

Antiretroviral Resistance Mutations Revised April 2001

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Antiretroviral Resistance Mutations

Revised April 2001

*A collaborative effort of the International AIDS Society-USA Resistance Testing Panel
and HIV InSite*

INTRODUCTION

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HIV InSite Medical Editor*

Antiviral resistance testing of HIV is assuming an increasingly important role in guiding the selection of treatment regimens, particularly in the setting of antiretroviral treatment failure. An international expert panel of the International AIDS Society-USA (IAS-USA) has published recommendations regarding resistance testing. HIV InSite has collaborated with the IAS-USA to develop a graphic representation of HIV-1 drug resistance mutations.

Given the many possible combinations of mutations, and the complexity of other factors that can contribute to treatment failure (including suboptimal adherence or inadequate drug absorption,

regimens of inadequate potency, and reservoirs of resistant HIV “archived” during past treatment), the panel has recommended expert interpretation of genotypic (and phenotypic) resistance testing results. These figures are therefore intended to be of use to experienced clinicians taking genotypic tests into account as one factor among several in selecting an antiretroviral regimen.

The number of possible combinations of mutations and polymorphisms is enormous, and the clinical relevance of only a fraction of these possible genotypes is known with assurance. Nevertheless, certain mutations or combinations have been consistently associated with failure of certain antiviral drugs or drug classes. The mutations presented in the figures are those chosen by the expert panel to be common, selected by available antiretroviral drugs, and associated with antiretroviral resistance.

Resistance Mutations Project panel, a sub-group of the Resistance Testing Guidelines panel: Richard T. D'Aquila, MD, Harvard Medical School, Boston, Massachusetts (Chair); Jonathan M. Schapiro, MD, National Hemophilia Center, Israel, and Stanford University School of Medicine, Stanford, California (Vice-chair); Brian Conway, MD, University of British Columbia, Vancouver, British Columbia, Canada; Françoise Brun-Vézinet, MD, PhD, Hôpital Bichat-Claude Bernard, Paris; France; Bonaventura Clotet, MD, PhD, Fundacio irsa CAIXA and HIV Unit, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; Lisa M. Demeter, MD, University of Rochester, Rochester, New

York; Victoria A. Johnson, MD, The University of Alabama at Birmingham, Birmingham, Alabama; Daniel R. Kuritzkes, MD, University of Colorado Health Sciences Center, Denver, Colorado; Clive Loveday, MD, PhD, The Royal Free Hospital Medical School, London, England; Douglas D. Richman, MD, University of California San Diego and San Diego Veterans Affairs Medical Center, La Jolla, California.

Please address comments and suggestions to resistance@iasusa.org.

HIV Clinical Trials 2001;2(4):346–355

Nucleoside RT Inhibitors

Abacavir										
Wild Type	M	K	D	K	L	Y	M	L	T	K
1	41	65	67	70	74	115	184	210	215	219
Mutant	L	R	N	R	V	F	V	W	Y	Q
									F	E

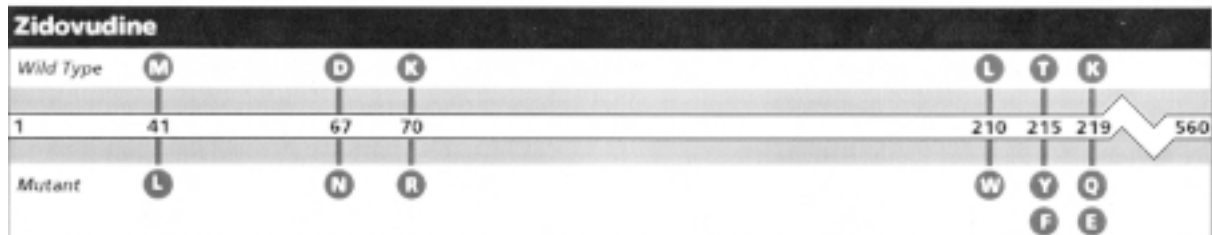
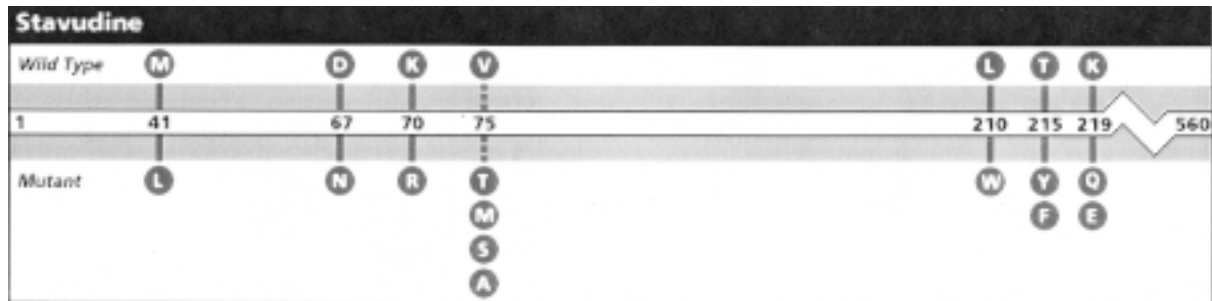
Didanosine										
Wild Type	K	L	M							
1	65	74	184							560
Mutant	R	V	V							

