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1 **Prevalence of Doravirine associated resistance mutations in HIV-1-infected antiretroviral-**
2 **experienced patients from two large databases in France and Italy**

3

4 **Running title:** Doravirine resistance in HIV-1 treated patients

5

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29 **ABSTRACT**

30

31 **Objectives:** Doravirine, a novel NNRTI, selects for specific mutations *in vitro*, including
32 mutations at reverse transcriptase (RT) positions 106, 108, 188, 227, 230 and 234. The aim of
33 this study was to examine the prevalence of doravirine-associated resistance mutations in
34 HIV-1-infected antiretroviral-experienced patients.

35 **Methods:** Doravirine-associated resistance mutations identified *in vitro* or *in vivo* were
36 studied in a set of 9199 HIV-1 RT sequences from HIV-1 antiretroviral-experienced patients,
37 including 381 NNRTI-failing patients in France and Italy between 2012 and 2017. The following
38 mutations were considered as resistance mutations: V106A/M, V108I, Y188L, G190S,
39 F227C/L/V, M230I/L, L234I, P236L, K103N+Y181C, K103N+P225H, K103N+L100I.

40 **Results:** The frequencies of doravirine-associated resistance mutations (total set versus
41 NNRTI-failing patients) were V106A/M (0.8% versus 2.6%), V108I (3.3% versus 9.2%), Y188L
42 (1.2% versus 2.6%), G190S (0.3% versus 2.1%), F227C/L/V (0.5% versus 1.8%), M230I/L (2.8%
43 versus 0%), L234I (0.1% versus 0.5%), K103N+Y181C (3.9% versus 3.9%), K103N+P225H (2.9%
44 versus 4.7%) and K103N+100I (1.7% versus 3.9%) with a significant higher proportion of these
45 mutations in the NNRTI-failing group ($p < 0.05$), except for M230I/L and K103N+Y181C. The
46 overall prevalence of sequences with at least 1 doravirine-associated resistance mutation was
47 12.2% and 34.9% in total set and NNRTI-failing patients ($p < 0.001$), respectively. In comparison,
48 the prevalence of common NNRTI mutations V90I, K101E/P, K103N/S, E138A/G/K/Q/R/S,
49 Y181C/I/V, G190A/E/S/Q were higher (8.9%, 7.9%, 28.6%, 12.6%, 14.2%, 8.9%, respectively).

50 **Conclusions:** These results suggest that doravirine resistance in antiretroviral-experienced
51 patients generally and specifically among NNRTI-failing patients is lower than resistance to
52 other NNRTIs currently used, confirming its distinguishing resistance pattern.

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56 INTRODUCTION

57 Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a major component of the
58 antiretroviral treatment for HIV patients, as they were the third recommended agent in the
59 WHO and European guidelines, and until recently in US guidelines.¹⁻³ First generation NNRTIs,
60 efavirenz and nevirapine, have a low-level genetic barrier to resistance and consequently the
61 prevalence of HIV-1 resistance to NNRTIs is the highest one of the several classes of
62 antiretrovirals, in HIV naïve as well in treated patients.⁴⁻⁶ Then, new NNRTIs drugs retaining
63 antiretroviral activity against viruses with K103N, E138K, Y181C and G190A, the most
64 prevalent NNRTI mutations, are needed.

65 Two large phase 3 studies have demonstrated the efficacy of doravirine, a new NNRTI, in a
66 population of naïve HIV patients in comparison to efavirenz (DRIVE-AHEAD) or boosted
67 darunavir (800/100) (DRIVE-FORWARD) in combination with two nucleoside reverse
68 transcriptase inhibitors (NRTIs).⁷⁻⁹ In the DRIVE-SHIFT trial, the switch to
69 doravirine/lamivudine/tenofovir disoproxil fumarate maintained virological suppression
70 through 48 weeks.¹⁰

71 The doravirine resistance profile is distinct from other NNRTIs with the *in vitro* selection of
72 mutations at reverse transcriptase (RT) positions 106, 108, 188, 227, 230, 234 and 236.¹¹⁻¹⁴
73 *In vivo*, the evidenced resistance mutation profiles were concordant: Y188L; V106I+F227C;
74 V106I/V+H221Y+F227C; F227C; V106A+P225H+Y318Y/F; V106T/M, F227C/R; Y318F/Y.⁷⁻⁹

75 We aimed to study the prevalence of doravirine-associated resistance mutations in HIV-1-
76 infected antiretroviral-experienced patients, and especially in NNRTI-failing patients to
77 investigate whether the previous NNRTI use could impair doravirine activity.

