Potential Role of Doravirine for the Treatment of Patients with Transmitted Drug Resistance

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Abstract

Background: Doravirine has a unique resistance profile but how this profile might increase its usefulness beyond first-line therapy in persons with susceptible viruses has not been well studied. We sought to determine scenarios in which doravirine would retain activity against isolates from ART-naive persons with transmitted drug resistance (TDR) and to identify gaps in available doravirine susceptibility data.

Methods: We analyzed published *in vitro* doravirine susceptibility data and applied the results to 42,535 RT sequences from ART-naïve persons published between 2017 and 2021. NNRTI-resistance mutations (DRMs) were defined as those with a Stanford HIV Drug Resistance Database doravirine penalty score either alone or in combination with other mutations.

Results: V106A, Y188L, F227C/L, M230L, and Y318F were associated with the greatest reductions in doravirine susceptibility. However, several DRMs and DRM combinations lacking these canonical resistance mutations had >10-fold reduced susceptibility including G190E, one isolate with G190S, three isolates with L100I+K103N, one isolate with K103N+P225H, and isolates with L100I+K103N+V108I and K101E+Y181C+G190A. Of the 42,535 ART-naive sequences, 3,374 (7.9%) contained a DRM of which 2,788 (82.6%) contained 1 DRM (n=33 distinct mutations), 426 (12.6%) contained 2 DRMs (79 distinct pairs of mutations), and 143 (4.2%) contained ³3 DRMs (86 distinct mutation patterns). Among the 2,788 sequences with one DRM, 112 (4.0%) were associated with ³3.0-fold reduced doravirine susceptibility while 2,625 (94.2%) were associated with <3.0-fold reduced susceptibility. Data were not available for individual DRMs in 51 sequences (1.8%). Among the 426 sequences with two DRMs, 180 (42.3%) were associated with ³3.0-fold reduced doravirine susceptibility while just 32 (7.5%) had <3.0 fold reduced susceptibility. Data were not available for 214 (50.2%) sequences containing 2 DRMs.

Conclusions: First-line therapy containing doravirine plus two NRTIs is expected to be effective in treating most persons with TDR as more than 80% of TDR sequences had a single DRM and as more than 90% with a single DRM were expected to be susceptible to doravirine. However, caution is required for the use of doravirine in persons with more than one DRM even if none of the DRMs are canonical doravirine-resistance mutations.

Background

Doravirine (DOR) is an HIV-1 non-nucleoside RT inhibitor (NNRTI) approved in 2018 for the initial treatment of HIV-1 infection. It is also highly effective at maintaining virologic suppression with other antiretrovirals in persons without a prior history of virological failure (VF) [1–4]. DOR has a unique *in vitro* susceptibility profile, which has prompted its consideration for use in persons with some forms of NNRTI-associated transmitted drug resistance (TDR) [5, 6]. A clinical trial designed to assess DOR in persons with TDR caused by the three most common transmitted NNRTI mutations, K103N, Y181C, and G190A, enrolled only nine persons [5].
Studies of mutations selected in vitro and in persons with VF while receiving DOR-containing antiretroviral therapy (ART) found that V106A, Y188L, F227C/L, M230L, and Y318F conferred the greatest reductions in DOR susceptibility. In 12 in vitro experiments V106A/M, V108I, H221Y, F227L/C/I, M230L, L234I, and Y318F were consistently reported to emerge [2, 3]. Among approximately 750 persons receiving DOR plus two NRTIs for initial ART, nine developed NNRTI-resistance mutations (DRMs) associated with reduced DOR susceptibility, including eight isolates with > 90-fold reduced susceptibility [1, 2, 7]. The selected DRMs included V106I (5 persons), F227C (5 persons), A98G (3 persons), V106A (2 persons), H221Y (2 persons), P225H (2 persons), Y318F (2 persons), V106M (1 persons), E138G (1 person), and Y188L (1 person). Two of the nine persons developed just one mutation (Y188L and Y318F). The remaining seven developed two or more mutations.

