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

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

Running title: Doravirine resistance in HIV-1 treated patients

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ABSTRACT

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

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

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

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

INTRODUCTION

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

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

The doravirine resistance profile is distinct from other NNRTIs with the *in vitro* selection of mutations at reverse transcriptase (RT) positions 106, 108, 188, 227, 230, 234 and 236. [11–14] *In vivo*, the evidenced resistance mutation profiles were concordant: Y188L; V106I+F227C; V106I/V+H221Y+F227C; F227C; V106A+P225H+Y318Y/F; V106T/M, F227C/R; Y318F/Y. [7–9]

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

MATERIALS AND 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/Polyclinic of Rome "Tor Vergata", INMI Spallanzani-IRCCS, and Modena Hospital). A total of 9199 HIV-1 RT sequences obtained between 2012 and 2017 from HIV-1 antiretroviral-experienced patients in routine clinical care were analysed. A follow-up of HIV viral load about 3 to 6 months; in case of 2 consecutive viral loads > 50 copies/mL, a resistance genotypic testing was performed on the second viral load. Among this set of sequences, 381 sequences were originated from NNRTI-failing patients (efavirenz, n=189; etravirine, n=32; nevirapine, n=66; rilpivirine, n=94). The following mutations identified *in vitro or in vivo* were considered as doravirine-associated mutations: RT V106A/M, V108I, Y188L, F227C/L/V, M230I/L, L234I, P236L, K103N+P225H, K103N+L100I. [8,11–14] K103N+Y181C and G190S were also considered in our analysis, as they are known to confer resistance to other NNRTIs. NNRTIs mutations associated with resistance to efavirenz, rilpivirine, nevirapine and etravirine were those listed in the ANRS algorithm (table of rules 2018; www.hivfrenchresistance.org), in the IAS list 2018 (www.iasusa.org) and in the Stanford HIV drug resistance database (https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/). Namely, efavirenz: L100I, K101E/P, K103N/S, V106A/M, V108I, Y181C/I/V, Y188C/H/L, G190A/E/S, P225H, M230L; etravirine: V90I, A98G, L100I, K101E/H/P, V106I, E138A/G/K/Q, V179D/F/T, Y181C/I/V, G190A/E/S, M230L; nevirapine: L100I, K101E/P, K103N/S, V106A/M, V108I, Y181C/I/V, Y188C/H/L, G190A/E/S, M230L; rilpivirine: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, G190A/E/S, H221Y, F227C, M230I/L.

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

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

Subtype was determined on the basis of the RT and protease coding regions by Smartgene algorithm (Smartgene®, Switzerland) or by phylogenetic analyses, using reference sequences of HIV-1 subtypes and circulating recombinant forms (CRF) from the Los Alamos Database (https://www.hiv.lanl.gov/content/sequence/HIV/mainpage.html). Between-group comparisons were carried out using Fisher's exact test.

RESULTS

Distribution of HIV-1 subtypes

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

Prevalence of doravirine and other NNRTIs resistance associated mutations

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

for the HIV-1 B subtype than non-B subtypes (3.3% versus 2.4%, p=0.009 and 2.6% versus 1.0%, p<0.001, respectively), in contrast to K103N+P225H (1.8% versus 3.7%, p<0.001).

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

Resistance to doravirine and other NNRTIs

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

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

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

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

Resistance in the NNRTI-failing group

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

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

DISCUSSION

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

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

As expected, the prevalence of the resistance associated to doravirine and other NNRTIs was higher in the population of HIV-1 antiretroviral treated patients than in our previous study that showed the rare occurrence of doravirine resistance associated mutations in HIV-1 infected antiretroviral naïve patients (n=137/9764, 1.4%). [15] For K103N, Y181C and E138A/K mutations, their prevalences observed in this study were more consequential than in the most recent French nationwide study in treated patients with a confirmed viral load > 50 copies/mL. [5]

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

V106I/V+H221Y+F227C; F227C; V106A+P225H+Y318Y/F; V106T/M, F227C/R; Y318F/Y. [7–9] Globally and except for the single Y318F not studied here, all these doravirine mutations were present at a low percentage, even in the NNRTI-failing patients in our study.

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

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

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

The results of interpreting doravirine resistance were different according to ANRS or Stanford algorithms (18.1% versus 42%) in the NNRTI-failing group. It could be explained together by 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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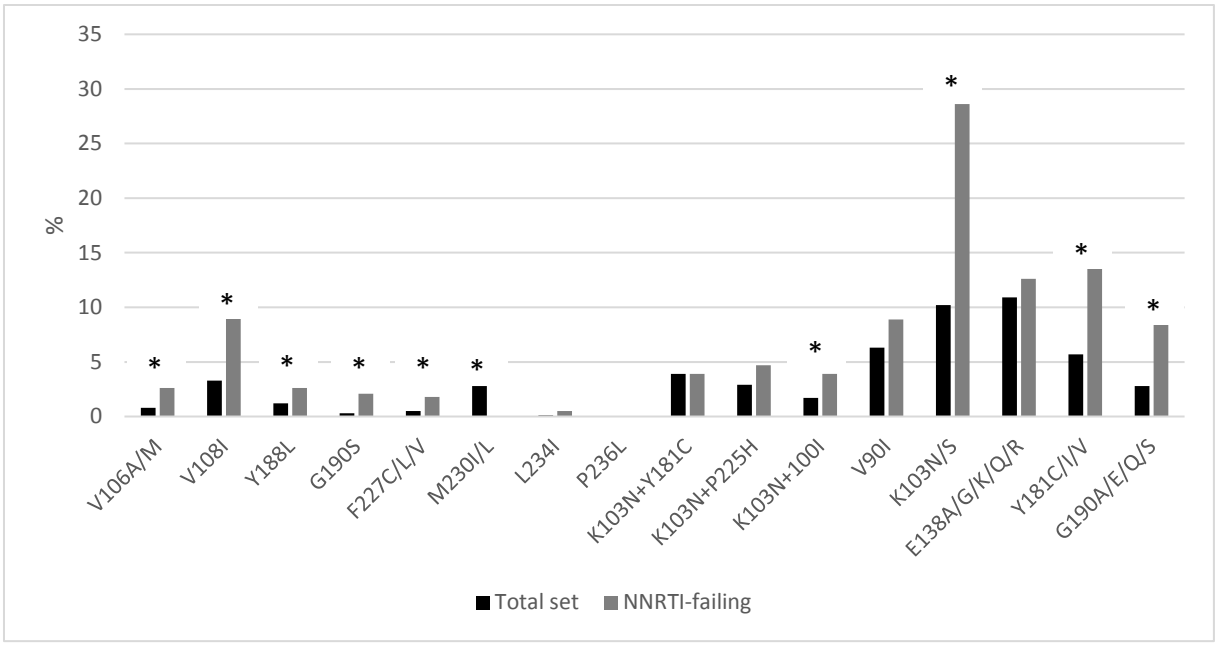

