

Drug Resistance Mutations in HIV-1

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New information continues to accumulate on drug resistance mutations in HIV-1 and their relevance to clinical practice. The Drug Resistance Mutations Group of the International AIDS Society-USA (IAS-USA), originally a subgroup of the IAS-USA Resistance Testing Guidelines Panel,¹ monitors the influx of information and maintains a current list of mutations that impact drug susceptibility. This list is published as the IAS-USA Drug Resistance Mutations Figures and is updated regularly. The most recent update and adaptation was published in this journal and posted on the IAS-USA Web site (www.iasusa.org) in December 2001.² The new graphic presented here includes relevant data presented at the 9th Conference on Retroviruses and Opportunistic Infections, held in Seattle, Wash, in February 2002.³

New Graphic Display

These new figures feature a simpler graphic display of the information for easier reference. The nucleotide reverse transcriptase inhibitor (nRTI) category, including only tenofovir disoproxil fumarate (tenofovir DF), has been combined with the nucleoside reverse transcriptase inhibitor (nRTI) category. For all mutations, the codon number, rather than a mark, appears on the gene. Finally, the nRTI-associated mutations (NAMs) are indicated as pink lines in the background. Where a codon number marks the NAM, data indicate that the

mutation confers resistance to the specific drug.

Content Changes

In this revision, "primary" or "secondary" mutations in the protease gene have been redefined as "major" or "minor" mutations to avoid confusion regarding the order in which the mutations may occur. In general, major mutations are either (1) selected first by the drug; or (2) are shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or replication. By themselves, major mutations have an effect on phenotype. In general, these mutations tend to be the major contact residues for drug binding. On the protease inhibitor figure, the codon numbers for major mutations are marked in boldface type (see key).

Minor mutations, in general, appear later than major mutations, and by themselves have not been shown to have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus carrying major mutations. On the protease gene figure, the codon numbers for minor mutations are marked in lightface type (see key).

Other changes to the figures include noting the effect of the E44D mutation on response to zidovudine, clarifying the role of the V108I and P225H mutations to efavirenz resistance, and adding an explanation of the M184V mutation and

its contribution to phenotypic resistance to abacavir.

Figure Pocket Card Available

The IAS-USA Drug Resistance Mutations Figures are now available on a pocket-sized folding card. To order copies, please call the IAS-USA at (415) 561-6720 or e-mail your request to resistance@iasusa.org.

Future Updates

The IAS-USA Drug Resistance Mutations Group will consider the next update after the 6th International Workshop on HIV Drug Resistance and Treatment Strategies, to be held in June 2002 in Seville, Spain. In the meantime, we welcome evidence-based comments to this paper. Please send your comments, along with the relevant supporting reference citations, to resistance@iasusa.org; submissions will be considered for the next update.

References

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2. International AIDS Society-USA Resistance Mutations Group. Update on drug resistance mutations in HIV-1. *Topics in HIV Medicine*. 2001;9(6):21-23.
3. 9th Conference on Retroviruses and Opportunistic Infections. Available at: <http://www.retroconference.org>. Accessed May 23, 2002.

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Multi-nRTI Resistance: 151 Complex	A	V	F	F	Q					
	62	75	77	116	151					
	V	I	L	Y	M					
Multi-nRTI Resistance: 69 Insertion Complex ¹	M	A	D	▼	K			L	T	K
	41	62	67	69	70			210	215	219
	L	V	N	insert	R			W	Y	Q
								F	E	
Multi-nRTI Resistance ² (NAMs)	M		D		K			L	T	K
	41		67		70			210	215	219
	L		N		R			W	Y	Q
								F	E	
Zidovudine ³⁻⁵	M		D		K			L	T	K
	41		67		70			210	215	219
	L		N		R			W	Y	Q
								F	E	
Didanosine ⁶			K		L					M
		65			74					184
		R			V					V
Zalcitabine			K	T	L					M
		65	69		74					184
		R	D		V					V
Stavudine ^{3,7}	M		D		K	V		L	T	K
	41		67		70	75		210	215	219
	L		N		R	T M S A		W	Y	Q
								F	E	
Abacavir ⁸	M		K	D	K	L		Y		M
	41		65	67	70	74		115		184
	L		R	N	R	V		F		V
										W
										Y
										Q
										E
Lamivudine ⁹	E							V		M
	44							118		184
	D							I		V
										I
Tenofovir DF ^{3,10}			K							
		65								
		R								

