

# Update of the Drug Resistance Mutations in HIV-1: 2007

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This version of the International AIDS Society–USA (IAS-USA) Drug Resistance Mutations Figures updates the figures published in this journal in August/September 2006.<sup>1</sup> The IAS-USA Drug Resistance Mutations Group is an independent, volunteer panel of experts with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As has been established for all IAS-USA panels, rotations of panel members has begun, where 1 or 2 panel members will periodically step down from panel participation and new members will join. The panel rotations are designed to ensure that all IAS-USA expert panels remain diverse in member affiliations and areas of expertise.

The figures are designed for use in identifying key 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.

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. The group 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) as well as drugs available in expanded access programs (EAPs) are included. They are listed in alphabetic order by drug class. 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.

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 lamivu-

dine or the nonnucleoside reverse transcriptase inhibitors [NNRTIs]).<sup>2-7</sup> The absence of detectable viral resistance following treatment failure may result from the presence of drug-resistant minority viral populations, nonadherence to medications, 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.

## Revisions to the Figures for the August/September 2007 Update

### Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors (nRTIs)

Recent work regarding thymidine analogue-associated mutations (TAMs) and mutations in the connection domain<sup>8</sup> have been described in user note 4, the first revision in this year's update. Because the clinical significance of mutations in the connection domain has not been determined, they have not been listed on the figure bars.

### Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

A bar has been added to this section for etravirine, an investigational drug newly available via an EAP, and is accompanied by user note 13, which gives additional information on the associated mutations.<sup>9</sup> The delavirdine bar has been removed because of its limited clinical role.

(continued, page 124)

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

**Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)<sup>1</sup>**

Multi-nRTI Resistance: 69 Insertion Complex<sup>2</sup> (affects all nRTIs currently approved by the US FDA)

M	A	▼ K				L	T	K
<b>41</b>	<b>62</b>	<b>69 70</b>				<b>210 215 219</b>		
L	V	Insert R				W	Y	Q
						F	E	

Multi-nRTI Resistance: 151 Complex<sup>3</sup> (affects all nRTIs currently approved by the US FDA except tenofovir)

	A	V	F	F	Q			
	<b>62</b>	<b>75 77</b>		<b>116</b>	<b>151</b>			
	V	I	L	Y	M			

Multi-nRTI Resistance: Thymidine Analogue-associated Mutations<sup>4,5</sup> (TAMs; affects all nRTIs currently approved by the US FDA)

M	D	K				L	T	K
<b>41</b>	<b>67</b>	<b>70</b>				<b>210 215 219</b>		
L	N	R				W	Y	Q
						F	E	

Abacavir <sup>6</sup>		K	L	Y	M			
	<b>65</b>	<b>74</b>		<b>115</b>	<b>184</b>			
	R	V		F	V			

Didanosine <sup>7,8</sup>		K	L					
	<b>65</b>	<b>74</b>						
	R	V						

Emtricitabine		K			M			
	<b>65</b>				<b>184</b>			
	R				V			
					I			

Lamivudine		K			M			
	<b>65</b>				<b>184</b>			
	R				V			
					I			

Stavudine <sup>4,5,9,10</sup>	M	D	K			L	T	K
	<b>41</b>	<b>67</b>	<b>70</b>			<b>210 215 219</b>		
	L	N	R			W	Y	Q
						F	E	

Tenofovir <sup>11</sup>		K	K					
	<b>65</b>	<b>70</b>						
	R	E						

Zidovudine <sup>4,5,9,10</sup>	M	D	K			L	T	K
	<b>41</b>	<b>67</b>	<b>70</b>			<b>210 215 219</b>		
	L	N	R			W	Y	Q
						F	E	

**Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)<sup>1,12</sup>**

Efavirenz			L	K	V	V	Y	Y	G	P
			<b>100 103 106 108</b>				<b>181</b>	<b>188 190</b>		<b>225</b>
			I	N	M	I	C	L	S	H
							I	A		

Etravirine <sup>13</sup> (expanded access)		V	A	L	K	V	V	Y	G	
		90	98	100	101	106	179	181	190	
		I	G	I	E	I	D	C	S	
					P		F	I	A	
							V	V		

Nevirapine		L	K	V	V	Y	Y	G	
		<b>100 103 106 108</b>				<b>181</b>	<b>188 190</b>		
		I	N	A	I	C	C	A	
				M		I	L	H	



*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) as well as drugs available in expanded access programs are included (listed in alphabetic order by drug class). 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.*

## 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; Haubrich et al, *AIDS*, 2002; Tozzi, *J Infect Dis*, 2004; Katzenstein et al, *AIDS*, 2003). NNRTI hypersusceptibility can be conferred by 2 distinct phenotypes: increased enzyme susceptibility to NNRTI (eg, V118I/T215Y) or decreased virion-associated levels of reverse transcriptase (eg, H208Y/T215Y and V118I/H208Y/T215Y). The viruses that contained less reverse transcriptase replicated less efficiently than those with wild-type levels of reverse transcriptase. (Clark et al, *Antivir Ther*, 2006). The clinical relevance of all these mutations has not been assessed.

