



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

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

5  
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29

30

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32 **Word count:** 1707.

33 **Keywords:** primary resistance, non-nucleoside reverse transcriptase inhibitors, doravirine.

34

35 **ABSTRACT**

36

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

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

49 **Results:** Among 9764 sequences, 52.99% and 47.01% of patients had B and non-B subtypes,  
50 respectively. Overall, the presence of at least one doravirine resistance associated mutation  
51 (n=137; 1.40%) or the K103N/Y181C mutations (n=5; 0.05%) was very rare. The most  
52 prevalent mutations were V108I (n=62; 0.63%), Y188L (n=18; 0.18%), H221Y (n=18;  
53 0.18%) and Y318F (n=23; 0.24%). The frequency of doravirine resistance mutations was  
54 similar between B and non-B subtypes. In comparison, the prevalence of rilpivirine,  
55 etravirine, nevirapine and efavirenz resistance was higher whatever the used algorithm  
56 (ANRS: 8.53%, 8.07%, 8.28% and 3.90%; Stanford: 9.90%, 10.02%, 7.47%, and 9.44%,  
57 respectively).

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

Confidential: for peer review only

## 60 INTRODUCTION

61

62 Intensive scale-up of antiretrovirals worldwide has led to a dramatic decrease in HIV-1 related  
63 morbidity and mortality. Despite this success, the expansion of treatment has been  
64 accompanied by a significant increase in the prevalence of both acquired and transmitted HIV  
65 drug resistance (TDR). TDR may impact response to therapy, leading to virologic failure and  
66 the evolution of further drug resistance. The increasing prevalence of TDR has been mostly  
67 driven by non-nucleoside reverse transcriptase inhibitors (NNRTIs), particularly in sub-  
68 Saharan Africa as a result of the extensive use of efavirenz and nevirapine. [1]

69 Doravirine is a novel HIV-1 NNRTI in phase III clinical development. Doravirine has an *in*  
70 *vitro* resistance profile that is distinct from other NNRTIs, retaining activity against viruses  
71 containing the most frequently transmitted NNRTIs mutations, such as K103N, E138K,  
72 Y181C and G190A [2]. Doravirine selects for distinct mutations *in vitro*, including mutations  
73 at positions 106, 108, 227 and 234 with multiple mutations required for significant levels of  
74 resistance [3]. Some studies characterized the *in vitro* phenotypic susceptibility of NNRTI-  
75 associated mutant viruses to doravirine. Only few single mutations were associated with >10-  
76 fold reduced susceptibility to doravirine, including V106A, Y188L and M230L. [4]  
77 Furthermore, the double and triple mutants V106A/F227L, V106/L234I,  
78 V106A/F227L/L234I or V106A/G190A/F227L all showed substantial resistance to  
79 doravirine. [3–5]

80 Recent phase III trials showed that doravirine has non-inferior efficacy when compared to  
81 darunavir/r (800/100 mg) or to efavirenz in combination with 2 NRTIs (tenofovir and  
82 emtricitabine or abacavir and lamivudine) in treatment-naïve patients. [6,7] Data on the

83 occurrence of doravirine-associated mutations in treatment-naïve patients is crucial to inform  
84 the further provision of treatment.

85 The aim of this study was to examine the prevalence of doravirine-associated mutations in  
86 HIV-1-infected treatment-naïve patients in Europe over time (2010-2016) across various  
87 subtypes and to compare this prevalence to those known for currently available NNRTIs:  
88 efavirenz, rilpivirine, nevirapine and etravirine.

89

## 90 MATERIALS AND METHODS

91

92 Bulk resistance genotypic tests were performed between 2010 and 2016 at 6 reference  
93 laboratories: 2 in Paris, France (Pitié-Salpêtrière and Bichat Claude Bernard hospitals), 3 in  
94 Italy (University of Rome “Tor Vergata”, INMI Spallanzani-IRCCS, Modena Hospital) and 1  
95 in Greece (Department of Hygiene Epidemiology and Medical Statistics, Medical School,  
96 National and Kapodistrian University of Athens, Athens, Greece). In addition, HIV-1 RT  
97 sequence data from drug-naïve patients were provided by a number of centers included in the  
98 ARCA database ([www.dbarca.net](http://www.dbarca.net)) in Italy without overlap with the above mentioned  
99 reference laboratories. Doravirine-associated mutations identified *in vitro* and used to define  
100 doravirine resistance in this study were: V106A/M, V108I, Y188L, V190S, H221Y,  
101 F227C/L/V, M230I/L, L234I, P236L, Y318F and K103N/Y181C. [2–5] HIV-1 with at least  
102 one of these mutations was considered as resistant.