78

79 MATERIALS AND METHODS

80 Resistance genotypic tests were performed at five reference laboratories, 2 in Paris (Pitié-
81 Salpêtrière and Bichat Claude Bernard hospitals) and 3 in Italy (University/Polyclinic of Rome
82 “Tor Vergata”, INMI Spallanzani-IRCCS, and Modena Hospital). A total of 9199 HIV-1 RT
83 sequences obtained between 2012 and 2017 from HIV-1 antiretroviral-experienced patients
84 in routine clinical care were analysed. A follow-up of HIV viral load about 3 to 6 months; in
85 case of 2 consecutive viral loads > 50 copies/mL, a resistance genotypic testing was performed
86 on the second viral load. Among this set of sequences, 381 sequences were originated from
87 NNRTI-failing patients (efavirenz, n=189; etravirine, n=32; nevirapine, n=66; rilpivirine, n=94).
88 The following mutations identified *in vitro* or *in vivo* were considered as doravirine-associated
89 mutations: RT V106A/M, V108I, Y188L, F227C/L/V, M230I/L, L234I, P236L, K103N+P225H,
90 K103N+L100I. ^{8,11-14} K103N+Y181C and G190S were also considered in our analysis, as they
91 are known to confer resistance to other NNRTIs. NNRTIs mutations associated with resistance
92 to efavirenz, rilpivirine, nevirapine and etravirine were those listed in the ANRS algorithm
93 (table of rules 2018; www.hivfrenchresistance.org), in the IAS list 2018 (www.iasusa.org) and
94 in the Stanford HIV drug resistance database ([https://hivdb.stanford.edu/dr-
95 summary/resistance-notes/NNRTI/](https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/)). Namely, efavirenz: L100I, K101E/P, K103N/S, V106A/M,
96 V108I, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, M230L; etravirine: V90I, A98G, L100I,
97 K101E/H/P, V106I, E138A/G/K/Q, V179D/F/T, Y181C/I/V, G190A/E/S, M230L; nevirapine:
98 L100I, K101E/P, K103N/S, V106A/M, V108I, Y181C/I/V, Y188C/H/L, G190A/E/S, M230L;
99 rilpivirine: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, G190A/E/S, H221Y,
100 F227C, M230I/L.

101 Resistance interpretation was made using the Smartgene® Integrated Database Network
102 System (SmartGene, Switzerland; <http://www.smartgene.com>) according to the Stanford
103 (<https://hivdb.stanford.edu/>) and the ANRS (table of rules 2018;

104 www.hivfrenchresistance.org) algorithms. Resistance and possible resistance were grouped
105 as resistance.

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

110 comparisons were carried out using Fisher's exact test.

111

112

113 **RESULTS**

114

115 **Distribution of HIV-1 subtypes**

116 Among the 9199 sequences, the distribution of subtypes was: 45.3% B, 27.3% CRF02_AG, 3.7
117 % A1, 2.5% C, 1.7% CRF06_cpx and 19.5% other various non-B. Among the 381 sequences of
118 NNRTI-failing patients, 252 (66.1%) were infected with a B subtype and 129 (33.9%) with a
119 non-B subtype. The distribution of the subtype (B versus non-B) was statistically different
120 between the all and NNRTI-failing group ($p < 0.001$).