However, there has been no comprehensive analysis of in vitro DOR susceptibility data. To assess the potential usefulness of DOR for treating persons with TDR, we analyzed published in vitro DOR susceptibility data. We then examined a large set of sequences from ART-naïve persons published between 2017 and 2021 in the Stanford HIV Drug Resistance Database (HIVDB). Using the analysis of published DOR susceptibility data, we sought to determine scenarios in which DOR would retain activity against isolates from persons with TDR and to identify gaps in published DOR susceptibility data.

Methods

Published in vitro susceptibility data

Because in vitro susceptibility data were reported by four laboratories using different assays, we analyzed the results from each laboratory separately. The main analysis used data from the Merck Research Laboratory (MRL) which published more than twice the amount of data published by the other laboratories combined. For DRM patterns with multiple available susceptibility results, we determined the median result. Results below 3-fold were reported as < 3-fold in accordance with the PhenoSense (Monogram BioSciences, South San Francisco) biological cut-off of 2.5-fold and the 3-fold cut-off used in a study that queried the Monogram database for isolates with single NNRTI DRMs [7, 8]. For the Monogram database single DRM study, which reported the median susceptibility of multiple isolates, we treated the reported median as two results in our analysis. The studies were published between 03/2014 and 12/2020. Our analysis of these studies was completed by June 1, 2022.

ART-naïve sequence dataset

We queried HIVDB for sequences of ART-naïve persons in studies published between 2017 and 2021. For each sequence we identified all NNRTI-resistance mutations with a mutation penalty score for DOR according to the HIVDB drug-resistance interpretation program. This included 37 mutations with penalty scores when they occurred alone and/or in combination with other mutations including A98G, L100I/V, K101E/P, K103N, V106A/I/M, V108I, E138K, V179F, Y181C/I/V, Y188C/H/F/L, G190A/C/E/Q/S/T/V, H221Y, P225H, F227C/I/L/V, M230I/L, L234I, P236L, and Y318F. Eighteen mutations that received a penalty score for one or more NNRTIs other than DOR were excluded including the highly polymorphic
mutations K103R, E138A, and V179D and the following additional 15 mutations of which most are rare or have a minimal effect on NNRTI susceptibility: K101H, K103H/S/T, E138G/Q/R, V179E/L, Y181F/G/S, K238N/T, and N348I.

Results

Analysis of published in vitro susceptibility data

Eight studies reported 196 DOR in vitro susceptibility results [7, 9–15]. Five studies reporting 136 results were published by authors at Merck Research Laboratories (MRL). Three studies reporting 60 susceptibility results were published by other research groups – National Cancer Institute (NCI) in the U.S., University of Sienna (Italy) and McGill University (Canada). The MRL studies used the PhenoSense assay for 109 results and an MT-2 cell reporter gene assay for 27 assays.

Figure 1. Doravirine in vitro susceptibility data for isolates with one, two, or three NNRTI-resistance mutations. The Y-axis indicates the pattern of mutations and the X-axis indicates the fold-reduction in susceptibility on a log$_2$ scale. Isolates with a fold-reduced susceptibility < 1.0 were jittered about 1.0 whereas those with a fold reduced susceptibility > 128 were jittered at this level. Each of the results were published by the Merck Research Laboratory and included 109 results generated by the Monogram Biosciences PhenoSense assay and 27 results generated by an in-house MT-2 cell reporter gene assay. Blue circles indicate clinical isolates containing common patterns of NNRTI-associated drug resistance mutations (DRMs). Green circles indicate median fold reduced susceptibilities of viruses containing a single DRM from a selection of viruses in the Monogram database [8]. Black circles indicate site-directed mutants containing common patterns of NNRTI-resistance mutations. Red circles indicate site-directed mutants containing patterns of NNRTI-resistance mutations that were selected either in vitro or in persons receiving doravirine.

