Update on Drug Resistance Mutations in HIV-1

A subgroup of the International AIDS Society–USA Resistance Testing Guidelines Panel has been convened to maintain a current database of HIV drug resistance mutations. The most recent update is provided.

In May, 2000 the International AIDS Society–USA Resistance Testing Guidelines Panel revised its recommendations on resistance testing in HIV-1 infection (Hirsch et al, JAMA, 2000), first published in 1998. The Resistance Testing Guidelines Panel continues to monitor the field to assess when updates are merited. Data continue to accumulate about the role of resistance testing in clinical practice. These new data tend to further support the recommendations published in 2000 and do not yet appear to warrant revising the current guidelines.

The 2000 guidelines included a list of mutations commonly associated with antiretroviral drug resistance, which has become widely used by clinicians involved in HIV medicine. To maintain a current list of mutations that impact drug susceptibilities, a subgroup of the Resistance Testing Guidelines Panel has been convened. This subgroup, the Resistance Mutations Project Panel (see sidebar), under the leadership of Drs Richard T. D'Aquila and Jonathan M. Schapiro, met at the 2001 Conference on Retroviruses and Opportunistic Infections in Chicago, Illinois.

The mutations figures have been updated here. A major change since the 2000 publication is that the distinction between primary and secondary has been removed for mutations in reverse transcriptase. The clinical significance of the mutations that appear first (ie, primary) versus those that appear later (ie, secondary) remains debatable, particularly for nucleoside reverse transcriptase inhibitors (nRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). In general, the clinical effects of many of these mutations overlap. Therefore the panel has decided, at this point, to suspend the use of the concept "primary versus secondary" for the reverse transcriptase inhibitor group as a whole. As a general rule, the magnitude of resistance increases as the number of mutations increases.

The distinction between primary and secondary mutations was kept for the protease inhibitors, because in the protease gene, those mutations that are listed as primary do have greater effects on drug susceptibility (eg, increasing the median inhibitory concentration [IC_{50}]) than do those that are listed as secondary. Other major changes include:

- A new investigational class of drugs, the nucleotide reverse transcriptase inhibitors, has been added. Tenofovir is currently available through an expanded access program.
- Mutations that affect the efficacy of lopinavir/ritonavir, which was recently approved by the US Food and Drug Administration (FDA), have been added.
- Mutations that lead to cross-resistance within the reverse transcriptase inhibitor and protease inhibitor classes have been added.

These figures will be updated regularly and be available on the International AIDS Society–USA Web site, www.iasusa.org, and through HIV InSite, http://hivinsite.ucsf.edu.

The Resistance Mutations Project Panel has begun to build a database of references (peer-reviewed, published articles and conference abstracts) that address the effect of mutations on drug susceptibility. When completed, the interactive database will be available online and will provide, for each mutation or mutation pattern represented in the mutations figures, the citation that demonstrates its clinical impact. The site will allow users to search the scientific literature using several identifiers (eg, mutation, class of drug, study type, authors). Other important issues will also be addressed on the site in the future, such as the interactions between mutations and the impact of drug levels on the effects of specific mutations in clinical settings.

The launch of this Web site 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 "resistance@iasusa.org."

Resistance Mutations Project Panel

The current members of the Resistance Mutations Project Panel, a subgroup of the Resistance Testing Guidelines Panel, are:

Chair
Richard T. D'Aquila, MD
Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

Vice-Chair
Jonathan M. Schapiro, MD
National Hemophilia Center, Yair, Israel, and Stanford University School of Medicine, Stanford, California