Lamivudine										
Wild Type	E	V	M							
1	44	118	184							560
Mutant	D	I	V							I

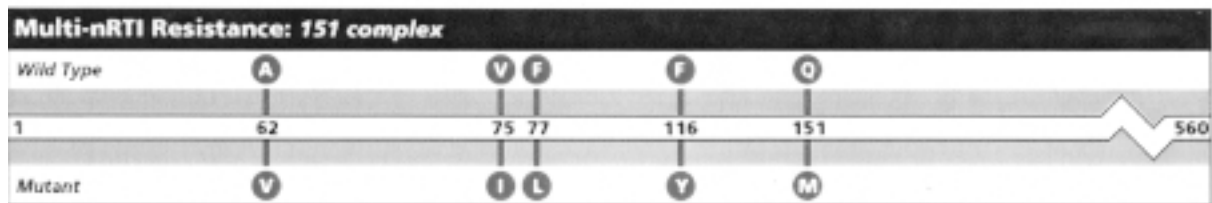
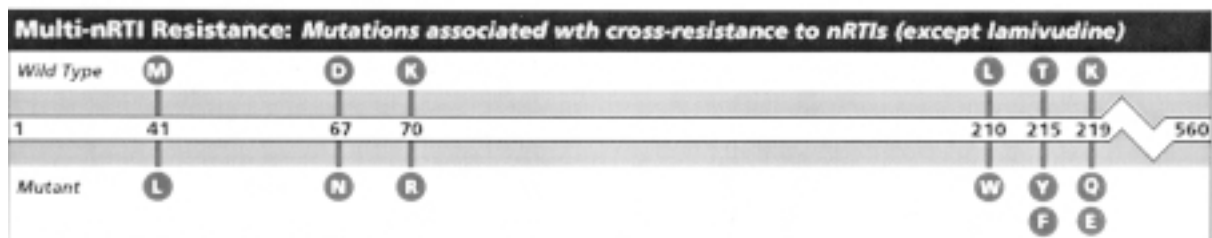
Note: Conflicting data exist regarding the significance of E44D and V118I, as indicated by the representation of these mutations in a lighter color. One article reports low-level increased phenotypic resistance to lamivudine (3TC) with E44D and/or V118I, in the absence of concurrent M184V (Hertogs et al. *Antimicrob Agents Chemother.* 2000;44:568-573). One abstract (D'Arminio-Monforte et al, 8th Conference on Retroviruses and Opportunistic Infections, 2001, Chicago, Abstract 447) reported no association over a short term between E44D or V118I and viral load responses to a lamivudine-containing combination regimen.