121

122 **Prevalence of doravirine and other NNRTIs resistance associated mutations**

123 Analyzing the overall dataset of HIV-1 antiretroviral-experienced patients, the most frequent
124 doravirine resistance associated mutations were V106A/M 0.8% (n=77), V108I 3.3% (n=307),
125 Y188L 1.2% (n=107), G190S 0.3% (n=24), F227C/L/V 0.5% (n=49), M230I/L 2.8% (n=256), L234I
126 0.1% (n=13), P236L 0% (n=0), K103N+Y181C 3.9% (n=361), K103N+P225H 2.9% (n=264) and
127 K103N+100I 1.7% (n=156) (figure 1). The prevalence of M230I/L and K103N+L100I was higher

128 for the HIV-1 B subtype than non-B subtypes (3.3% versus 2.4%, $p=0.009$ and 2.6% versus
129 1.0%, $p<0.001$, respectively), in contrast to K103N+P225H (1.8% versus 3.7%, $p<0.001$).
130 In comparison, the prevalence of common NNRTIs mutations V90I, A98G, L100I, K101E/P,
131 K103N/S, E138A/G/K/Q/R, V179D/F/T, Y181C/I/V, Y188C/H/L, G190A/E/S, T225H were 6.3%
132 (580), 2.5% (231), 1.0% (94), 2.4% (219), 10.2% (934), 10.9% (1001), 1.5% (137), 5.7% (521),
133 1.7% (153), 2.8% (258), 1.4% (130), respectively (figure 1). Some mutations were more
134 frequent in HIV-1 B subtype [L100I (1.6% versus 0.6%, $p<0.001$), E138A/G/K/Q/R (14.3% versus
135 8.0%, $p<0.001$), V179D/F/T (2.0% versus 1.1%, $p<0.001$), G190A/E/S (2.9% versus 2.7%,
136 $p=0.004$)] or in HIV-1 non-B subtypes [V90I (4.2% versus 8.0%, $p<0.001$), A98G (1.8% versus
137 3.1%, $p<0.001$), K103N/S (8.7% versus 11.3%, $p<0.001$), and T225H (1.2% versus 1.6%,
138 $p<0.001$)]. There was no difference between B and non-B subtypes for E138K (4.0% versus
139 3.1%, $p=0.407$).

140

141 **Resistance to doravirine and other NNRTIs**

142 The overall prevalence of sequences with at least 1 doravirine resistance associated mutation
143 was 12.2% ($n=1119$). Considering the ANRS algorithm, 5.6% ($n=512$) of sequences were
144 considered resistant to doravirine. In comparison, the prevalence of sequences considered as
145 resistant were significantly higher for efavirenz (18.8%, $n = 1725$), etravirine (8.4%, $n=776$),
146 nevirapine (17.9%, $n=1647$) and rilpivirine (22.3%, $n=2050$), ($p<0.001$) (figure 2A). Similarly,
147 with the Stanford algorithm, the prevalence of sequences considered as resistant to doravirine
148 was 16.0% ($n=1468$), and lower than those for efavirenz 24.8% ($n=2277$), etravirine 24.6%
149 ($n=2267$), nevirapine 24.9% ($n=2294$) and rilpivirine 24.7% ($n=2269$) ($p<0.001$) (figure 2B).

150

151 **Prevalence of doravirine and NNRTIs resistance associated mutations in the NNRTI-failing**
152 **group (n=381)**

153 Analyzing the NNRTI-failing patients, among the doravirine resistance associated mutations,
154 the most frequent mutations were V106A/M 2.6% (10), V108I 9.2% (35), Y188L 2.6% (10),
155 G190S 2.1% (8), F227C/L/V 1.8% (7), M230I/L 0% (0), L234I 0.5% (2), P236L 0%, K103N+Y181C
156 3.9% (15), K103N+P225H 4.7% (18) and K103N+L100I 3.9% (15) (figure 1). The following
157 mutations are statistically more prevalent ($p<0.05$) in the NNRTI-failing group comparing to
158 the whole set of sequences: V106A/M, V108I, Y188L, G190S, F227C/L/V and K103N+L100I.
159 Only M230I/L was statistically more prevalent in the whole group than in the NNRTI-failing
160 group ($p<0.001$) (figure 1). Furthermore, the mutation F227C/L/V was less frequent in B versus
161 non-B subtypes (0.8% versus 3.9%, $p=0.047$).

162 In comparison, the prevalence of common NNRTIs mutations V90I, A98G, L100I, K101E/P,
163 K103N/S, E138A/G/K/Q/R, V179D/F/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, T225H were
164 8.9% (n=34), 3.4% (n=13), 4.2% (n=16), 7.9% (n=30), 28.6% (n=109), 12.6% (n=48), 5.2%
165 (n=20), 14.2% (n=54), 4.7%, (n=18), 8.9% (n=34), 5.2% (n=20), respectively (figure 1). No
166 association was observed between these common mutations and HIV subtype.