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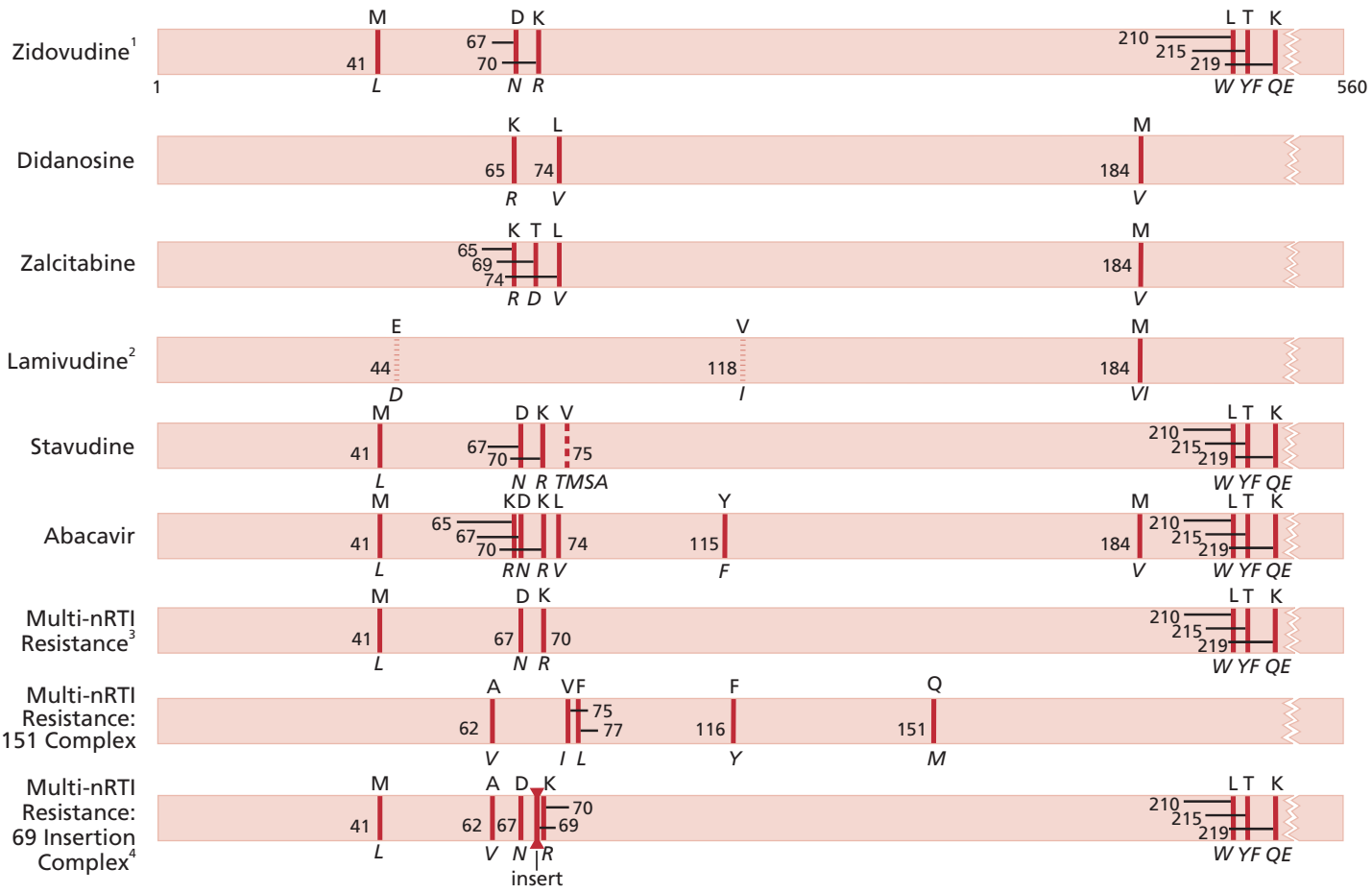
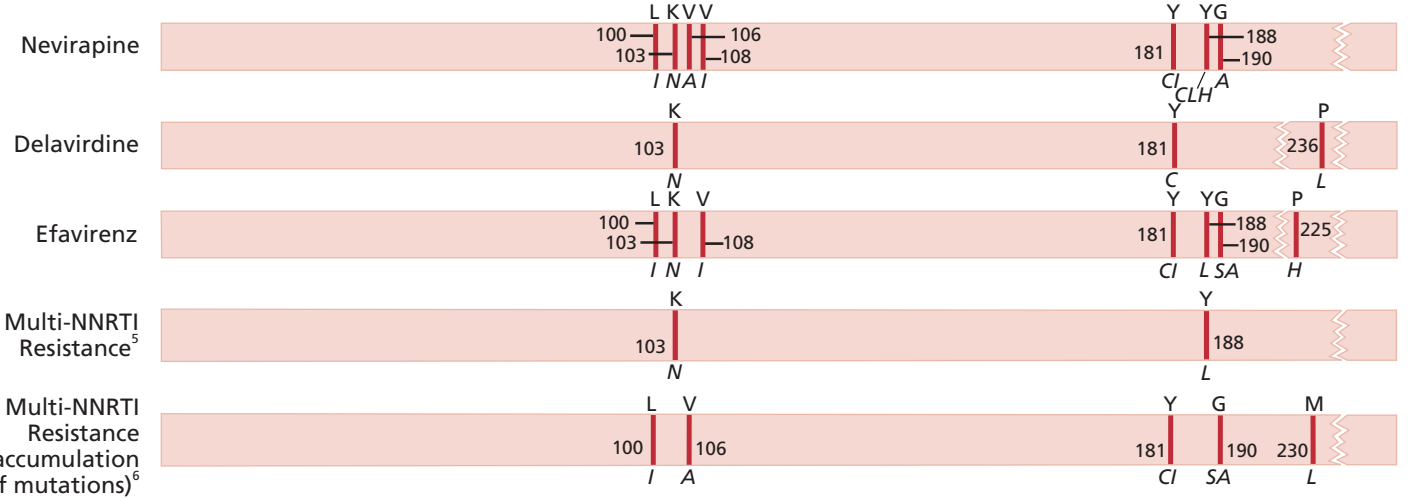
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside Reverse Transcriptase Inhibitors