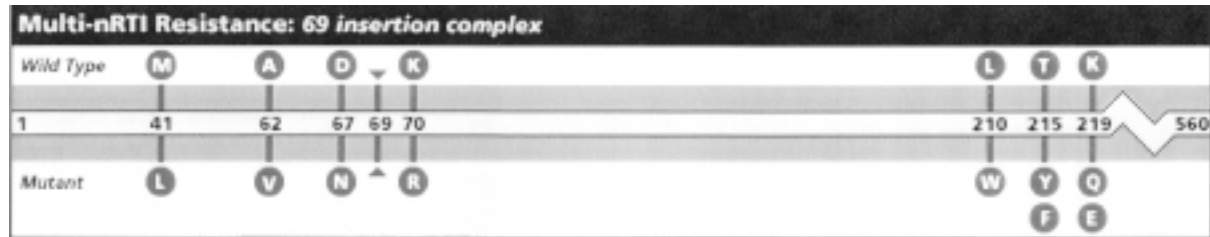
A

Figure 1. (A-C) Mutations in the HIV-1 reverse transcriptase (RT) gene associated with reduced susceptibility to nucleoside and nucleotide RT inhibitors. (Figure 1 continues.)



Note: RT mutation M184V may temporarily partially reverse the effects of the above mutations on zidovudine resistance. However, if more than 3 of the above mutations are present, the additional presence of M184V is not likely to reverse phenotypic zidovudine resistance.



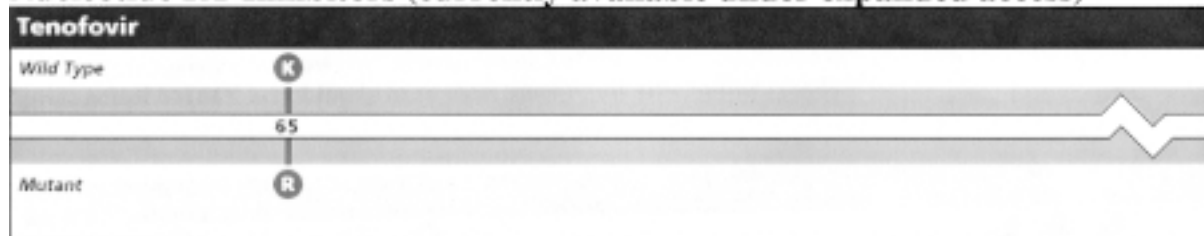


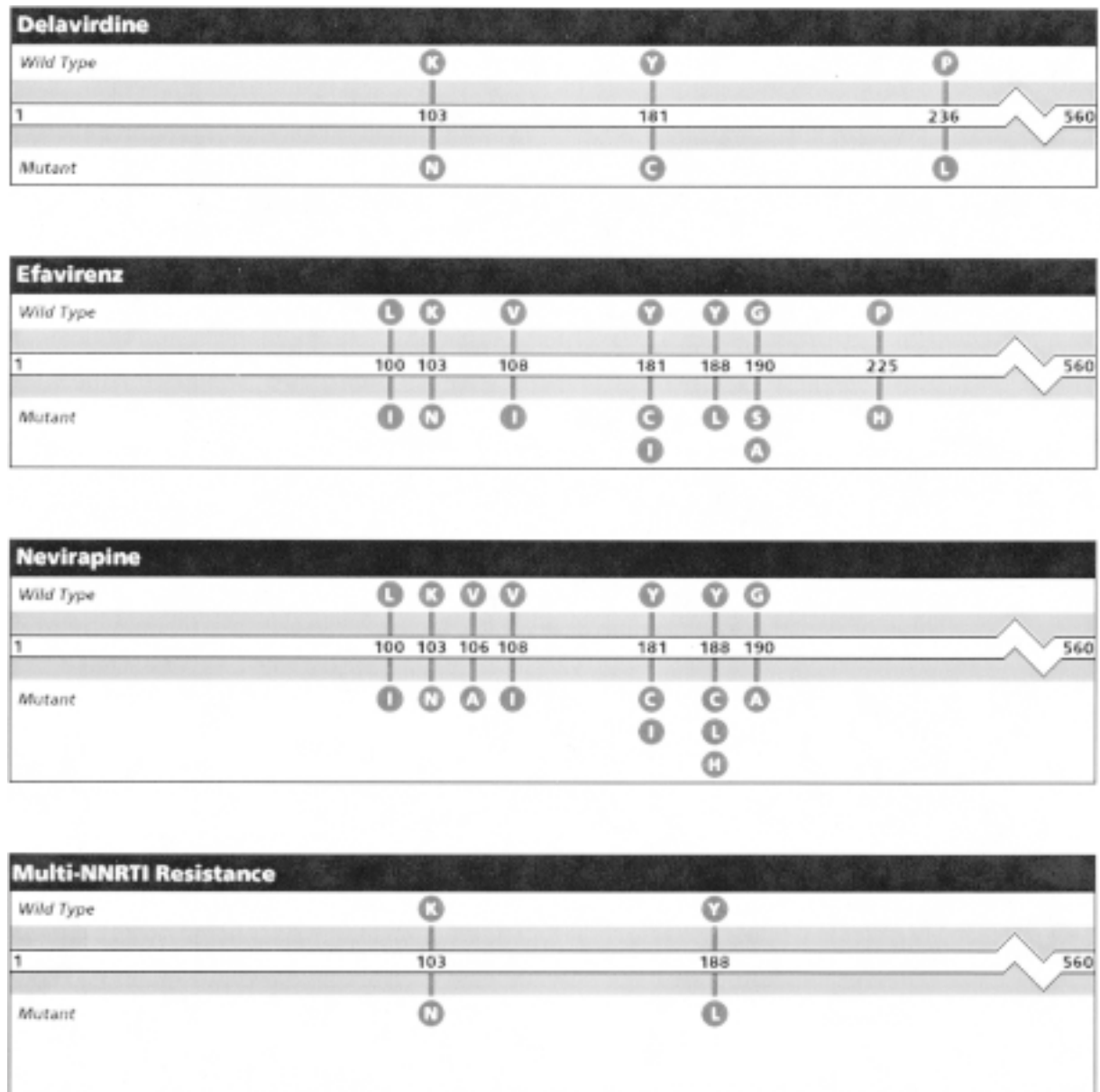
Note: The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, and others), is associated with resistance to multiple nRTIs. As shown in the diagram, the 69 insertion mutation is often accompanied by mutations at other sites.