Susceptibility data from the MRL studies were available for 86 isolates with 22 different single DRMs, 46 isolates with 20 different pairs of DRMs, and 20 isolates with 12 different patterns containing three DRMs. Among the 22 different single DRMs, four had been selected in vitro and/or in vivo by DOR and had a reduced susceptibility $\geq 3.0$ fold including Y188L (> 64-fold; 8 results), Y318F (11-fold; 2 result), V106A (9.6-fold; 3 results) and V106M (3.4-fold; 1 result). Three other mutations also had a reduction in susceptibility $\geq 3.0$ fold including G190E (18-fold; 1 result), Y181V (5.1-fold; 2 results), and G190S (3.0-fold; 6 results).

Among the 20 different pairs of mutations, 9 patterns containing V106A, Y188L, F227C/L, or M230L had median reductions in susceptibility $\geq 36$-fold. Eight patterns without any of these canonical DOR-associated mutations had median reductions in susceptibility ranging from 3.3 to 7.9-fold including K103N + P225H (7.9-fold; 2 results), V108I + Y181C (6.9-fold; 2 results), L100I + K103N (5.7-fold; 9 results),
K103N + V108I (4.6-fold; 2 results), A98G + K103N (4.0-fold, 1 result), K103N + Y181C (3.8-fold, 5 results),
Y181C + G190A (3.5-fold, 3 results), and A98G + Y181C (3.3-fold, 1 result).

Among the 12 patterns of mutations containing three NNRTI-associated DRMs, the five containing V106A,
F227C, or M230L had > 64-fold reductions in susceptibility. Two patterns lacking any canonical DOR-
resistance mutations had > 10-fold reductions in susceptibility including L100I + K103N + V108I and
K101E + Y181C + G190S.

Supplementary Table 1 summarizes in vitro susceptibility data published by the McGill, Sienna, and NCI
research groups. The McGill research group tested viruses selected in vitro by DOR including V106A/I/M,
V108I, H221Y, F227L, M230L, L234I, and Y318F. Their fold reductions in susceptibility differed from those
of the MRL group in that isolates with V108I + Y318F or H221Y + L234I were associated with high-level
reductions in DOR susceptibility.

The Sienna group tested a panel of 10 site-directed mutants containing representative patterns of two to
four NNRTI-associated DRMs. Although this panel was created prior to the approval of DOR, three isolates
lacking canonical DOR-associated DRMs had > 10-fold reductions in susceptibility including K103N +

The NCI group tested 32 site-directed mutants associated with reduced NNRTI susceptibility. Its results
diverged from the other research groups in that K103N, E138K, and the uncommon NRTI-resistance
mutation D67E had 7.0, 8.2, and a 70-fold reduction in DOR susceptibility, respectively.

**Predicted in vitro susceptibilities for ART-naïve sequences**

HIVDB contained 42,535 one-per-person RT sequences from ART-naïve persons during the five-year
period encompassing 2017 to 2021 reported in 168 published studies. Overall, 3,374 (7.9%) had
sequences with a mutation that had a penalty score for DOR. Of these, 2,788 (82.6%) contained a single
DRM (n = 33 different mutations), 426 (12.6%) contained two DRMs (n = 79 pairs of mutations), and 143
(4.2%) contained three or more DRMs (n = 86 patterns of mutations). Of the 3,374 sequences with a
mutation that had a DOR penalty score, the most common subtypes were B (49.7%), C (12.3%), A (8.2%),
CRF01_AE (8.0%), and CRF02_AG (7.1%). The distribution of sequences by region included Asia (31.5%),
Europe (29.7%), Africa (26.1%), Latin America (11.9%) and North America (0.7%).