167

168 **Resistance in the NNRTI-failing group**

169 The overall prevalence of sequences with at least 1 doravirine resistance associated mutations
170 was 34.9% (n=133). Considering the ANRS algorithm, 18.1% (n=69) of sequences were
171 considered as resistant to doravirine. This prevalence was significantly lower than the
172 prevalence of sequences considered as resistant to other NNRTIs by ANRS algorithm: 36.5%
173 (n=139) were genotypically resistant to nevirapine ($p<0.001$), 51.7% (n = 197) to efavirenz
174 ($p<0.001$), 21.9% (n=88) to etravirine ($p=0.107$) and 55.6% (n=212) to rilpivirine ($p<0.001$)

175 (Figure 1A). With the Stanford algorithm, the resistance to doravirine was 42.0% (n=160) and
176 not different from etravirine and rilpivirine resistance, whereas the resistance to the first
177 generation NNRTIs was higher: efavirenz (52.0%, n=209, p<0.001) and nevirapine (56.2%,
178 n=214, p<0.001) (Figure 1B).

179

180

181 **DISCUSSION**

182 Our study evidenced a low prevalence of doravirine resistance associated mutations in HIV-1-
183 infected antiretroviral-treated patients in Italy and France. This prevalence was significantly
184 lower than those for other NNRTIs in use, especially first generation NNRTIs.

185 In this study, the proportion of non-B subtypes was high (54.6%), with a large variety of
186 subtypes, and slightly higher than in our previous study on doravirine resistance in HIV-1
187 antiretroviral-naïve patients (47.0%).¹⁵ However, it was similar to the prevalence of non-B
188 subtypes in antiretroviral-naïve chronically HIV-infected patients in 2015/2016 in France
189 (54.8%).⁵

190 As expected, the prevalence of the resistance associated to doravirine and other NNRTIs was
191 higher in the population of HIV-1 antiretroviral treated patients than in our previous study
192 that showed the rare occurrence of doravirine resistance associated mutations in HIV-1
193 infected antiretroviral naïve patients (n=137/9764, 1.4%).¹⁵ For K103N, Y181C and E138A/K
194 mutations, their prevalences observed in this study were more consequential than in the most
195 recent French nationwide study in treated patients with a confirmed viral load > 50 copies/mL.
196⁵

197 In the DRIVE clinical trials conducted in HIV-1 antiretroviral naïve patients, the evidenced
198 resistance mutation profiles at failure were as follow: Y188L; V016I+F227C;

199 V106I/V+H221Y+F227C; F227C; V106A+P225H+Y318Y/F; V106T/M, F227C/R; Y318F/Y. ⁷⁻⁹

200 Globally and except for the single Y318F not studied here, all these doravirine mutations were
201 present at a low percentage, even in the NNRTI-failing patients in our study.

202 In DRIVE-SHIFT, conducted in virologically suppressed patients, no doravirine resistance
203 associated mutations were evidenced in patients achieving the protocol-defined virological
204 failure. Of note, 24 participants had a virus with baseline NNRTI mutations (K103N, Y181C and
205 G190A) and 23/24 who switched to doravirine/lamivudine/tenofovir disoproxil fumarate
206 remained suppressed during the 48 week follow-up. ¹⁶ This suggests, that the most frequent
207 NNRTI mutations at RT mutation positions 103, 181 and 190, should probably not impact the
208 doravirine activity *in vivo*. K103N+Y181C and G190S, although not DOR-associated resistant
209 substitutions, were included in our analysis as they confer resistance to other NNRTIs. In our
210 study, the prevalence of the K103N+Y181C and G190S was low and did not impact the global
211 resistance of doravirine.

212 Some small significant differences were observed in the present study for the prevalence of
213 some doravirine mutations, according to the HIV-1 subtypes (M230I/L, K103N+L100I more
214 frequent in B subtype and K103N+P225H more frequent in non-B subtypes). In another study,
215 it has been shown that Y188L and V106M were more frequent in C subtype while V106A was
216 less frequent in non-B subtypes. ¹⁷

217 One limitation of the study is the relatively low number of NNRTI value. However, when the
218 resistance test was performed in case of virological failure for these antiretroviral treated
219 patients, more patients had probably previously been exposed to NNRTIs.