Amino Acid Letter Codes									
A Alanine	E Glutamic acid	H Histidine	L Leucine	P Proline	S Serine	W Tryptophan			
C Cysteine	F Phenylalanine	I Isoleucine	M Methionine	Q Glutamine	T Threonine	Y Tyrosine			
D Aspartic acid	G Glycine	K Lysine	N Asparagine	R Arginine	V Valine				
⋮ Seldom observed in patient isolates				⌵ Insertion Mutation					

The clinical significance of the mutations that appear first (ie, primary) versus those that appear later (ie, secondary) remains debatable, particularly for nRTIs and 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.

Nucleotide RT Inhibitors (currently available under expanded access)

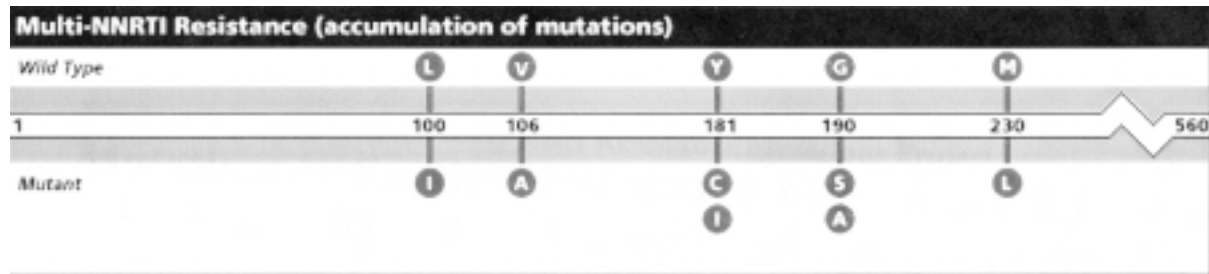




Note: Either of these mutations by itself can substantially reduce the clinical utility of all currently approved NNRTIs.

A

Figure 2. (A-B) Mutations in the HIV-1 reverse transcriptase (RT) gene associated with reduced susceptibility to nonnucleoside RT inhibitors. (Figure 2 continues.)