Among the 2,788 sequences with a single DRM, 112 (4.0%) were associated with ≥3.0 fold reduced DOR
susceptibility, 2,625 (94.2%) were associated with < 3.0 fold reduced susceptibility. Susceptibilities were
not available for 51 (1.8%) sequences (Table 1). The 112 sequences associated with ≥3.0 fold-reduced
susceptibility included three with the canonical resistance mutations V106A, Y188L, and Y318F and four
with the non-canonical resistance mutations V106M, Y181V, and G190S/E.
Table 1
Published Susceptibility for HIV-1 Isolates with a Single NNRTI-Associated Drug Resistance Mutation (DRM) Ordered by Frequency in the ART-Naïve Dataset

<table>
<thead>
<tr>
<th>DRM&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Number of sequences</th>
<th>Fold-Reduced Susceptibility&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Median</th>
<th>#tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>V106I</td>
<td>1137</td>
<td>&lt;3.0&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K103N</td>
<td>817</td>
<td>&lt;3.0&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V108I</td>
<td>158</td>
<td>&lt;3.0&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G190A</td>
<td>123</td>
<td>&lt;3.0&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y181C</td>
<td>102</td>
<td>&lt;3.0&lt;sup&gt;7&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A98G</td>
<td>91</td>
<td>&lt;3.0&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K101E</td>
<td>76</td>
<td>&lt;3.0&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E138K</td>
<td>49</td>
<td>&lt;3.0&lt;sup&gt;10&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H221Y</td>
<td>45</td>
<td>&lt;3.0&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y188L*</td>
<td>40</td>
<td>106&lt;sup&gt;8&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V106M</td>
<td>27</td>
<td>3.4&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G190E</td>
<td>17</td>
<td>18&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>G190S&lt;sup&gt;3&lt;/sup&gt;</td>
<td>11</td>
<td>3.0&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V106A*</td>
<td>8</td>
<td>9.6&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P225H</td>
<td>8</td>
<td>&lt;3.0&lt;sup&gt;2&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>F227L*</td>
<td>8</td>
<td>&lt;3.0&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Y188C</td>
<td>6</td>
<td>&lt;3.0&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Y318F*</td>
<td>5</td>
<td>11&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>The table includes phenotypic susceptibility data published by the Merck Research Laboratory and Monogram PhenoSense assays. <sup>2</sup>Susceptibility data were not available for 12 mutations including two canonical doravirine DRMs, F227C and M230L that occurred in five sequences and ten additional mutations L100V, K101P, V179F, Y181I, G190Q, F227I/V, M230I, L234I and P236L which occurred in 46 sequences. Mutations followed by an asterisk are considered canonical doravirine DRMs. <sup>3</sup>The median fold-reduction in the Monogram single mutation database study was < 3.0 for G190S.
<table>
<thead>
<tr>
<th>DRM²</th>
<th>Number of sequences</th>
<th>Fold-Reduced Susceptibility³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median #tests</td>
</tr>
<tr>
<td>Y181V</td>
<td>4</td>
<td>5.1₂</td>
</tr>
<tr>
<td>Y188H</td>
<td>3</td>
<td>&lt;3.0₃</td>
</tr>
<tr>
<td>L100I</td>
<td>2</td>
<td>&lt;3.0₃</td>
</tr>
</tbody>
</table>

¹The table includes phenotypic susceptibility data published by the Merck Research Laboratory and Monogram PhenoSense assays. ²Susceptibility data were not available for 12 mutations including two canonical doravirine DRMs, F227C and M230L that occurred in five sequences and ten additional mutations L100V, K101P, V179F, Y181I, G190Q, F227I/V, M230I, L234I and P236L which occurred in 46 sequences. Mutations followed by an asterisk are considered canonical doravirine DRMs. ³The median fold-reduction in the Monogram single mutation database study was <3.0 for G190S.

Among the 426 sequences with two DRMs, 180 (42.3%) were associated with ≥3.0 fold reduced DOR susceptibility, 32 (7.5%) were associated with <3.0 fold reduced DOR susceptibility, and susceptibility data were not available for 214 (50.2%) sequences (Table 2). These 214 sequences included 24 containing one or two canonical resistance mutations and 33 containing a non-canonical DRM with reduced susceptibility ≥3-fold. The remaining 157 sequences did not contain a canonical resistance mutation or a DRM with ≥3-fold reduced susceptibility.
Table 2
Published Susceptibility for HIV-1 Isolates with Two NNRTI-Associated Drug-Resistance Mutations (DRMs) Ordered by Frequency in the ART-Naïve Dataset

