K65R, L74V/I and M184V/I Mutations are Associated with Hypersusceptibility to 1st and Next Generation NNRTIs

Table 1: Effects of Non-TAM NRTI Mutations on NNRTI Susceptibility in Clinical Specimens

<table>
<thead>
<tr>
<th>Mutations</th>
<th>ZDV</th>
<th>EFV</th>
<th>NVP</th>
<th>ETR</th>
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<tbody>
<tr>
<td>K65R</td>
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<tr>
<td>L74V/I</td>
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<tr>
<td>M184V/I</td>
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</table>

Table 2: Site-Directed Mutants: Effects of K65R, M184V or L74V on NNRTI Susceptibility

<table>
<thead>
<tr>
<th>SDM</th>
<th>ABC</th>
<th>FTC</th>
<th>3TC</th>
<th>TFV</th>
<th>ZDV</th>
<th>EFV</th>
<th>NVP</th>
<th>ETR</th>
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RESULTS

Clinical specimens containing isolated mutations K65R, M184V or L74V demonstrated significantly increased susceptibility to EFV, NVP and the next generation NNRTI ETR. NNRTI hypersusceptibility (FC < 0.4) in particular is frequently seen in clinical isolates with those resistance motifs (Table 1).

Clinical samples with M184V/I, and with either K65R or L74V/I, demonstrated robust reductions in FC and high proportions with hypersusceptibility to 1st and next generation NNRTIs (Table 1, Figures 1a, 2a, 3a, 4).

Analyses of the L74V/I mutation was limited to a small number of clinical specimens bearing this mutation in isolation (n=20 for EFV, NVP; N=5 for ETR). Similarly, only 12 clinical specimens with isolated K65R were tested against ETR (Table 1).

All SDMs were tested in 20 independent experiments. Compared to wildtype virus, K65R, M184V and L74V exhibited significantly reduced FC to 1st and next generation NNRTIs (Table 2; Figures 1b, 2b, 3b).

Strong sensitizing effects for ZDV were also noted in SDMs and, particularly, in clinical specimens bearing the resistance motifs studied herein.

CONCLUSIONS

Non-TAM mutations K65R, L74V/I and M184V/I are associated with reduced fold change and hypersusceptibility to first and next generation NNRTIs.

These findings were validated in site-directed mutants and in clinical specimens from the Monogram database.

NNRTI hypersusceptibility may have relevance for the design and success of 1st or 2nd line ART regimens, particularly those containing double NNRTI therapy with a 1st or next generation NNRTI.

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REFERENCES