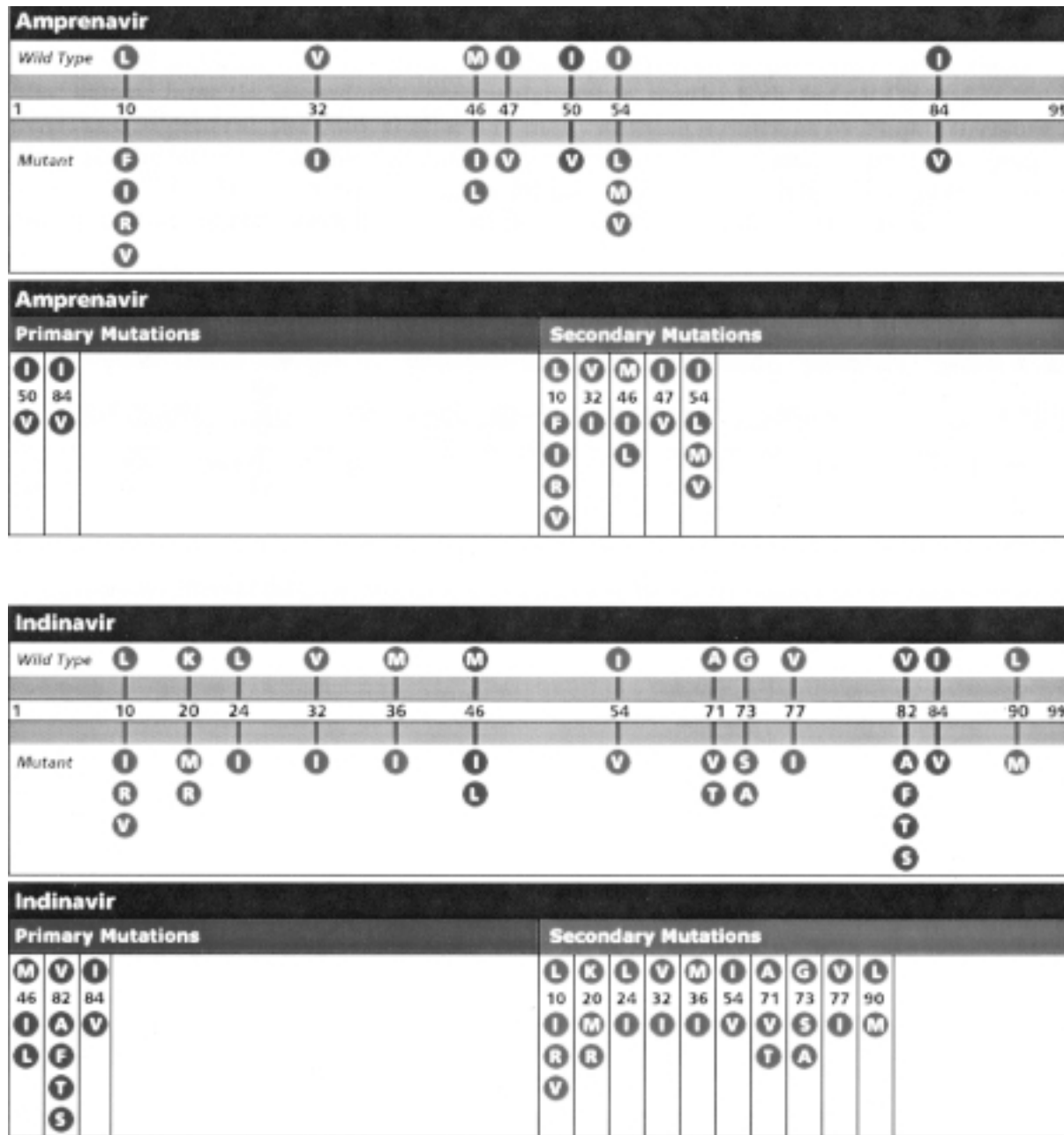


Note: Accumulation of these mutations (2 or more) substantially reduces the clinical utility of all of the currently approved NNRTIs.

Amino Acid Letter Codes							
A Alanine	E Glutamic acid	H Histidine	L Leucine	P Proline	S Serine	W Tryptophan	
C Cysteine	F Phenylalanine	I Isoleucine	M Methionine	Q Glutamine	T Threonine	Y Tyrosine	
D Aspartic acid	G Glycine	K Lysine	N Asparagine	R Arginine	V Valine		

The clinical significance of the mutations that appear first (ie, primary) versus those that appear later (ie, secondary) remains debatable, particularly for nRTIs and 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.