103 NNRTIs mutations associated with resistance to efavirenz, rilpivirine, nevirapine and  
104 etravirine were those listed in the ANRS algorithm (table of rules 2017;  
105 [www.hivfrenchresistance.org](http://www.hivfrenchresistance.org)), in the IAS list 2017 ([www.iasusa.org](http://www.iasusa.org)) and in the Stanford HIV  
106 drug resistance database (HIVdbversion 8.5; [Journal of Antimicrobial Chemotherapy: under review](https://hivdb.stanford.edu/dr-</a></p></div><div data-bbox=)



107 [summary/resistance-notes/NNRTI/](#). Namely, efavirenz: L100I, K101E/P, K103N/S,  
108 V106A/M, V108I, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, M230L; etravirine: V90I,  
109 A98G, L100I, K101E/H/P, V106I, E138A/G/K/Q, V179D/F/T, Y181C/I/V, G190A/E/S,  
110 M230L; nevirapine: L100I, K101E/P, K103N/S, V106A/M, V108I, Y181C/I/V, Y188C/H/L,  
111 G190A/E/S, M230L; rilpivirine: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V,  
112 Y188L, G190A/E/S, H221Y, F227C, M230I/L.

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

117 Subtype was determined on the basis of the reverse transcriptase (RT) and protease coding  
118 regions by Smartgene algorithm (Smartgene®, Switzerland) or by phylogenetic analyses,  
119 using reference sequences of HIV-1 subtypes and circulating recombinant forms (CRF) from  
120 the Los Alamos Database (<https://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html>).

121 Between-group comparisons were carried out using Fisher's exact test.

122

## 123 RESULTS

124

### 125 Distribution of HIV-1 subtypes in antiretroviral-naïve patients

126 A total a 9764 reverse transcriptase sequences obtained between 2010 and 2016 for HIV-1  
127 treatment-naïve patients in routine clinical care were analyzed: 4939 were performed between  
128 2010-2012 and 4825 between 2013 and 2016. The distribution of subtypes was: 52.99% B  
129 subtypes and 47.01% non-B subtypes. Subtypes with prevalence higher than 3.00% included

130 CRF02\_AG (14.62%), A (6.28%), C (3.35%) and F (3.19%). There was a significant increase  
131 of non-B subtypes in 2013-2016 with respect to 2010-2012 (49.43% vs. 42.68%, respectively,  
132  $p < 0.001$ ).

133

#### 134 **Prevalence of doravirine resistance associated mutations**

135 The overall prevalence of sequences with at least 1 doravirine resistance associated mutation  
136 was 1.40% (n = 137). The number of sequences with 1, 2, 3 and 4 doravirine resistance  
137 associated mutations was 127 (1.30%), 8 (0.08%), 1 (0.01%) and 1 (0.01%), respectively. The  
138 presence of the double mutant K103N/Y181C was 0.05% (n=5). This overall prevalence was  
139 significantly lower than the prevalence of sequences with at least 1 resistance associated  
140 mutations for other NNRTIs: efavirenz (4.31%, n = 421), nevirapine (4.31%, n = 421),  
141 rilpivirine (7.73%, n=755) or etravirine (11.72%, n = 1143) ( $p < 0.001$ ) (Figure 1).

142 Among the doravirine resistance associated mutations, the most frequent mutations were  
143 V108I (0.63%; n=62), Y188L (0.18%; n=18), H221Y (0.18%; n=18) and Y318F (0.24%;  
144 n=23) (Figure 2). The other doravirine resistance associated mutations were very rare:  
145 V106A/M (0.08%; n=8), G190S (0.05%; n=5), F227C/L/V (0.12%; n=12), M230I/L (0.04%;  
146 n=4), L234I (0.01%; (n=1), P236L (0.03%; n=3), K103N/Y181C (0.05%, n=5). In  
147 comparison, the prevalence of common NNRTIs mutations were K103N/S (2.13%; n=208),  
148 E138A/G/K/Q/R (6.52%; n=637), Y188C/H/L (0.23%; n=22) and G190A/E/S (0.52%; n=51)  
149 (Figure 2). Between 2010-2012 and 2013-2016, there was only a significant increase for  
150 K103N/S (2.04% versus 2.98%,  $p = 0.003$ ) and in G190A/E/S (0.32% versus 0.77%,  $p =$   
151 0.003).

