

Update of the Drug Resistance Mutations in HIV-1: 2005

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Since 2000, the International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group has worked as an independent entity and forged a collaborative process to identify key HIV-1 drug resistance mutations. The goal of the group is to quickly deliver accurate and unbiased information to clinical practitioners on HIV-1 resistance. This April 2005 version of the IAS-USA Drug Resistance Mutations Figures replaces the version published in this journal in October 2004.

The IAS-USA Drug Resistance Mutations Figures are designed for use in identifying mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiologic studies of transmission of drug-resistant virus. A number of amino acid substitutions, particularly minor mutations, represent polymorphisms that, in isolation, may not reflect prior drug selective pressure or reduced drug susceptibility.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance most commonly develops to lamivudine or the

nonnucleoside reverse transcriptase inhibitors).¹⁻⁵ This paradox may involve patient nonadherence, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

A copy of the current recommendations for antiretroviral resistance testing from the IAS–USA HIV Resistance Testing Guidelines Panel⁶ can be found on the IAS–USA Web site at www.iasusa.org.

Revisions to the Figures for the 2005 Update

Two major changes have been included in this April 2005 version of the figures and user notes. First, on the figures, the bars representing multidrug resistance mutations have been moved to the bottom of the drug class. The only exception is that the multi-nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) bar remains at the top of the nRTI class, because of the pervasive effect of the thymidine analogue-associated mutations (TAMs), the E44D and the V118I in conferring resistance to all nRTIs.

In addition, user notes have been revised to focus on current, more clinically focused information. These new user notes provide additional detail, where necessary, to the information presented in the figures. Other changes to the figures and user notes are described below.

Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

In this version, the definitions of nucleoside (or nucleotide)-associated mutations

(NAMs) and TAMs have been clarified (see user note 2). In brief, the TAMs (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) are a subset of the NAMs. The TAMs are distinguished as bold mutations on the multi-nRTI bar; E44D and V118 are shown in normal weight type.

For lamivudine, the E44D and V118I have been removed from the list as specific lamivudine-associated mutations. Originally, the E44D and V118I were understood to confer a low level of resistance to lamivudine.⁷ From subsequent studies, it has become evident that E44D and V118I are mutations that contribute to zidovudine resistance and thus contribute to cross resistance to the other nRTIs, including lamivudine.⁸

For zalcitabine, T69D now is marked in a lighter-weight type than the other mutations to indicate that it is rare and less important than other mutations, such as the TAMs, in conferring resistance to zalcitabine.⁹ In the future, the group plans to weight the mutations in the nRTI and NNRTI classes, as is currently done with the major and minor protease inhibitor (PI) mutations.

The D67N has been deleted from the Multi-nRTI Resistance: 69 Insertion Complex bar, now located at the bottom of the nRTI list. A recent analysis found no evidence of the D67N in 200 sequences from clinical isolates containing the insertion.¹⁰

Nonnucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

A new user note has been included referencing both the nRTIs and the nonnucleoside (or nucleotide) reverse transcriptase inhibitors (NNRTIs) on the issue of
(continued, page 56)

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

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)¹

	M	E	D	K	V	L	T	K	
Multi-nRTI Resistance ²	41	44	67	70	118	210	215	219	
Zidovudine ^{3,4}	41	44	67	70	118	210	215	219	
Stavudine ^{3,4}	41	44	65	67	70	118	210	215	219
Didanosine ^{5,6}			65		74				
Zalcitabine ⁷			65	69	74			184	
Abacavir ⁸			65		74	115		184	
Lamivudine			65					184	
Emtricitabine ⁹			65					184	
Tenofovir ¹⁰			65						

Multi-nRTI Resistance: 69 Insertion Complex¹¹ (affects all nRTIs currently approved by the US FDA)

M	A	K	L	T	K	
41	62	69	70	210	215	219

Multi-nRTI Resistance: 151 Complex¹² (affects all nRTIs currently approved by the US FDA except tenofovir)

V	I	L	Y	M
62	75	77	116	151

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)^{1,13}

	L	K	V	V	Y	Y	G	
Nevirapine	100	103	106	108	181	188	190	
Delavirdine	103	106			181	188		236
Efavirenz	100	103	106	108	181	188	190	225

Multi-NNRTI Resistance¹⁴ (affects all NNRTIs currently approved by the US FDA)

K	V	Y
103	106	188

Multi-NNRTI Resistance: Accumulation of Mutations¹⁵ (affects all NNRTIs currently approved by the US FDA)

