PHENOTYPIC DORAVIRINE SUSCEPTIBILITY AFTER NNRTI EXPOSURE IN THE PRESTIGIO REGISTRY

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BACKGROUND

- Doravirine (DOR) is an NNRTI recently licensed for first-line as well as maintenance HIV-1 ART. DOR showed non-inferior efficacy to darunavir and efavirenz based regimens, as well as in presence of transmitted NNRTI mutations, such as K103N or G190A, in a small group of treatment naïve patients.
- DOR susceptibility was found to be not affected by most single NNRTI mutations except for V106A, Y188L and M230L, and clinically relevant combinations of NNRTI mutations.
- This study aimed to investigate the *in vitro* susceptibility to DOR in viruses harboring NNRTI mutations obtained from persons living with HIV-1 (PLWH).

METHODS

- Plasma samples were collected from 20 PLWH enrolled in the Italian PRESTIGIO Registry, which includes subjects with documented genotypic resistance to NRTI, NNRTI and PI plus either genotypic resistance to INSTI or virological failure to an INSTI regimen without an integrase genotype.
- Identification of DOR RAMs was carried out according to IAS-USA DRMs list (V106AIMT, Y188CLH, G190E, P225H, F227CLR, M230L, L234I) and major Stanford HIVdb mutations (V106AIM, Y188L, G190ES, M230L).
- Recombinant HIV-1 expressing patient derived PR-RT were used to assess *in vitro* susceptibility to DOR through a TZM-bl cell based phenotypic assay measuring fold-change (FC) values with respect to the NL4-3 virus.
- Patients' demographics and laboratory data were described by median (Q1-Q3) or frequency (%). Statistical analysis included Mann-Whitney, Kruskal-Wallis test and Spearman correlation coefficient.

RESULTS

Table 1. Patients' characteristics

Gender, male	18 (90%)
Age, years	51 (43-53)
Time since HIV-1 diagnosis, years	22 (18-26)
Time on ART, years	19 (16-22)
Previous AIDS events	11 (55%)
HIV-RNA, log_{10} copies/mL	4.42 (3.36-5.15)
CD4+, cells/µL	195 (69-278)
CD8+, cells/µL	1012 (402-1412)
CD4+/CD8+ ratio	0.2 (0.1-0.5)

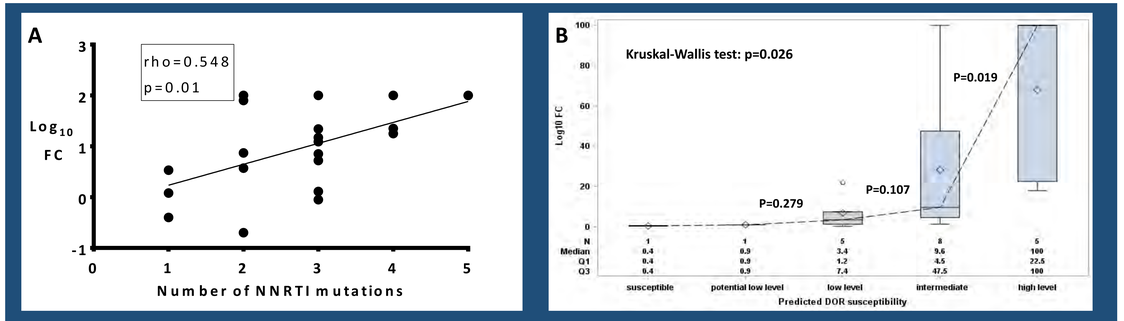


Figure 1. DOR FC values correlated with the *number of major Stanford NNRTI mutations* detected in each virus (A) and with the *levels of predicted DOR susceptibility* by Stanford HIVdb algorithm (B).

RESULTS

Patients' characteristics are described in Table 1. At sample collection, 11 subjects (55%) were receiving NNRTI (ETV=10, RPV=1), while 7 (35%), 6 (30%) and 7 (35%) had been exposed to 1, 2 and 3 NNRTI, respectively.

Table 2. Genotypic and phenotypic susceptibility to DOR and related treatment data about NNRTI exposure.