152

#### 153 **Resistance**

154 As one mutation was considered as resistance to doravirine, 1.45% (n=142) of samples were  
155 resistant to doravirine in comparison with 8.53% (n=833) to rilpivirine, 8.07% (n=788) to  
156 etravirine, 8.28% (n=809) to nevirapine and 3.90% (n=348) to efavirenz according to the  
157 2017 ANRS algorithm. These results were slightly different according to the Stanford  
158 algorithm: 9.90% (n=967) for rilpivirine, 10.02% (n=979) for etravirine, 7.47% (n=730) for  
159 nevirapine and 9.44% (n=828) for efavirenz.

160 There was no relationship between any subtypes and the presence of any doravirine associated  
161 mutations. Indeed, the overall prevalence of sequences with at least 1 doravirine resistance  
162 associated mutation and considered as resistant variants was 1.59% (n=84) and 1.29% (n=58)  
163 in B versus non-B subtypes, respectively ( $p=0.168$ ). In contrast, according to both ANRS and  
164 Stanford algorithms, the prevalence of resistance was statistically higher for B than non-B  
165 subtypes for nevirapine and rilpivirine (table 1). The resistance to etravirine was also  
166 statistically higher for B subtypes only with the Stanford algorithm (table 1).

167

## 168 **DISCUSSION**

169

170 This is the first study evaluating the prevalence of doravirine resistance associated mutations  
171 in a large European database of antiretroviral-naïve HIV-1-infected patients. These results  
172 showed that the prevalence of doravirine resistance associated mutations in HIV-1-infected  
173 treatment-naïve patients in Greece, Italy and France is very low, significantly lower than other  
174 NNRTIs resistance associated mutations, antiretrovirals potentially recommended as first line  
175 regimen. [8–10] This occurrence was stable over time and not related to any HIV-1 subtype.

176 The proportion of non-B subtypes was higher in our study (47.01%) compared to the  
177 continuous HIV drug resistance surveillance program (SPREAD) taking place in 27 countries

178 in Europe from 2002 to 2007 (32.66%), or to the last study in France among 1318 French  
179 patients diagnosed at the time of primary HIV-1 infection in 2007–2012 (33.70%) or in Italy  
180 in 4323 drug naïve individuals between 2010 and 2014 (30.80%). [11–13] However, this  
181 higher prevalence of non B subtypes is consistent with the continuous increase of the non-B  
182 subtypes in Europe or the high prevalence of non-B subtypes observed recently in Greece.  
183 [13–15] Thus, our study provides a representative view of HIV subtypes circulating in  
184 Western Europe.

185 The resistance to NNRTIs was higher for B than non B subtypes in this study, except for  
186 doravirine resistance which was not impacted by HIV subtypes. It is according to several  
187 studies showing that transmitted drug resistance was higher in HIV-1 subtype B infected men  
188 having sex with men in primary infection or in chronically antiretroviral naïve HIV-1 infected  
189 patients in France, as well as in previous European report. [12,16]

190 In *in vitro* studies, the HIV resistance mutations associated to doravirine with the highest fold  
191 change were V106A, Y188L and M230L. [4] In the DRIVE-FORWARD clinical study,  
192 resistance to doravirine emerged in one participant as a multiple mutant (V106I, H221Y and  
193 F227C) in the context of non-compliance. [6] In DRIVE-AHEAD, in the doravirine group,  
194 the NNRTI mutations were for 1.6% of patients: Y188L; V106I, F227C; V106V/I, H221H/Y,  
195 F227C; F227C; V106A, P225H, Y318Y/F; V106M/T, F227C/R. [7] In our study, the  
196 prevalence of these resistance mutations was very low (<0.2%) and the double or triple HIV  
197 mutants showing the highest level of *in vitro* resistance were virtually absent (<0.001%). [3–  
198 5]