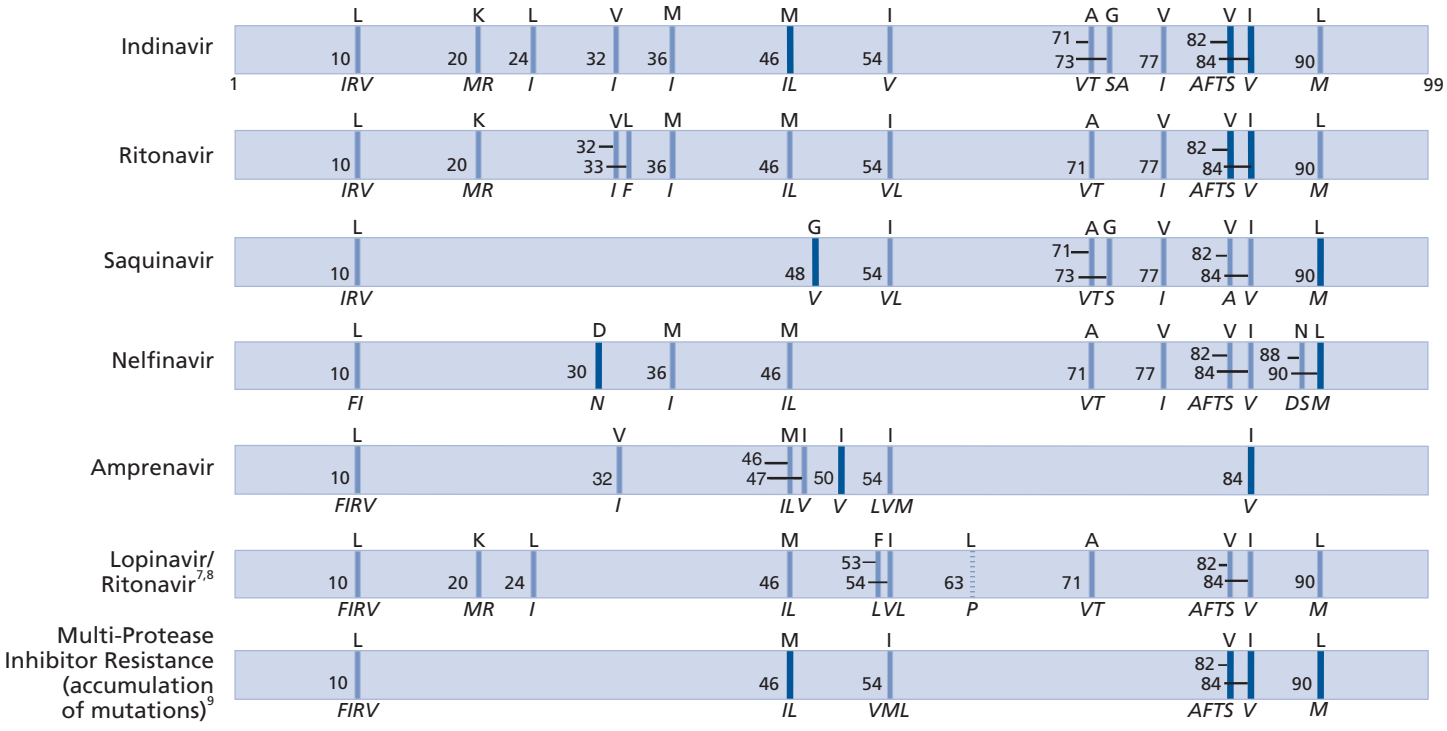
Nucleotide Reverse Transcriptase Inhibitor (currently available under expanded access program)

Nonnucleoside Reverse Transcriptase Inhibitors



MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO PROTEASE INHIBITORS

Protease Inhibitors



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 substitutions that confer viral resistance. The number shows the position of the mutation in the protein. The mutation selected in vitro with stavudine (red dotted bar) is rarely seen in patients having treatment failure. 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. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. The figures are adapted from Hirsch et al, JAMA, 2000. Updated April 2001.

Amino acid abbreviations are: *A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.*

Footnotes

[1] 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.

[2] One article reports increased low-level phenotypic resistance to lamivudine with E44D and/or V118I mutations, in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother*, 2000). One abstract (D'Arminio-Monforte 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.

[3] Mutations associated with cross-resistance to nRTIs (except lamivudine).

[4] The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, or others), is associated with resistance to several nRTIs. The 69 insertion is often accompanied by mutations at other sites.

[5] K103N or Y188L by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

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

[7] 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, Sitges, Spain, Abstract 89) and no primary mutations have yet been identified. Further clinical experience and research are needed to better define the mutations that affect the effectiveness of lopinavir/ritonavir.

[8] Protease mutation L63P is common in viruses that have never been exposed to protease inhibitors (Kozal et al, *Nat Med*, 1996), and may be more prevalent in viruses from patients in whom a protease inhibitor-containing regimen has failed. However, by itself, protease mutation L63P does not cause any appreciable increase in the IC_{50} for any protease inhibitor. L63P is listed for lopinavir/ritonavir (and not any other protease inhibitor) because the prescribing information approved by the FDA lists it as one of the multiple mutations that together predict a lack of viral load response to lopinavir/ritonavir-containing regimens.

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