Patient ID	HIVdb NNRTI RAMs	HIVdb predicted susceptibility	Mean IC_{50} ± SD, nM	FC	NNRTI exposure at sample collection	Previous exposure to NNRTI
1	A98G, K103N, Y181C, P225H	R	28.6±12.0	17.9	ETV	EFV, NVP
2	L100I, K103N, V179VI, K238N	I	19.5±8.0	12.2	ETV	EFV
3	K103N, Y181V	LLR	11.8±0.6	7.4	ETV	NVP
4	K103KNRS, Y181C, **G190S**, H221HY	R	36.1±3.6	22.5	ETV	none
5	E138Q, V179E, Y181C	PLLR	1.5±0.2	0.9	none	EFV, NVP
6	V108I, Y181C	I	5.9±0.8	3.7	none	EFV, ETV, NVP
7	V106I, **Y188L**, K238N	R	>150	100	none	EFV
8	Y181C, H221Y, M230I	I	128.2±33.2	80.1	RPV	ETV
9	A98G	LLR	5.4±0.1	3.4	none	NVP
10	L100I, E138R, V179L	LLR	35.1±15.6	21.9	ETV	none
11	K103N, Y181I	LLR	0.3±0.01	0.2	none	EFV, ETV, NVP
12	K103N, E138A, P225H, **M230L**	R	>150	100	none	ETV
13	K101E, Y181C, G190A	I	8.4±1.6	5.3	none	EFV, ETV
14	L100V, K101H, V179F, Y181C, G190A	I	>150	100	ETV	NVP, RPV
15	K101E, Y181C, G190A	I	2.1±0.2	1.3	ETV	none
16	E138K, **G190E**	R	>150	100	ETV	EFV, RPV
17	K103N	S	0.6±0.04	0.4	none	EFV, ETV, NVP
18	V108I, E138A, Y181V	I	23.8±5.4	14.9	ETV	EFV, NVP
19	Y181I	LLR	1.8±0.02	1.2	ETV	none
20	L100I, K103N, E138G	I	11.3±2.3	7	none	EFV, ETV

Stanford HIVdb DOR RAMs are in bold, while IAS-USA DOR RAMs are underlined. Levels of predicted DOR susceptibility: S, susceptible; PLLR, potential low-level resistance; LLR, low-level resistance; I, intermediate; R, high-level resistance.

RESULTS

- DOR RAMs were identified in 4/20 (20%) sequences according to both Stanford HIVdb and IAS-USA DRMs list. By querying Stanford HIVdb algorithm, intermediate or high-level resistance to DOR were predicted in 13/20 (65%) sequences (Table 2).
- Mean DOR half-maximal inhibitory concentration (IC_{50}) for wild-type strain NL4-3 was 1.6±0.04 nM. With clinically derived viruses, the median DOR FC value was 9.8 (1.8-65.7), while FC values were 17.9 (7.4-80.1) and 3.7 (0.7-53.5) (p=0.105) in patients receiving and not receiving NNRTI, respectively.
- DOR FC values correlated with the number of NNRTI major Stanford mutations (Figure 1A) and with the DOR resistance levels by HIVdb algorithm (Figure 1B), but not with the number of previously experienced NNRTI (r = -0.167; p=0.483), viral load (r = -0.121; p=0.612), time of exposure to NNRTI (r = 0.044; p=0.855) or time elapsed since last exposure to NNRTI (r = -0.330; p=0.155).
- Median DOR FC values were significantly higher in viruses harboring major DOR RAMs according to both HIVdb (FC 100 [41.9-100] vs. 6.2 [1.2-17.2]) and IAS-USA lists (FC 100 [38.4-100] vs. 6.2 [1.2-20.2]) (Figure 2).

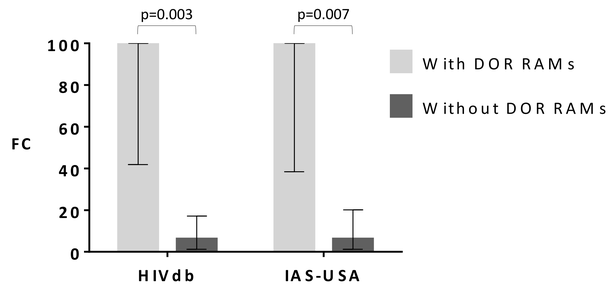


Figure 2. Comparison of DOR FC values according to the presence of DOR RAMs

CONCLUSIONS

- DOR activity decreases with increasing numbers of NNRTI mutations, even in the absence of specific DOR RAMs.
- Prediction of DOR activity can be inferred with good accuracy by HIVdb, however intermediate susceptibility categories include viruses with a wide FC range.
- The IAS-USA DRMs list can also be used as a simple DOR susceptibility reference.

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