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 naive 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 RMs.

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 RMs (Figure 2).
- Phenotypic susceptibility to Doravirine was determined through a T2M-bl cell-based assay and expressed as fold-change (FC) with respect to the reference wild-type virus (Figure 3).

RESULTS

MeditRHS 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.

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 RMs 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.

Figure 1. Generation of V106I, V106M 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 T2M-bl cell line-based phenotypic assay.

Figure 4. Fold-change values for site directed mutants

<table>
<thead>
<tr>
<th></th>
<th>NL4.3 (B)</th>
<th>HXB2 (B)</th>
<th>CRF02_AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>V106I</td>
<td>0.7</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>V106A</td>
<td>3.4</td>
<td>19.9</td>
<td>NA</td>
</tr>
<tr>
<td>V106M</td>
<td>9.4</td>
<td>27.3</td>
<td>13.5</td>
</tr>
<tr>
<td>Y188L</td>
<td>&gt;100</td>
<td>NA</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

Table 1. Fold-change values for site directed mutants.