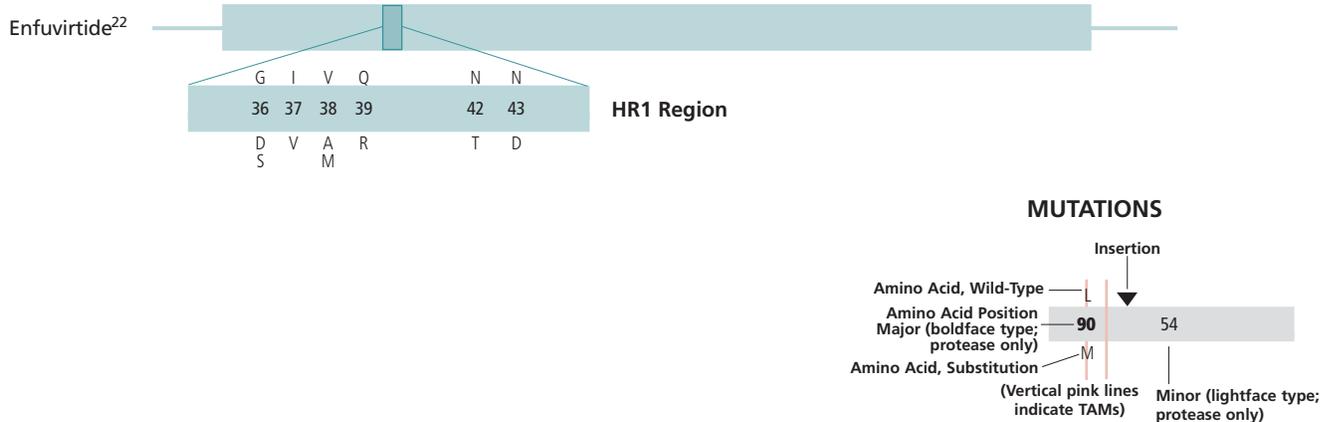
L	V	Y	G	M
100	106	181	190	230

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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS^{16,17}

Indinavir	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			
Ritonavir	L	K		V	L	M	M	I	A	V	V	I	L			
	10	20		32	33	36	46	54	71	77	82	84	90			
Saquinavir	L						G	I	A	G	V	V	I	L		
	10						48	54	71	73	77	82	84	90		
Nelfinavir ¹⁸	L		D		M	M		A	V	V	I	N	L			
	10		30		36	46		71	77	82	84	88	90			
(Fos) amprenavir	L			V		M	I	I	I	G		I	L			
	10			32		46	47	50	54	73		84	90			
Lopinavir/ ritonavir 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
Atazanavir	L	K	L	V	L	M	M	G	I	I	A	G	V	I	N	L
	10	20	24	32	33	36	46	48	50	54	71	73	82	84	88	90
Tipranavir/ ritonavir (expanded access) ²⁰	L	K		L		M		I		V	I	L				
	10	20		33		46		54		82	84	90				
Multi-protease Inhibitor (PI) Resistance: Accumulation of Mutations ²¹ (affects all PIs currently approved by the US FDA)																
	L			V		M		I		V	I	L				
	10			32		46		54		82	84	90				

MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



The International AIDS Society–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug.

The mutations listed have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. In addition, the group only reviews data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded access protocols are included. User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact.

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. HR1 indicates first heptad repeat; nRTI indicates nucleoside reverse transcriptase inhibitor; NAMs indicates nRTI-associated mutations; TAMs indicates thymidine-associated mutations; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor.

User Notes

1. Numerous nucleoside (or nucleotide) reverse transcriptase inhibitor (nRTI) mutations, such as the M41L, L210W, and T215Y mutations, may lead to viral hypersusceptibility to the nonnucleoside reverse transcriptase inhibitors (NNRTIs) in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens in NNRTI treatment-naïve individuals (Shulman et al, *AIDS*, 2004; Demeter et al, 11th CROI, 2004; Haubrich et al, 11th CROI, 2004; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003).