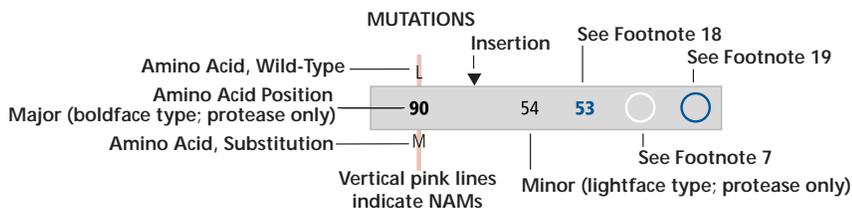
Nonnucleoside Reverse Transcriptase Inhibitors

Multi-NNRTI Resistance ¹¹					K					Y		
					103					188		
					N					L		
Multi-NNRTI Resistance (accumulation of mutations) ¹²					L	V			Y	G	M	
					100	106			181	190	230	
					I	A			C	S	L	
									I	A		
Nevirapine					L	K	V	V	Y	Y	G	
					100	103	106	108	181	188	190	
					I	N	A	I	C	C	A	
									I	L	H	
Delavirdine ¹³					K				Y		P	
					103				181		236	
					N				C		L	
Efavirenz ^{13,14}					L	K	V		Y	Y	G	P
					100	103	108		181	188	190	225
					I	N	I		C	L	S	H
									I	A		

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

Protease Inhibitors¹⁵

Multi-Protease Inhibitor Resistance (accumulation of mutations) ¹⁶	L				M					I			V	I	L				
	10				46					54			82	84	90				
	F				I					V			A	V	M				
	I				L					M			F						
	R									L			T						
	V												S						
Indinavir ¹⁷	L	K	L		V	M	M			I		A	G	V	V	I	L		
	10	20	24		32	36	46			54		71	73	77	82	84	90		
	I	M	I		I	I	I			V		V	S	I	A	V	M		
	R	R					L					T	A		F				
	V														T				
Ritonavir	L	K			V	L	M	M				A		V	V	I	L		
	10	20			32	33	36	46				71		77	82	84	90		
	F	M			I	F	I	I				V		I	A	V	M		
	I	R					L					T			F				
	V														T				
Saquinavir	L									G			A	G	V	V	I	L	
	10									48			71	73	77	82	84	90	
	I									V			V	S	I	A	V	M	
	R									L			T						
	V																		
Nelfinavir	L				D		M	M					A		V	V	I	N	L
	10				30		36	46					71		77	82	84	88	90
	F				N		I	I					V		I	A	V	D	M
	I						L						T			F		S	
																T			
																S			
Amprenavir	L				V		M	I	I	I			G				I	L	
	10				32		46	47	50	54			73				84	90	
	F				I		I	V	V	L			S				V	M	
	I						L			V									
	R									M									
	V																		
Lopinavir/ Ritonavir ^{18,19}	L	K	L		V	L	M	I	I	F	I	L		A	G		V	I	L
	10	20	24		32	33	46	47	50	53	54	63		71	73		82	84	90
	F	M	I		I	F	I	V	V	L	V	P		V	S		A	V	M
	I	R					L			L	L			T			F		
	R																T		
	V																S		



For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate 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 nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor. The figures were last published in this journal in December 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

¹The 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. Some other amino acid changes from the wild-type T in codon 69 without the insertion may also be associated with broad nRTI resistance.

²Multi-nRTI-associated mutations (NAMs): mutations associated with cross-resistance to nRTIs (except lamivudine).

³The reverse transcriptase mutation M184V may enhance susceptibility. This effect may be overcome by an accumulation of NAMs. The clinical significance of this effect is not known.

