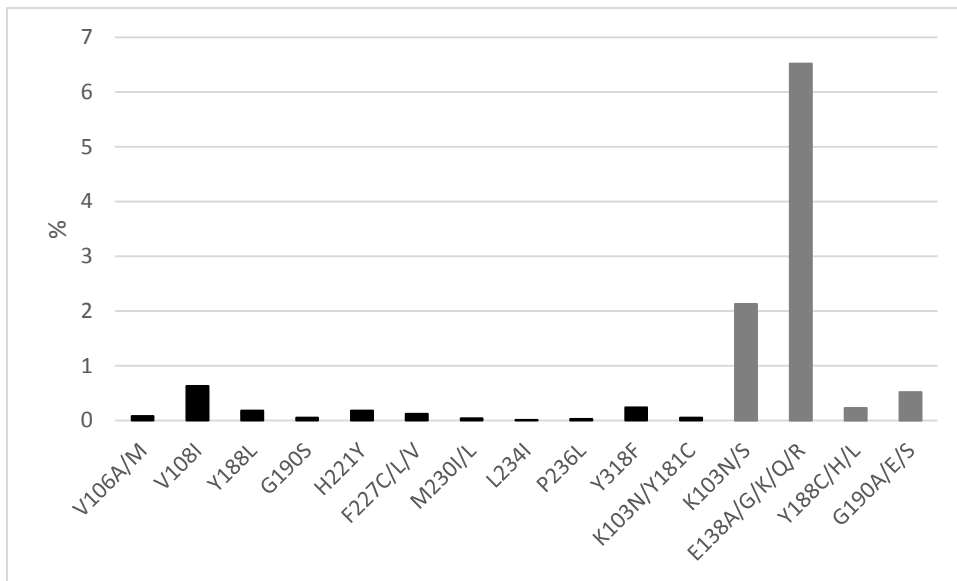
285 Figure 1: Percent of Reverse Transcriptase sequences with at least one resistance mutation to
286 NNRTI

287 Doravirine (DOR), Efavirenz (EFV), Rilpivirine (RPV), Nevirapine (NVP) and Etravirine
288 (ETR).

289 * : $p < 0.0001$

290

291



292

293

294 Figure 2: Prevalence of Reverse Transcriptase sequences with at least one individual resistance
 295 mutation to Doravirine or other NNRTI

296 In black: mutations associated with resistance to doravirine, in grey: mutations associated to other
 297 NNRTIs

298