2. 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 thymidine analogue-associated mutations (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.

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

4. Multi-nRTI resistance mutations, also known as nucleoside analogue-associated mutations (NAMs), are associated with resistance to numerous nRTIs. The M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E are known as TAMs. 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, *J Acquir Immune Defic Syndr*, 2004). Mutations at the C-terminal reverse transcriptase domains (amino acids 293–560) outside of regions depicted on the figure bars may prove to be important for HIV drug resistance. Mutations in the connection (A371V) and RNase H (Q509L) domains of reverse transcriptase are coselected on the same genome as TAMs and increase significantly zidovudine resistance when combined with TAMs. They also increase, although to a much lesser extent, cross-resistance to lamivudine, abacavir, and tenofovir but not to stavudine or didanosine (Brehm et al, *Antivir Ther*, 2006). When the polymerase domain contains TAMs, mutations in the connection domain (E312Q, G335C/D, N348I, A360I/V, V365I, and A376S) increase resistance to zidovudine from 11-fold to as much as 536-fold over wild-type reverse transcriptase (Nikolenko et al, *Proc Natl Acad Sci USA*, 2007). Three mutations (N348I, T369I, and E399D) in the reverse transcriptase C-terminus are associated with the increased resistance to zidovudine and to NNRTIs. Mutations at this level could modulate NNRTI resistance by affecting dimerization of p66/p51 heterodimers (Gupta et al, *Antivir Ther*, 2006). Since the clinical relevance of these mutations has

not been demonstrated, they are not depicted on the figure bars.

5. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the setting of TAMs, 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).

6. 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).

7. 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 mutation in vivo is unclear.

8. 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*, 2005). The K70R and M184V mutations are not associated with a decreased virologic response to didanosine in vivo (Molina et al, *J Infect Dis*, 2005).

9. 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.

10. 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).

11. The K65R mutation 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).

12. 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). The K103N or Y188L mutation alone prevents 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).

13. The impact of most mutations depends on the simultaneous presence of Y181C; Y181C has impact only when present with 1 or more of these mutations. Substantial virologic response was still seen in clinical trials despite the presence of single mutations (Vingerhoets et al, *Antivir Ther*, 2007).

14. The same mutations usually emerge whether or not PIs are boosted with low-dose ritonavir, although the relative frequency of mutations may differ. Data on the selection of mutations in antiretroviral-naïve patients in whom a boosted PI is failing are very limited. Numerous mutations are often necessary to significantly impact virologic response to a boosted PI. Although numbers vary for the different drugs, 3 or more mutations are often required.

15. 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 the 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.

16. Ritonavir is not listed separately as it is currently used at therapeutic doses as a pharmacologic booster of other PIs. At higher doses tested previously in humans, ritonavir administered as monotherapy produces mutations similar to those produced by indinavir (Molla, *Nature Med*, 1996).

17. HIV-1 Gag cleavage site changes can cause PI resistance in vitro. It has been observed that mutations in the N-terminal part of *gag* (MA: E40K; L75R; K113E and CA: M200I; A224A/V), outside the cleavage site, contribute directly to PI resistance by enhancing the overall Gag processing by wild-type protease. (Nijhuis et al, *PLoS Med*, 2007). The clinical relevance of these mutations has not been assessed.

18. In most patients in whom an atazanavir/ritonavir-containing regimen was failing virologically, accumulations of the following 13 mutations were found (L10F/I/V, G16E, L33F/I/V, M46I/L, I54L/V/M/T, D60E, I62V, A71I/T/L, V82A/T, I84V, I85V, L90M, and I93L). Seven mutations were retained in an atazanavir score (L10F/I/V, G16E, L33F/I/V, M46I/L, D60E, I84V, I85V); the presence of 3 or more of these mutations predicts a reduced virologic response at 3 months, particularly when L90M was present (Vora et al, *AIDS*, 2006; <http://www.hivfrenchresistance.org/2006/tab2.html>). A different report (Bertoli et al, *Antivir Ther*, 2006) found that the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations were associated with 92%, 93%, 75%, and 0% virologic response to atazanavir/ritonavir: L10C/I/V, V32I, E34Q, M46I/L, F53L, I54A/M/V, V82A/F/I/T, I84V; presence of I15E/G/L/V, H69K/M/N/Q/R/T/Y, and I72M/T/V improved the chances of response. For unboosted atazanavir, the presence of 0, 1, 2, or greater than or equal to 3 of the following mutations was associated with 83%, 67%, 6%, and 0% response rates: G16E, V32I, K201/M/R/T/V, L33F/I/V, F53L/Y, I64L/M/V, A71I/T/V, I85V, I93L/M.