199 Overall, our results showed that primary resistance is currently less frequent for doravirine  
200 than for other second generation NNRTIs such as etravirine and rilpivirine. This difference  
201 could be explained by some resistance mutations associated to etravirine or rilpivirine, like  
202 V90I, A98G, V106I, V179D/F/T and especially E138A, which are not included in the

203 doravirine resistance associated mutation list. For example, E138A was present in 4.2% of  
204 sequences in this study. Similarly, the prevalence of the E138A polymorphic substitution  
205 which can decrease rilpivirine susceptibility was 3.2% (95% CI 1.9%–4.6%) in 2010/11 in  
206 antiretroviral naïve chronically HIV-1 infected patients in France. [16] One limitation of this  
207 study is its descriptive aspect. It should be interesting to further study the impact of these  
208 studied resistance mutations to doravirine virological response.

209 According to Lambert-Niclot's analysis using both the IAS and ANRS lists, 5% of the  
210 samples from treatment-naïve patients had primary rilpivirine resistance associated mutations  
211 from 2008 to 2011. [17] Notably, the prevalence of primary resistance to rilpivirine increased  
212 over time since it nearly doubled during our study (8.53%). As the doravirine resistance  
213 mutations were different from the other NNRTIs, we can expect no or low impact of the  
214 prevalence increase of resistance mutations for the other NNRTIs, in the context of  
215 transmitted drug resistance.

216 These results are very reassuring in the perspective of the use of doravirine in naïve patients  
217 since doravirine remains active against the commonly transmitted efavirenz and rilpivirine  
218 mutations *in vitro*. However, the role of doravirine *in vivo* remains to be confirmed through  
219 clinical observation, particularly because patients harboring NNRTI-resistant virus were  
220 deliberately excluded from clinical trials completed so far.

221

222

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234

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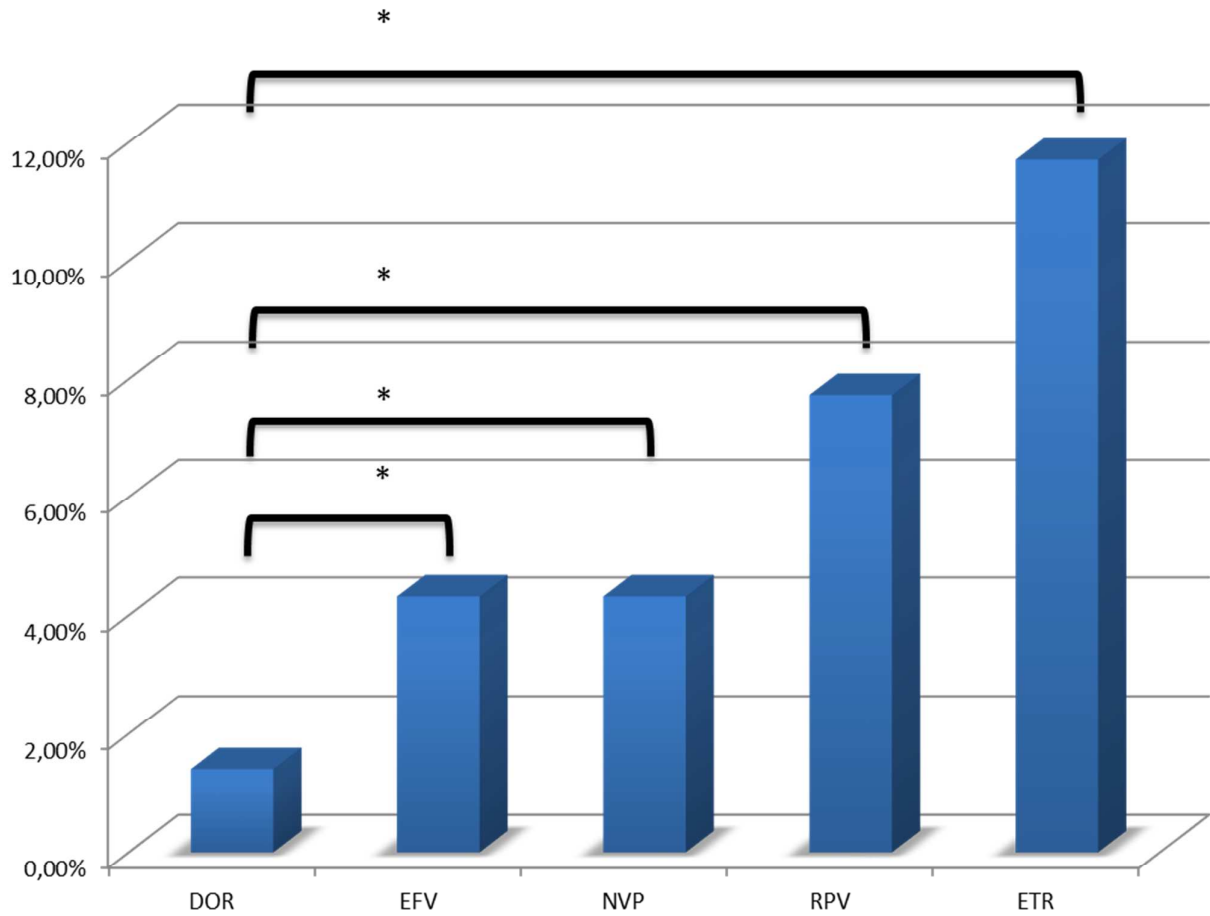


