The HIV-1 Protease Resistance Mutation I50L Is Associated with Increased Susceptibility to PIs other than Atazanavir

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Background

The HIV-1 protease inhibitor (PI) resistance has been characterized by a mutational profile relative to other PIs. It has been previously demonstrated that the protease substitution I50L is a primary mutation encoding resistance to atazanavir.

By analyzing the resistance database (1) in the laboratory strain 63-2 and three clinical isolates revealed that the presence of I50L led to increased susceptibility for 6 PIs (other than atazanavir).

Biochemical and biochemical studies revealed that the presence of I50L led to increased affinity for protease by PIs other than atazanavir.

We previously presented the prevalence of I50L between 1998 and 2005 in a large genotypic database and the impact of I50L alone and in combination with 1 to primary PI mutations on predicted PI susceptibility.

Here we report the further study of a large genotypic database for isolates containing the protease mutation I50L. By analyzing the mutational profiles of these sequences, we extend the characterization of I50L.

We examined its contribution to clinically relevant sequences, we extend the characterization of I50L.

Methods

We reviewed routine clinical isolates received at Virco (excluding clinical trials) between 1999 and 2006 for the presence of HIV-1 protease isolates were compared with other sequences in the database having like patterns of primary PI mutations as defined by IAS-USA.

The isolates could have other secondary PI mutations that were not considered in these analyses.

Using vircoTYPE (R), the median predicted FC value for each mutational pattern was determined for all PIs, in the absence and presence of I50L, respectively. For each mutational profile, a ratio of the median predicted FC (in the presence of I50L) to the absence of I50L (in 50% of I50L) was determined for all PIs.

Discussed-related shifts in predicted FC were evaluated using relevant specific-lifeoxazole-based Clinical Lab OFFs (CL02, 2006) and 3 possible resistance categories: Major Response, Reduced Response or None Response. A change across two categories in mutation was deemed Major and a change across one category was deemed Minor.

Results

Figure 1: The prevalence of I50L observed in the database ranged from 0.1% (LPV/r-) to 19.4% (APV/r+).

The prevalence of I50L increased from 0.2% in the period up to 2005 (prior to atazanavir’s approval) to 0.7% in 2006 (Figure 1).

We examined a total of 254,813 routine clinical isolates: of which 46% contained I50L (Table 1).

A further subset of a minimum of ≥ 3 samples in each profile yielded 107 and 37,088 samples with and without I50L, respectively (Table 2).

For comparison, a similar analysis of the sensitizing effect of the reverse transcriptase mutation M184V on resistance to zidovudine was evaluated.

An examination of 563 mutational profiles in presence and absence of M184V revealed that while the presence of M184V caused a minor or one-category shift in sensitivity to zidovudine for 10% of the mutational profiles, no profiles showed a major or two-category shift in sensitivity (data not shown).

The authors wish to thank Pierre Lescop for his help in assessing the M184V-related shift in zidovudine resistance category as well as other members of Virco BVBA and Labgibis group for their collective work in making this study possible.

Table 1: Summary of relationship between PI susceptibility and presence of I50L.

<table>
<thead>
<tr>
<th>PI</th>
<th>% of Isolates with I50L</th>
<th>% of Isolates without I50L</th>
<th>Median Predicted FC Ratio</th>
<th>Fold Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATV/r</td>
<td>19.4% (6/31)</td>
<td>41.9% (13/31)</td>
<td>0.47</td>
<td>0.50%</td>
</tr>
<tr>
<td>DRV/r</td>
<td>6.5% (2/31)</td>
<td>45.2% (14/31)</td>
<td>0.19</td>
<td>0.04%</td>
</tr>
<tr>
<td>APV/r</td>
<td>0% (0/31)</td>
<td>6.5% (2/31)</td>
<td>0.18</td>
<td>0.03%</td>
</tr>
</tbody>
</table>

| Table 2: The motif and mutation profiles in Resistome Core due to I50L-related shifts in retroviral protease interacts (3+) |

<table>
<thead>
<tr>
<th>Profile</th>
<th>Major Shift</th>
<th>Reduced Shift</th>
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Discussion

The PI atazanavir was approved by various regulatory health authorities beginning in June 2003. The subsequent rise in the prevalence of the resistance mutation I50L is consistent with the increased availability of this PI. The prevalence of I50L in our database has reached a plateau at 0.7% in 2006.

Previous studies concluded that I50L conferred resistance to atazanavir and susceptibility to other PIs.

For comparison, a similar analysis of the sensitizing effect of the reverse transcriptase mutation M184V on resistance to zidovudine was evaluated.

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Conclusions

The prevalence of PI mutation I50L is associated with resistance to atazanavir and increased susceptibility to other PIs in a variety of protease mutational backgrounds.

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