Figure 1: Prevalence of RT sequences with at least one individual doravirine or other NNRTI (>8%) resistance associated mutations in the total set (black) and in the NNRTI-failing group (grey)

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

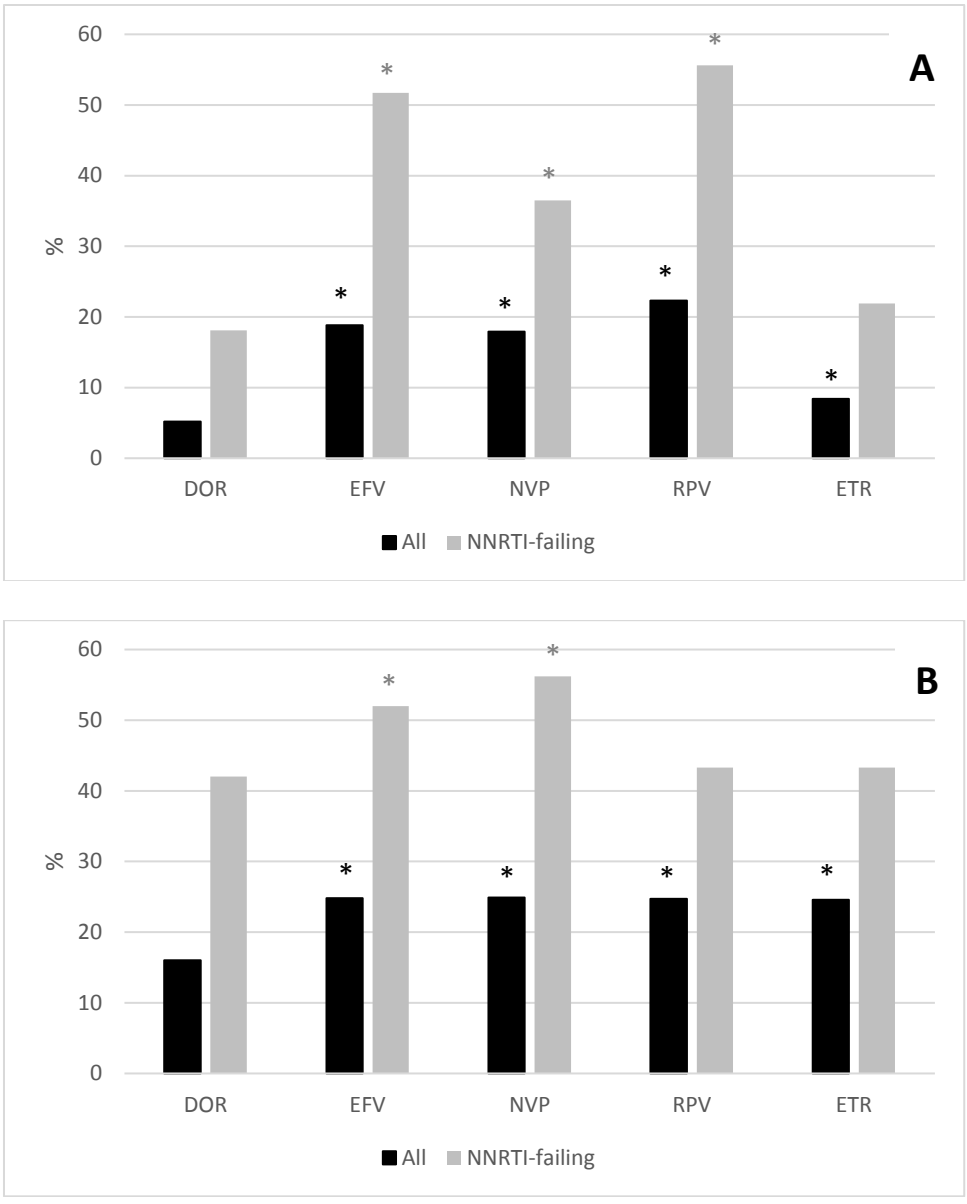

Figure 2: Percentage of RT sequences associated with NNRTI resistance in the whole data set and in the group of NNRTI-failing patients according to the ANRS (A) or Stanford (B) algorithm

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

*P<0.001: statistically different from Doravirine