Phenotypic analysis of the impact of V106I in HIV-1 reverse transcriptase on resistance to Doravirine

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AIM

In order to understand the impact of the HIV-1 reverse transcriptase (RT) natural polymorphism V106I on Doravirine resistance, we investigated:

- The prevalence of V106I in therapy naïve individuals joining the MEDITRES consortium
- The phenotypic susceptibility of Doravirine in both site-directed mutants carrying V106I on the genetic background of laboratory adapted wild-type viruses and in clinically derived recombinant viruses harboring V106I and no other major NNRTI RAMs.

METHODS

- MeditRes HIV is a consortium that includes ART naïve people living with HIV newly diagnosed in France, Greece, Italy, Portugal and Spain during the years 2018-2021.
- We measured the phenotypic susceptibility to Doravirine:
  - in site directed mutants containing V106I, V106A, V106M or Y188L mutations in subtype B (NL4-3, HXB2) and CRF02_AG genetic background (Figure 1).
  - in a subset of recombinant viruses with clinically derived RT-RNAse H coding region harboring V106I and no other major NNRTI RAMs (Figure 2).
- Phenotypic susceptibility to Doravirine was determined through a TZM-bl cell-based assay and expressed as fold-change (FC) with respect to the reference wild-type virus (Figure 3).

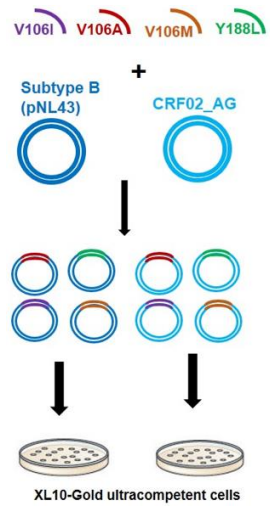

Figure 1. Generation of V106I, V106M, V106A and Y188L subtype B and subtype AG plasmids, by using the QuikChange II XL Site-Directed Mutagenesis kit (Agilent). The presence of the specific mutation in all constructs was verified by Sanger sequencing.

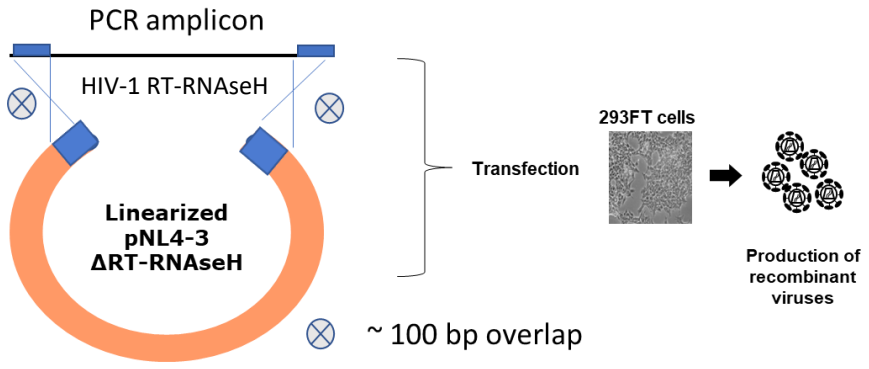

Figure 2. Generation of recombinant viruses harboring clinically derived HIV-1 genomic region including reverse transcriptase and RNAseH coding region

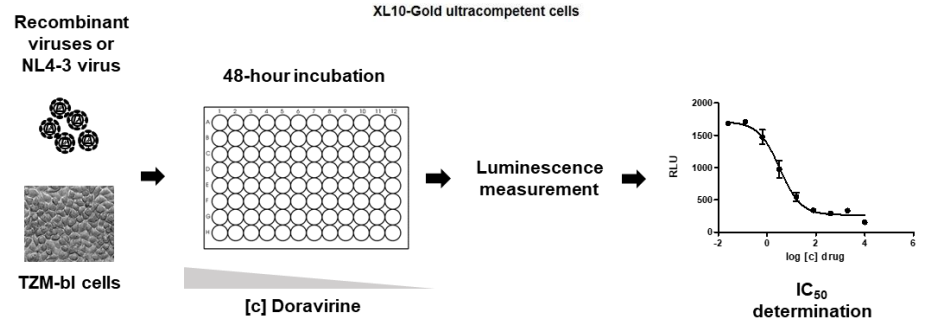

Figure 3. Determination of doravirine susceptibility through a TZM-bl cell line-based phenotypic assay