⁴One study reported that the E44D or V118I mutation confers lamivudine resistance in a zidovudine-resistant background (Hertogs et al, *Antimicrob Agents Chemother*, 2000). Analysis from AIDS Clinical Trials Group 241 associated the E44D mutation with a significantly worse response to treatment with zidovudine and didanosine, with or without nevirapine (Precious et al, *AIDS*, 2000).

⁵The D/C/S substitutions in reverse transcriptase 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 T215Y may emerge quickly from T215D/C/S in the presence of drug; in vivo relevance is possible but not yet proven.

⁶One of the following (K65R, L74V) by itself or a combination of a few of the following (NAMs, E44D, T69D/N, V118I) can lead to didanosine resistance.

⁷V75T/M/S/A are seldom observed in patients in whom stavudine has failed.

⁸When present with NAMs, the M184V mutation is selected by abacavir and contributes to phenotypic resistance to

abacavir. However, when present alone, the M184V mutation does not appear to be associated with a reduced virologic response to abacavir.

⁹One article reports that the E44D or V118I mutation confers low-level resistance to lamivudine when accompanied by several of the NAMs (M41L, D67N, L210W, T215Y/F, K219Q/E) in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother*, 2000). One abstract (D'Arminio-Monforte et al, 8th CROI, 2001), reported no association over the short term between E44D or V118I and virologic response to a lamivudine-containing combination regimen.

¹⁰In vitro data suggest that 4 or more NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) will lead to a significant degree of resistance; the actual clinical cut-off for tenofovir DF IC₅₀ or a detailed relationship between specific multiple NAMs and tenofovir DF IC₅₀ has not yet been published. Clinical trial results indicate reduced plasma HIV-1 RNA responses to tenofovir DF in groups of patients in whose plasma virus 3 or more NAMs, including either M41L or L210W, were identified (Miller et al, 9th CROI 2002). The group of patients with plasma virus in which any accumulation of D67N, K70R, T215Y/F, or K219Q/E were identified (in the absence of detection of M41L or L210W) did not have a diminished average HIV-1 RNA response to tenofovir DF in that data set.

¹¹The K103N or Y188L mutation by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

¹²Accumulation of these mutations (2 or more) substantially reduces the clinical utility of all of the currently approved NNRTIs.

¹³There are some in vitro data suggesting that the Y318F 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 Y318F mutation on efavirenz 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.

¹⁴V108I and P225H each contribute to efavirenz resistance when present in combination with other NNRTI mutations. Although V108I or P225H alone does not confer measurable resistance in laboratory strains of HIV-1, their presence in a clinical isolate may indicate prior selection for efavirenz-resistant variants.

¹⁵The Drug Resistance Mutations Group has reclassified resistance mutations in the protease gene as either “major” or “minor” rather than “primary” or “secondary” (if known).

Major: In general, major mutations are either (1) selected first by the drug; or (2) are shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. By themselves, major mutations have an effect on phenotype. In general, these mutations tend to be the major contact residues for drug binding.

Minor: In general, minor mutations appear later than major mutations, and by themselves have not been shown to have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus carrying major mutations.

¹⁶Accumulation of these mutations (4 or 5 or more) is likely to cause multi-protease inhibitor resistance.

¹⁷For indinavir, the mutations listed as major may not be the first mutations selected, but they are present in most patient isolates in combination with other mutations.

¹⁸Major and minor mutations have not been designated for lopinavir/ritonavir-associated resistance since there are currently no clear data defining degrees of influence with this drug combination. The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The product information states that 7 or

8 mutations confer resistance to the drug. However, more recent data suggest as few as 4 mutations can be associated with high-level resistance (Prado et al, *AIDS*, 2002). Further clinical experience and research are needed to better define the mutations that affect the effectiveness of lopinavir/ritonavir.

¹⁹Protease 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 IC₅₀ for any protease inhibitor. L63P is listed for lopinavir/ritonavir (and not any other protease inhibitor) because the prescribing information approved by the US Food and Drug Administration lists it as one of the numerous mutations that together predict a lack of viral load response to lopinavir/ritonavir-containing regimens.

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