Update on Drug Resistance Mutations in HIV-1

Data continue to accumulate about the role of resistance testing in clinical practice. The Drug Resistance Mutations Group of the International AIDS Society–USA (see sidebar) is charged with monitoring the field and maintaining a current list of mutations that impact drug susceptibilities. The Drug Resistance Mutations Group reviewed data presented in June, 2001, at the 5th International Workshop on HIV Drug Resistance and Treatment Strategies in Scottsdale, Arizona, and discussed other recent developments. The figures presented on the following pages have been updated accordingly, since the June, 2001 publication in this journal.

Major revisions made since the June, 2001 publication include:

- New placement of the multidrug-resistance bars at the top of the drug classes.
- New graphic display of the nucleoside reverse transcriptase inhibitor (nRTI)-associated mutations (NAMs; M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E), the mutations associated with cross-resistance to the nRTIs, except lamivudine. The NAMs are shown in light pink vertical lines in the nRTI and nucleotide reverse transcriptase inhibitor classes.
- The addition of 5 mutations that affect the efficacy of lopinavir/ritonavir (V32I, L33F, I50V, I47V, and G73S) based on data presented at the 5th International Workshop on HIV Drug Resistance and Treatment Strategies. Until more data become available, the lopinavir/ritonavir-associated mutations are presented as neither “primary” nor “secondary.”

These figures will be updated regularly and will be available on the International AIDS Society–USA Web site, www.iasusa.org.

The Drug Resistance Mutations Group is building an online database of references (peer-reviewed, published articles, and conference abstracts) that will provide state-of-the-art information on the effect of mutations on drug susceptibility, the interactions between mutations, and the impact of drug levels on the effects of specific mutations in clinical settings. For each mutation or mutation pattern marked in the mutations figures, the database will include findings from the scientific literature that demonstrate clinical impact. Users will be able to search by mutation, class of drug, study type, authors, and other key aspects.

The launch of this database will be announced in Topics in HIV Medicine and at www.iasusa.org. Comments on the current mutations figures can be addressed via e-mail to info@iasusa.org.

The Drug Resistance Mutations Group

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO REVERSE TRANSCRIPTASE INHIBITORS

### Nucleoside Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Mutations in the Reverse Transcriptase Gene</th>
<th>Associated with Reduced Susceptibility to Reverse Transcriptase Inhibitors</th>
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</thead>
<tbody>
<tr>
<td>Multi-nRTI Resistance: 151 Complex</td>
<td>A 75 77 116 151</td>
<td></td>
</tr>
<tr>
<td>Multi-nRTI Resistance: 69 Insertion Complex</td>
<td>M D K L V Y M</td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>M K D L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>M D K L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
<tr>
<td>Zalcitabine</td>
<td>M K D L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
<tr>
<td>Stavudine</td>
<td>M D K L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
<tr>
<td>Abacavir</td>
<td>M K D L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>M K D L V R N T</td>
<td>Multi-nRTI Resistance: (NAMs)</td>
</tr>
</tbody>
</table>

### Nucleotide Reverse Transcriptase Inhibitor

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<th>Mutations in the Reverse Transcriptase Gene</th>
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</tr>
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<tbody>
<tr>
<td>Tenofovir DF</td>
<td>L 65 67 70</td>
<td>Multi-nRTI Resistance: 151 Complex</td>
</tr>
</tbody>
</table>

### Nonnucleoside Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Mutations in the Reverse Transcriptase Gene</th>
<th>Associated with Reduced Susceptibility to Reverse Transcriptase Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-NNRTI Resistance:</td>
<td>Y 188</td>
<td></td>
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<tr>
<td>Multi-NNRTI Resistance:</td>
<td>Y 188</td>
<td></td>
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<tr>
<td>Multi-NNRTI Resistance:</td>
<td>Y 188</td>
<td></td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Y 188</td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Y 188</td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Y 188</td>
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</tbody>
</table>
For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the italicized letter(s) below indicates the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. NAMs indicates multi-NRTI-associated mutations; NRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor. The figures are adapted in part from Hirsch et al., 2000, and are updated regularly. Date of last revision: November 15, 2001.