2. Multi-nRTI resistance mutations, also known as nucleoside-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as thymidine-associated mutations (TAMs; in bold type on the figure). TAMs are a subset of NAMs that are selected by the thymidine analogues zidovudine and stavudine and are associated with cross-resistance to all nRTIs currently approved by the US FDA (Larder et al, *Science*, 1989; Kellam et al, *Proc Natl Acad Sci USA*, 1992; Calvez et al, *Antivir Ther*, 2002; Kuritzkes et al, *JAIDS*, 2004). The E44D and the V118I increase the level of resistance to zidovudine and stavudine, and correspondingly increase cross-resistance to the other nRTIs. The significance of E44D or

V118I when each occurs in isolation is unknown (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

3. The presence of the M184V mutation appears to delay or prevent emergence of TAMs (Kuritzkes et al, *AIDS*, 1996). This effect may be overcome by an accumulation of TAMs or other mutations. The clinical significance of this effect of M184V is not known.

4. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215, conferring increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naïve patients (Riva et al, *Antivir Ther*, 2002; Chappey et al, *Antivir Ther*, 2003; Violin et al, *AIDS*, 2004). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *J Virol*, 2004; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).

5. The K65R mutation may be selected by didanosine and is associated in vitro with decreased susceptibility to the drug (Winters et al, *Antimicrob Agents Chemother*, 1997). The impact of the K65R in vivo is unclear.

6. The presence of 3 of the following—M41L, D67N, L210W, T215Y/F, and K219Q/E—has

been associated with resistance to didanosine (Marcelin et al, *Antimicrob Agents Chemother*, in press). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).

7. Limited clinical use of zalcitabine has resulted in very limited data on resistance and cross-resistance. The K65R, L74V, and 184V mutations, alone or in combination with any of the TAMs, can lead to resistance to zalcitabine in vitro (Parikh et al, *Antivir Ther*, 2003; Gu et al, *Antimicrob Agents Chemother*, 1994; Zhang et al, *Antimicrob Agents Chemother* 1994). The T69D alone leads to a modest increase (2-fold change) in zalcitabine resistance (not bolded on the figure) (Fitzgibbon, *Antimicrob Agents Chemother*, 1992).

8. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000; Lanier et al, *Antivir Ther*, 2004). When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo (Lanier et al, *Antivir Ther*, 2004). The M184V plus 4 or more TAMs resulted in no virologic response to abacavir in vivo (Lanier et al, *Antivir Ther*, 2004).

9. There are limited data on the effects of emtricitabine mutations in vivo. It is assumed that if resistance to emtricitabine emerges, the virus will also be resistant to lamivudine, and vice versa. New mutations that confer resistance or cross-resistance to emtricitabine may exist, but have not yet been described.

10. The K65R is associated with a reduced virologic response to tenofovir in vivo (Miller et al, *J Infect Dis*, 2004). A reduced response occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W (Miller et al, *J Infect Dis*, 2004). Slightly increased treatment responses to tenofovir in vivo were observed if M184V was present (Miller et al, *J Infect Dis*, 2004).

11. The 69 insertion complex consists of a substitution at codon 69 (typically T69S) and an insertion of 2 or more amino acids (S-S, S-A, S-G, or others). The 69 insertion complex is associated with resistance to all nRTIs currently approved by the US FDA when present with 1 or more TAMs at codons 41, 210, or 215 (Miller et al, *J Infect Dis*, 2004). Some other amino acid changes from the wild-type T at codon 69 without the insertion may also be associated with broad nRTI resistance.

12. Tenofovir retains activity against the Q151M complex of mutations (Miller et al, *J Infect Dis*, 2004).

13. The long-term virologic response to sequential NNRTI use is poor, particularly when 2 or more mutations are present (Antinori et al, *AIDS Res Hum Retroviruses*, 2002; Lecossier et al, *J Acquir Immune Defic Syndr*, 2005).

14. The K103N or Y188L mutation alone can substantially reduce the clinical utility of all NNRTIs currently approved by the US FDA (Antinori et al, *AIDS Res Human Retroviruses*, 2002). The V106M mutation is more common in HIV-1 subtype C than in subtype B, and confers cross-resistance to all currently approved NNRTIs (Brenner et al, *AIDS*, 2003; Cane et al, *J Clin Micro*, 2001).

15. Accumulation of 2 or more of these mutations substantially reduces the clinical utility of all NNRTIs currently approved by the US FDA.

16. In general, the same mutations emerge whether or not the protease inhibitors (PIs) are boosted with low-dose ritonavir, although there is some difference in the relative frequency of various mutations. However, with regimens that include boosted PIs, multiple mutations may be required to result in less virologic activity. More data are needed to make specific comparisons between a particular boosted PI and a nonboosted PI.