Figure 1: Percent of Reverse Transcriptase sequences with at least one resistance mutation to NNRTI Doravirine (DOR), Efavirenz (EFV), Rilpivirine (RPV), Nevirapine (NVP) and Etravirine (ETR).

\* :  $p < 0.0001$

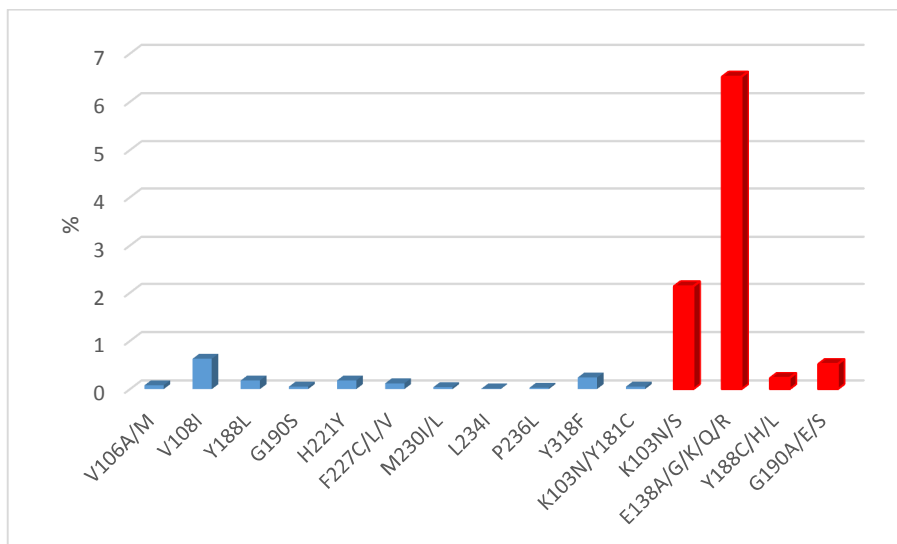


Figure 2: Prevalence of Reverse Transcriptase sequences with at least one resistance mutation to Doravirine or other NNRTI

In blue: mutations associated with resistance to doravirine, in red: mutations associated to other NNRTIs

	ANRS algorithm			Stanford algorithm		
	B	Non-B		B	Non-B	
Efavirenz, n (%)	212 (4.02)	136 (3.72)	P=0.500	485 (9.73)	343 (9.08)	P=0.320
Nevirapine, n (%)	590 (11.19)	219 (5.12)	P<0.001	423 (8.02)	307 (6.83)	P=0.025
Etravirine, n (%)	443 (8.40)	345 (7.68)	P=0.190	574 (10.88)	405 (9.01)	P=0.002
Rilpivirine, n (%)	488 (9.26)	345 (7.68)	P=0.006	565 (10.71)	402 (8.94)	P=0.003

Table 1: HIV resistant variants according to the B and non-B subtypes.