B



A

Figure 3. (A-D) Mutations in the HIV-1 protease gene associated with reduced susceptibility to protease inhibitors. (Figure 3 continues.)

Lopinavir/Ritonavir														
Wild Type	L	K	L		M	F	I	L	A		V	I	L	
1	10	20	24		46	53	54	63	71		82	84	90	99
Mutant	F I R V	M R	I		I L	L V L		P V T			A V F T S		M	

Lopinavir/Ritonavir												
Primary Mutations					Secondary Mutations							
	L 10 F I R V	K 20 M R	L 24 I	M 46 I L	F 53 L	I 54 V L	L 63 P	A 71 V T	V 82 A F T S	I 84 V	L 90 M	

Notes: The accumulation of 6 or more of these mutations is associated with diminished response to lopinavir/ritonavir. Accumulation of 7 or 8 or more of these mutations makes response to lopinavir/ritonavir unlikely. The mutations listed are based on one report 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.

Protease mutation L63P is common in viruses that have never been exposed to protease inhibitors (Kozal et al. *Nat Med.* 1996;2:753-759) and may be more prevalent in viruses from patients in whom a protease inhibitor-containing regimen has failed. However, by itself, 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 FDA lists it as one of the several mutations that when together with other mutations predict a lack of viral load response to lopinavir/ritonavir-containing regimens. For these reasons, L63P is designated in a lighter color.

Nelfinavir												
Wild Type	L	D	M	M		A	V		V	I	N	L
1	10	30	36	46		71	77		82	84	88	90 99
Mutant	F I	N	I	I L		V T	I		A F T S	V	D S	M

Nelfinavir												
Primary Mutations					Secondary Mutations							
D 30	L 90				L 10 F I	M 36 I	M 46 I L	A 71 V T	V 77 I	V 82 A F T S	I 84 V	N 88 D S

Ritonavir													
Wild Type	L	K	V	L	M	M	I	A	V	V	I	L	
1	10	20	32	33	36	46	54	71	77	82	84	90	99
Mutant	F	M	I	F	I	I	V	V	I	A	V	M	
	I	R				L	L	T		F			
	R									T			
	V									S			

Ritonavir													
Primary Mutations							Secondary Mutations						
V	I						L	K	V	L	M	M	I
82	84						10	20	32	33	36	46	54
A	V						F	M	I	F	I	I	V
F							I	R				L	V
T							R						T
S							V						

Saquinavir													
Wild Type	L			G	I	A	G	V	V	I	L		
1	10			48	54	71	73	77		82	84	90	99
Mutant	I			V	V	V	S	I		A	V	M	
	R				L		T						
	V												

Saquinavir													
Primary Mutations							Secondary Mutations						
G	L						L	I	A	G	V	V	I
48	90						10	54	71	73	77	82	84
V	M						I	V	V	S	I	A	V
							R	L	T				
							V						

Multi-Protease Inhibitor Resistance (accumulation of mutations)													
Wild Type	L			M	I			V	I	L			
1	10			46	54			82	84	90	99		
Mutant	F			I	V			A	V	M			
	I			L	M			F					
	R				L			T					
	V							S					

Multi-Protease Inhibitor Resistance (accumulation of mutations)									
Primary Mutations					Secondary Mutations				
M	V	I	L		L	I			
46	82	84	90		10	54			
I	A	V	M		F	V			
L	F				I	M			
	T				R	L			
	S				V				

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

Amino Acid Letter Codes											
A	Alanine	E	Glutamic acid	H	Histidine	L	Leucine	P	Proline	S	Serine
C	Cysteine	F	Phenylalanine	I	Isoleucine	M	Methionine	Q	Glutamine	T	Threonine
D	Aspartic acid	G	Glycine	K	Lysine	N	Asparagine	R	Arginine	V	Valine
										W	Tryptophan
										Y	Tyrosine
● Primary Mutations				● Secondary Mutations							

The distinction between primary and secondary mutations was kept for protease inhibitors because those mutations that are listed as primary do have greater effects on drug susceptibility (eg, increasing the IC₅₀) than do those that are listed as secondary.

D