17. Resistance mutations in the protease gene are classified as either "major" or "minor," if data are available.

Major mutations in the protease gene are defined in general either as those selected first in the presence of the drug; or those shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. Major mutations have an effect on drug susceptibility phenotype. In general, these mutations tend to be the primary contact residues for drug binding.

Minor mutations generally emerge later than major mutations, and by themselves do not have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus containing major mutations. However, some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype B clades, such as K201/R and M36I in protease.

18. In some HIV-1 non-B subtypes, D30N is selected less frequently than other PI mutations (Gonzalez et al, *Antivir Ther*, 2004).

19. Major and minor designations have not been assigned for mutations associated with lopinavir boosted with low-dose ritonavir (lopinavir/ritonavir) because no clear data yet define degrees of influence with this drug combination. However, the accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.

20. Tipranavir boosted with low-dose ritonavir (tipranavir/ritonavir) is not yet approved by the US FDA, but it is available through an expanded-access protocol. No substantial data are available regarding mutations associated with clinical failure of tipranavir/ritonavir when it is the first PI used. In PI-experienced patients, accumulation of mutations at positions 33, 82, 84, and 90 correlated with virologic response. Responses were greater when fewer than 3 of these mutations were present, but larger data sets did not confirm the role of the L90M in resistance to tipranavir. Subsequently, analyses of data from phase II studies in PI-experienced patients identified mutations associated with reduced susceptibility or virologic response. These include: I10V, I13V, K20 M/R/V, L33F, E35G, M36I, N43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. These data must be considered preliminary, and they require further confirmation and validation before their clinical utility can be considered (Schapiro et al, 12th CROI, 2005; Kohlbrenner et al, DART, 2004; Mayers et al, *Antivir Ther*, 2004; Kohlbrenner et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003).

21. Accumulation of these mutations contributes to broad multi-PI resistance (Palmer et al, *AIDS*, 1999; Shafer et al, *Ann Intern Med*, 1998). The genotypic threshold for resistance (ie, the number of mutations needed to have an impact) is higher with PIs boosted with low-dose ritonavir than with PIs that are not boosted.

22. Although resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene, wild-type viruses in the depicted HR1 region vary 500-fold in susceptibility. Such pretreatment susceptibility differences were not associated with differences in clinical responses (Labrosse et al, *J Virol*, 2003). Furthermore, mutations or polymorphisms in other regions of the envelope (eg, the HR-2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *Proc Natl Acad Sci USA*,

2002; Reeves et al, *J Virol*, 2004; Xu et al, *Antimicrob Agents Chemother*, 2005). Thus, testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure (Reeves et al, *J Virol*, 2004; Menzo et al, *Antimicrob Agents Chemother*, 2004; Poveda et al, *J Med Virol*, 2004; Sista et al, *AIDS*, 2004; Su C et al, *Antivir Ther*, 2004).

Amino acid abbreviations: 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.

hypersusceptibility. As described in user note 1, numerous nRTI mutations may lead to viral hypersusceptibility to the NNRTIs and thus may improve subsequent virologic response to NNRTI-containing regimens.^{11–15}

Protease Inhibitors

A comment has been added on the mutations that emerge with PIs that are boosted with low-dose ritonavir and those that emerge with PIs that are not boosted (see user note 16). In general: (1) the same mutations emerge whether or not the PIs are boosted, although there is some difference in the relative frequency of various mutations with boosted versus unboosted PIs; and (2) more mutations are required to impact susceptibility with regimens including a boosted PI.

The lopinavir/ritonavir mutations have been designated as minor mutations (see user note 19). Previously, the lopinavir/ritonavir mutations had not been assigned as either major or minor. The initial data analysis for this drug focused on the number of mutations associated with resistance rather than degree of impact for individual mutations. This approach, which complicates the major/minor designation, is likely to be used for future analyses of other PIs that are boosted with low-dose ritonavir.

Future Revisions of the Figures

As part of the recent revisions to the user notes, the IAS-USA Drug Resistance Mutations Group is developing a table for the IAS-USA Web site (www.iasusa.org) on emerging issues in HIV-1 resistance and available resistance data for drugs in development that have completed phase 2 trials. Other issues under discussion for future versions of the figures and notes include comments on transmitted drug resistance, and the indication of nonsubtype-B mutations.

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Comments?

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes. Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at resistance2005@iasusa.org or by fax at 415-544-9401. Please include your name and institution.

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maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, the publication of out-to-date figures is counterproductive.

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