220 The results of interpreting doravirine resistance were different according to ANRS or Stanford
221 algorithms (18.1% versus 42%) in the NNRTI-failing group. It could be explained together by
222 differences in the set mutations list for a same RT position and also in the number of

223 considered positions. For example, the following RT mutations are not taking into account in
224 the ANRS algorithm: L100I, K101E/P, V106I, Y181C/I/V, P225H, F227C, L234I.

225 Our study shows, according to the Stanford algorithm, 42% of doravirine resistance in the
226 NNRTI-failing group which was higher than recently evidenced in NNRTI-experienced patients
227 in another study (18.8%).¹⁷ Several factors could explain this difference. The studied
228 doravirine mutations were not strictly similar between the two studies. Indeed, we
229 investigated a larger set of mutations with the inclusion of mutations G190S, F227C/V, M230I,
230 L234I, P236L, K103N+Y181C and K103N+L100I, as well as the F227C and the L234I alone and
231 not only in association with the V106A/M.

232 In conclusion, these results suggest that doravirine resistance in antiretroviral-experienced
233 patients generally and specifically among NNRTI-failing patients is significantly lower than
234 resistance to other NNRTIs currently used, confirming its distinguishing resistance pattern. In
235 addition, these results are reassuring in the perspective of the use of doravirine in
236 antiretroviral-treated patients and exposed to previous use of NNRTIs after availability of a
237 genotype.

238

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244

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250

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256

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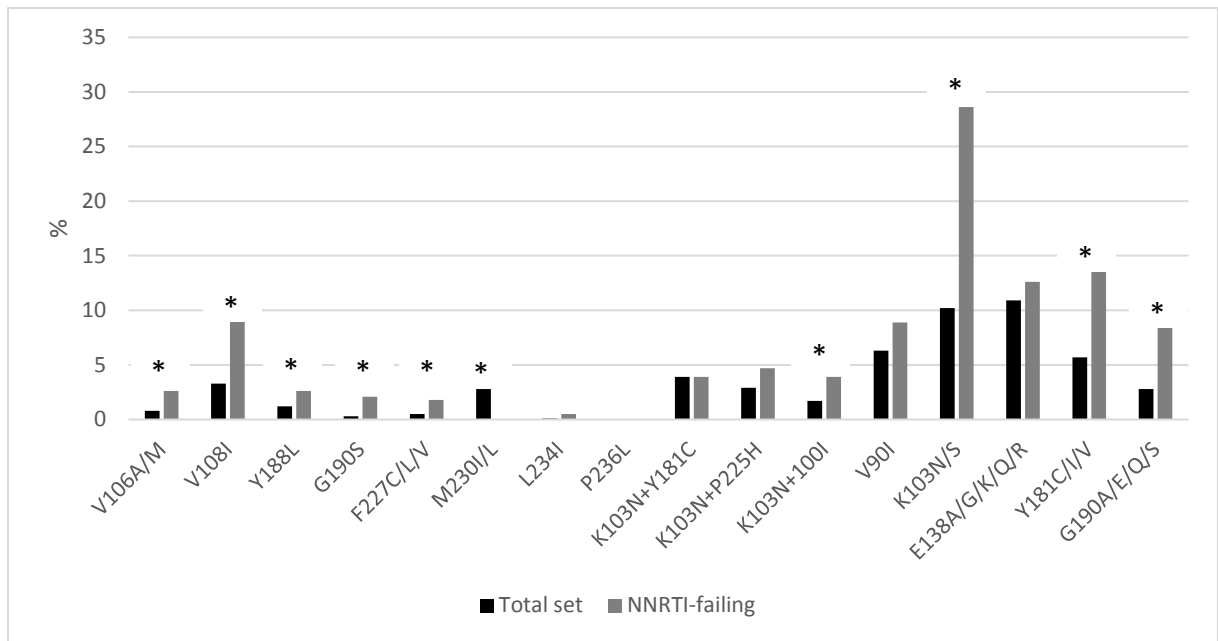
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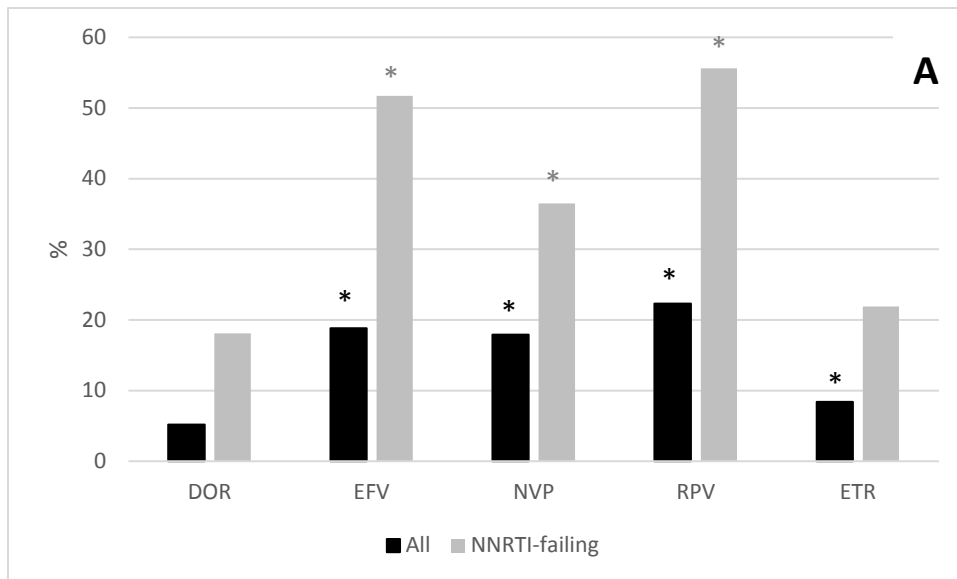
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314 Figure 1: Prevalence of RT sequences with at least one individual doravirine or other NNRTI
 315 (>8%) resistance associated mutations in the total set (black) and in the NNRTI-failing group
 316 (grey)