<table>
<thead>
<tr>
<th>DRM²</th>
<th>Number of sequences</th>
<th>Fold-Reduced Susceptibility³</th>
<th>Median</th>
<th>#tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>K103N, P225H</td>
<td>58</td>
<td>7.9₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L100I, K103N</td>
<td>32</td>
<td>5.7₉</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K101E, G190A</td>
<td>18</td>
<td>&lt;3.0₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K103N, Y181C</td>
<td>16</td>
<td>3.8₅</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K103N, V108I</td>
<td>15</td>
<td>4.6₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A98G, K103N</td>
<td>15</td>
<td>4₁</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K103N, G190A</td>
<td>14</td>
<td>&lt;3.0₄</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y181C, G190A</td>
<td>10</td>
<td>3.5₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A98G, Y181C</td>
<td>9</td>
<td>3.3₁</td>
<td></td>
<td></td>
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<tr>
<td>K103N, Y188L</td>
<td>8</td>
<td>&gt;64₁</td>
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<td>V106I, Y188L</td>
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<td>&gt;64₁</td>
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<td>&gt;64₁</td>
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<td></td>
</tr>
<tr>
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<td>2</td>
<td>&gt;64₁</td>
<td></td>
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<tr>
<td>V106M, F227C</td>
<td>1</td>
<td>&gt;64₂</td>
<td></td>
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</table>

¹The table includes phenotypic susceptibility data published by the Merck Research Laboratory and Monogram PhenoSense assays. ²Data was not available for 214 isolates including 24 that contained ≥1 canonical doravirine DRM, 33 that contained ≥1 DRM associated with low-level reductions in doravirine susceptibility (Table 1), and 157 containing mutations that individual were not associated with reduced susceptibility.

Discussion
Several canonical DOR resistance mutations alone or in combination with other mutations were associated with >10-fold and often much greater reductions in DOR susceptibility including V106A, Y188L, F227C/L, M230L, and Y318F. Several other mutations were associated with greatly reduced
susceptibility when they occurred in combination with canonical resistance mutations including A98G (with F227C), V106M/I (with F227C), P225H (with V106A), and L234I (with V106A). A98G, V106I, and P225H alone did not reduce DOR susceptibility. The only isolate with V106M alone with susceptibility data had 3.4-fold reduced susceptibility. L234I alone was not studied.

Although the isolates with the highest levels of reduced susceptibility in the MRL dataset usually had a canonical DOR resistance mutation, several other mutations and mutation combinations had reductions in susceptibility > 10-fold including G190E, one isolate with G190S, three isolates with L100I + K103N, two isolates with K103N + P225H, and one isolate each with L100I + K103N + V108I and K101E + Y181C + G190A. Several other combinations of two mutations were associated with median reductions in susceptibility of 3 to 8-fold.

The disparities in the DOR susceptibility results for viruses containing the same NNRTI-resistance mutations in the MRL dataset can result from several factors. First, two different assays were used. Second, some isolates were site-directed mutants whereas others were clinical isolates. Third, clinical isolates often have NRTI-resistance mutations which typically reduce NNRTI susceptibility [16] and polymorphic mutations which can reduce or increase NNRTI susceptibility [17].

Our analysis indicates several gaps in existing susceptibility data for several individual mutations including V106M, Y181I/V, G190E, and L234I and suggests the need for additional data for viruses containing two or more non-canonical DOR-resistance mutations. Such data will provide a more complete picture of the potential usefulness of DOR for treating persons with TDR and for using DOR as an additional drug in persons with few other treatment options. Indeed, the amount of phenotypic susceptibility data for DOR is less than that of other NNRTIs at similar stages of clinical development. For example, 493 susceptibility results are available for rilpivirine even though rilpivirine has a much lower potential for use in persons with pre-existing NNRTI resistance.