19. Darunavir (formerly TMC-114), boosted with ritonavir, was approved by the US FDA in June 2006. Resistance data are therefore still preliminary and limited. HIV RNA response to boosted darunavir correlated with baseline susceptibility and the presence of multiple specific PI mutations. Reductions in response were associated with increas-

ing numbers of the mutations indicated in the bar. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V versus V11I). Further study and analysis in other populations are required to refine and validate these findings.

20. The mutations depicted on the chart bar cannot be considered to be comprehensive since little relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug.

21. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the bar is associated with a reduced virologic response to lopinavir/ritonavir (Masquelier et al, *Antimicrob Agents Chemother*, 2002; Kempf et al, *J Virol*, 2001). The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. In contrast, in those in whom lopinavir/ritonavir is their first PI used, resistance to this drug at the time of virologic rebound is rare. However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I are associated with high-level resistance (Mo et al, *J Virol*, 2005; Friend et al, *AIDS*, 2004; Kagan et al, *Protein Sci*, 2005).

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

23. Accumulation of more than 2 mutations at positions 33, 82, 84, and 90 correlate with reduced virologic response to tipranavir/ritonavir, although an independent role for L90M was not found. Detailed analyses of data from phase II and III trials in PI-experienced patients identified mutations associated with reduced susceptibility or virologic response. These include: L10V, I13V, K20M/R, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, and I84V. Accumulation of these mutations is associated with reduced response. Subsequent genotype-phenotype and genotype-virologic response analyses determined some mutations have a greater effect than others (eg, I84V versus I54M). Refinement and clinical validation of these findings are pending (Schapiro et al, CROI, 2005; Mayers et al, *Antivir Ther*, 2004; Hall et al, *Antivir Ther*, 2003; McCallister et al, *Antivir Ther*, 2003; Parkin et al, CROI, 2006; Bacheler et al, European HIV Drug Resistance Workshop, 2006).

24. 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 in the envelope (eg, the HR2 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, *Antivir Ther*, 2004).

25. Maraviroc activity is limited to patients with only CCR5 (R5)-using virus detectable; CXCR4 (X4)-CCR5 mixed tropic viruses and X4-using viruses do not respond to maraviroc treatment. Some cases of virologic failure during maraviroc therapy are associated with outgrowth of X4 virus that pre-exists as a minority population below the level of assay detection. Mutations in the HIV-1 gp120 molecule that allow the virus to bind to R5 receptors in the presence of drug have been described in viruses from some patients whose virus remained R5 at the time of virologic failure. A number of such mutations have been identified, and the phenotypic manifestation of this drug resistance is a reduction in the maximal percentage inhibition (MPI) rather than the increase in the 50% inhibitory concentration (IC<sub>50</sub>; defined by fold increase) that is characteristic of resistance to other classes of antiretrovirals. The resistance profile for maraviroc is too complex to be depicted on the figures. The frequency and rate at which maraviroc resistance mutations emerge are not yet known.

26. Raltegravir failure was associated with integrase mutations in 2 distinct genetic pathways defined by 2 or more mutations including: (1) a signature (major) mutation at either Q148H/K/R or N155H; and (2) 1 or more minor mutations unique to each pathway. Minor mutations described in the Q148H/K/R pathway include L74M + E138A, E138K, or G140S. The most common mutation pattern in this pathway is Q148H + G140S; this Q148H + G140S pattern exhibits the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this primary mutation plus either L74M, E92Q, T97A, E92Q + T97A, Y143H, G163K/R, V151I, or D232N (Hazuda et al, *Antivir Ther*, 2007).

(continued from page 119)

### Protease Inhibitors

The L76V mutation has been added to the fosamprenavir/ritonavir, indinavir/ritonavir, and lopinavir/ritonavir bars. In the protease inhibitor (PI) category, user note 20 has been updated to reflect the relative lack of recent data regarding indinavir/ritonavir and nelfinavir.

### Entry Inhibitors Resistance

The section formerly called “Mutations in the GP41 Envelope Gene Associated with Resistance to Entry Inhibitors” has been relabeled as “Mutations in the Envelope Gene Associated with Resistance to Entry Inhibitors” and includes a bar for the recently FDA-approved drug maraviroc. The resistance profile for maraviroc is too complex to be depicted on this graphic (see the user note). The enfuvirtide bar has been revised so that the mutations of the first heptad repeat (HR1) region of the gp41 envelope gene appear similarly to those in other bars.

### Integrase Inhibitors

A bar for the investigational drug raltegravir has been placed in the newly added category of “Mutations in the Integrase Gene Associated with Resistance to Integrase Inhibitors.” Raltegravir is available via an EAP. User note 26 discusses the 2 distinct genetic pathways seen in which integrase mutations are associated with raltegravir failure.<sup>10</sup>

### 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 **resistance2007“at”iasusa.org** or by fax at 415-544-9401. Please include your name and institution.

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