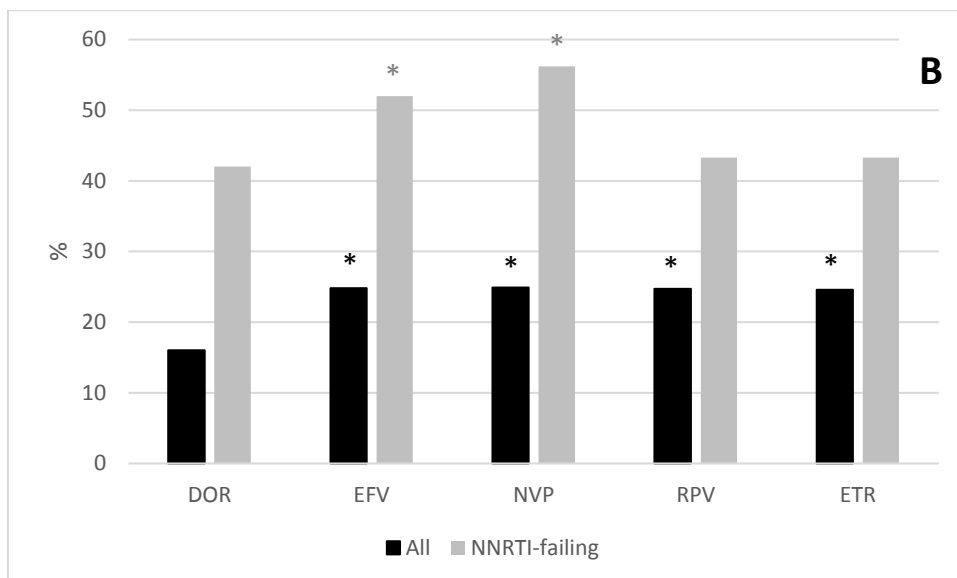
317 *P<0.05: statistically different between total set and NNRTI-failing group

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325 Figure 2: Percentage of RT sequences associated with NNRTI resistance in the whole data set
326 and in the group of NNRTI-failing patients according to the ANRS (A) or Stanford (B)
327 algorithm

328 DOR: doravirine, EFV: efavirenz, NVP: nevirapine, RPV: rilpivirine, ETR: etravirine

329 *P<0.001: statistically different from Doravirine

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