Footnotes

1. The 69 insertion complex, consisting of a mutation at codon 69 (typically 766R) and followed by an insertion of 2 or more amino acids (S-R, S-A, S-G, or others), is associated with resistance to several NRTIs. The 69 insertion is often accompanied by mutations at other sites. Some other amino acid changes from the wild-type T in codon 69 without the insertion may also be associated with broad NRTI resistance.


3. Reverse transcriptase mutation M184V may temporarily partially reverse the effects of the mutations shown here on zidovudine susceptibility. However, if more than 3 of the listed mutations are present, the additional presence of M184V is not likely to reverse phenotypic zidovudine resistance.

4. The D674S substitutions in RT codon 215 do not confer zidovudine resistance and suggest that virus evolved from the zidovudine-resistant mutant T215Y to a variant that is more fit in the absence of drug. In vitro studies indicate that 215Y may emerge quickly from 215DS/2 in the presence of drug. In vivo relevance is possible but not yet proven.

5. One of the following (K65R/L74V) by itself or a combination of a few of the following (NAMs, E44D, T99D/N, V118I) can lead to didanosine resistance.

6. V75 I76MSA are seldom observed in patients in whom stavudine has failed.

7. One article reports that E44D and/or V118I mutations confer low-level resistance to lamivudine when accompanied by several of the NAMs (41L, 67N, 210W, 215Y/F, 219G/I), in the absence of a current M184V mutation (Hertogs et al, Antimicrob Agents Chemother, 2000). One abstract (9 Aminos-Monteiro et al. 8th Conference on Retroviruses and Opportunistic Infections, 2001, Chicago, Abstract 447) reported no association over the short term between E44D or V118I and viral load responses to a lamivudine-containing combination regimen.

8. In viro data suggest that 4 or more NAMs (M41L, D67N, K70R, L210W, T215Y/F, 219G/I) will lead to a significant degree of resistance: the actual clinical cut-off for tenofovir DC, or a detailed relationship between specific multiple NAMs and tenofovir DC, has not yet been published. Clinical trial results presented by Gilead to the FDA Advisory Committee in September 2001 (unpublished) indicated that tenofovir was responsive to tenofovir DF in groups of patients in whose plasma virus 3 or more NAMs including either M41L or L210W were identified. The patients of groups with plasma virus in which any accumulation of D67N, K70R, T215Y/F or K219Q were identified in the absence of detection of M41L or L210W did not have a diminished average HIV RNA response to tenofovir DF in that dataset.

9. The K103N or Y188L mutation by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

10. Accumulation of these mutations (2 or more) substantially reduces the clinical utility of all of the currently approved NNRTIs.

11. There are some in viro data suggesting that the Y118F mutation, alone or in the presence of K103N and Y181C, decreased susceptibility to delavirdine in primary HIV infection. This mutation was observed only rarely in clinical isolates. An effect of the Y118F mutation on dextrin susceptibility in vitro was detected if the K103N mutation was also present. However, confirmatory data and/or analyses in clinical HIV infection are needed to confirm clinical relevance.

12. Accumulation of these mutations (4 or 5 or more) will likely cause multi-protease inhibitor resistance.

13. For indinavir, the mutations listed as primary may not be the first mutations selected, but they are present in most patient isolates in combination with other mutations.

14. Primary mutations versus secondary mutations have not been designated for lopinavir/ritonavir-associated resistance since there are currently no clear data defining which mutation(s) (isare) selected first with this drug combination. The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The accumulation of 7 or 8 or more of these mutations makes a response to lopinavir/ritonavir unlikely. The mutations listed are based on one report (Kempf et al., 4th International Workshop on HIV Drug Resistance and Treatment Strategies, 2000, Stiges, Spain, Abstract B9). Further clinical experience and research are needed to better define the mutations that affect the effectiveness of lopinavir/ritonavir.