RESULTS

MeditRes HIV includes **2705** patients from 2018 to 2021. The prevalence of V106I in the dataset was **2.85%**. FC values for site directed mutants in the NL4.3, HXB2 and CRF02_AG background are shown in Figure 4 and Table 1.

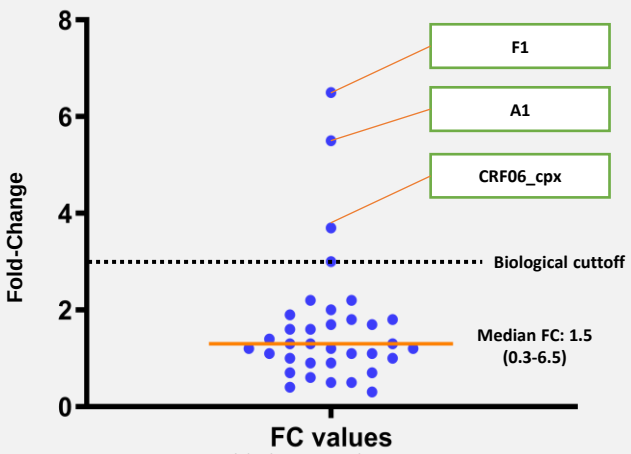

Figure 5. Fold-change values

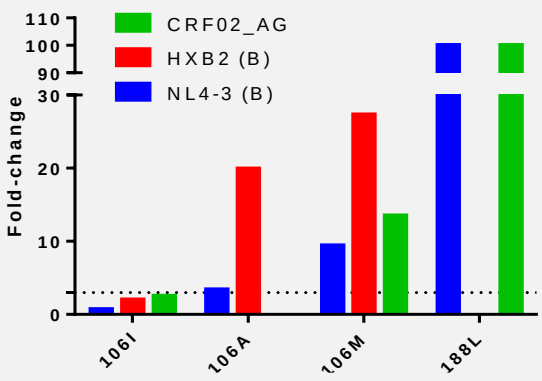

Figure 4. Fold-change values for site directed mutants

	NL4.3 (B)	HXB2 (B)	CRF02_AG
V106I	0.7	2.0	2.5
V106A	3.4	19.9	NA
V106M	9.4	27.3	13.5
Y188L	>100	NA	>100

Table 1. Fold-change values for site directed mutants

The panel of clinically derived viruses tested so far includes 20 subtypes B and 15 non-B subtypes (2 A1, 2 CRF02_AG, 3 CRF06_cpx, 1 CRF44_BF, 2 D, 4 F1 and 1 URF). The median Doravirine FC values were 1.5 (range 0.3-6.5), 1.2 (range 0.3-1.9), and 2.5 (range 0.5-6.5) in the whole data set, in the B and non-B subtypes, respectively. Only three non-B clinical isolates showed FC values higher than Doravirine biological cutoff (3.0) (CRF06_cpx, FC=3.7; A1, FC=5.5; F1, FC=6.5).

CONCLUSIONS

The prevalence of V106I through the years 2018-2021 remains low in the MeditRes HIV countries. The natural polymorphism V106I did not decrease the susceptibility to Doravirine in both site-directed mutants and most of clinical isolates, differently from the NNRTI RAMs V106A and V106M. Occasional non-B subtype isolates with decreased susceptibility to Doravirine prompt for further analysis to determine the possible impact on Doravirine *in vivo*.

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