DOR has been reported to display inhibitory quotients (trough concentration / antiviral IC$_{50}$ in 100% human serum) of 68, 39, 27, and 25 against wildtype viruses and viruses with K103N, Y181C, and K103N + Y181C, respectively [11, 18]. This indicates that DOR may retain inhibitory activity against many viruses with low-level reductions in susceptibility such as that observed for most of the two-mutation DRM patterns lacking canonical DOR-resistance mutations. However, the inhibitory activity of DOR against viruses from ART-naïve persons with TDR cannot necessarily be extrapolated to those persons with pre-treatment resistance who previously received an NNRTI because NNRTI-experienced persons are likely to have a more complex quasispecies containing more NNRTI-associated DRMs than observed in ART-naïve persons.

Conclusions

This study suggests that first-line therapy containing DOR plus two NRTIs is expected to be an effective regimen for treating most ART-naïve persons with TDR as more than 80% of TDR sequences had a single
DRM and as more than 90% with a single DRM are expected to be highly susceptible to DOR. However, among those with two DRMs for which susceptibility tests were available, most had DRM patterns associated with a $\geq 3.0$ fold-reduction in susceptibility. Therefore, our data suggest caution in the use of DOR for persons with more than one DRM even if none of the DRMs are canonical DOR resistance mutations. This study also identifies several gaps in the available \textit{in vitro} DOR susceptibility data that if filled would provide more confidence in the use of DOR beyond the approved indication for first-line therapy.

**Declarations**

**Ethics approval and consent to participate**

Not applicable

**Consent for publication**

Not applicable

**Availability of data and materials**

The data supporting the findings of this study are available within the article and the supplementary information files.

**Competing interests**

MZ received grants for research activities from Gilead Sciences, Merck Sharp and Dohme, Theratechnologies and ViiV Healthcare and personal fees for advisory boards and training activities from Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Theratechnologies and ViiV Healthcare outside the submitted work. We declare no competing interests.

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**Authors' contributions**

SR and RWS conceived the idea, analyzed the data. RWS wrote the original draft. SR, JMS, FS, MZ and SK reviewed multiple drafts and provided edits to the manuscript. The funder of the study had no role in study design, data collection or data analysis.

**Acknowledgements**

Not applicable
References


Figures
Figure 1

Doravirine \textit{in vitro} susceptibility data for isolates with one, two, or three NNRTI-resistance mutations. The Y-axis indicates the pattern of mutations and the X-axis indicates the fold-reduction in susceptibility on a log\textsubscript{2} scale. Isolates with a fold-reduced susceptibility <1.0 were jittered about 1.0 whereas those with a fold reduced susceptibility >128 were jittered at this level. Each of the results were published by the Merck Research Laboratory and included 109 results generated by the Monogram Biosciences PhenoSense.
assay and 27 results generated by an in-house MT-2 cell reporter gene assay. Blue circles indicate clinical isolates containing common patterns of NNRTI-associated drug resistance mutations (DRMs). Green circles indicate median fold reduced susceptibilities of viruses containing a single DRM from a selection of viruses in the Monogram database [8]. Black circles indicate site-directed mutants containing common patterns of NNRTI-resistance mutations. Red circles indicate site-directed mutants containing patterns of NNRTI-resistance mutations that were selected either in vitro or in persons receiving doravirine.

Susceptibility data from the MRL studies were available for 86 isolates with 22 different single DRMs, 46 isolates with 20 different pairs of DRMs, and 20 isolates with 12 different patterns containing three DRMs. Among the 22 different single DRMs, four had been selected in vitro and/or in vivo by DOR and had a reduced susceptibility ≥3.0 fold including Y188L (>64-fold; 8 results), Y318F (11-fold; 2 results), V106A (9.6-fold; 3 results) and V106M (3.4-fold; 1 result). Three other mutations also had a reduction in susceptibility ≥3.0 fold including G190E (18-fold; 1 result), Y181V (5.1-fold; 2 results), and G190S (3.0-fold; 6 results).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table.S1.docx
- Table.S2.xlsx