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

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group is marking 5 years as an independent volunteer panel of experts focused on identifying key HIV-1 drug resistance mutations. The goal of the effort is to quickly deliver accurate and unbiased information on these mutations to HIV clinical practitioners.

This October/November 2005 version of the IAS–USA Drug Resistance Mutations Figures replaces the version published in this journal in March/April 2005. 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 [NNRTIs]).[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 Panel[6] can be found on the IAS–USA Web site at www.iasusa.org.

Revisions to the Figures for the October/November 2005 Update

Nucleoside (or Nucleotide) Reverse Transcriptase Inhibitors

In this October/November 2005 version of the figures and user notes, the zalcitabine bar has been removed because zalcitabine is no longer commercially available. In the previous version, the thymidine analogue-associated mutations (TAMs; M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) as well as the E44D and V118I appeared at the top of the nRTI class on a multi-nRTI resistance bar. The list has been revised to include only TAMs and has been moved to the bottom of the drug class with the other multi- nucleoside reverse transcriptase inhibitor (nRTI)-resistance pathways. Also, the vertical pink lines previously used to show the nRTI cross-resistance associated with TAMs plus E44D and V118I have been removed from the figures. The changes were made because other mutations may lead to multi-drug resistance within the nRTI class (eg, K65R).

Protease Inhibitors

In the protease inhibitor (PI) category, newer data prompted numerous additions and changes to the list of mutations associated with atazanavir resistance. As described in user note 18, the accumulation of these mutations is associated with high-level resistance to atazanavir. Similarly, various changes have been made with regard to mutations associated with resistance to tipranavir. This drug was approved by the US Food and Drug Administration in July 2005 and data have become available to begin to better describe relevant mutations. The other specific changes in the PI category include: for (fos)amprenavir, the addition of position 82 and the substitutions associated with this new minor mutation; for lopinavir/ritonavir, the designation of mutations at 3 positions—32, 47, and 82—as major; and for ritonavir, the addition of the minor mutation, I50V. The multi-PI resistance bar has now been removed. In general, as major and minor substitutions associated with resistance to drugs within the PI class accumulate, susceptibility to certain PIs may decrease.

(continued, page 130)

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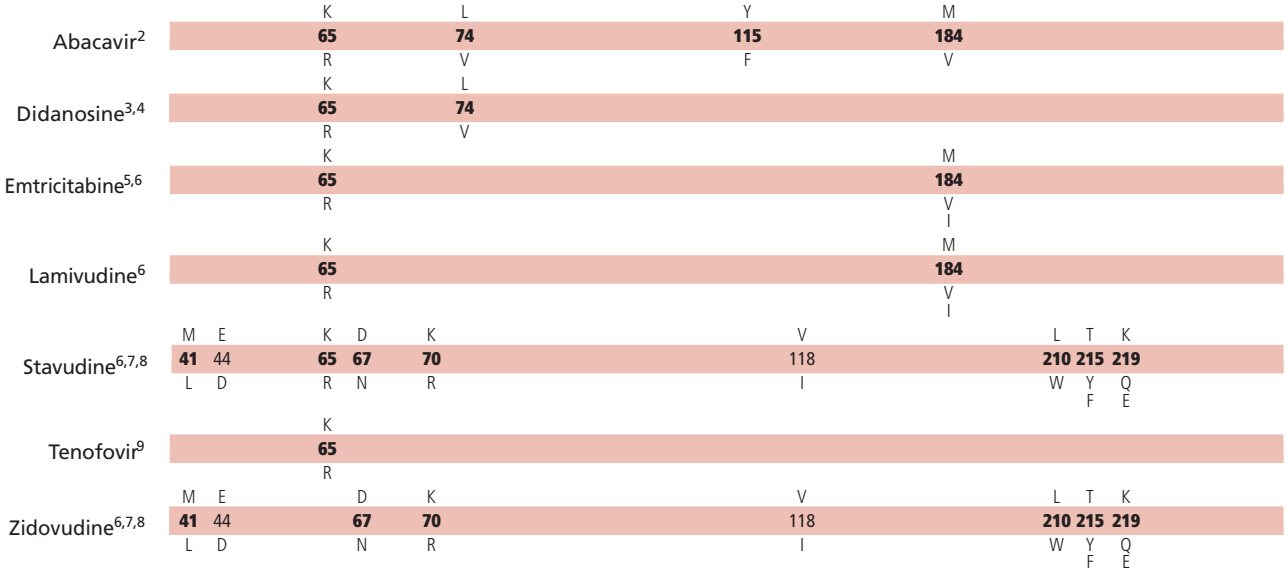
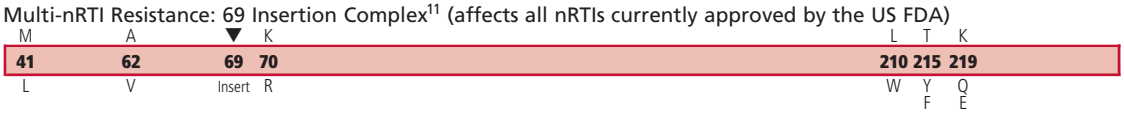
MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (nRTIs)[1]



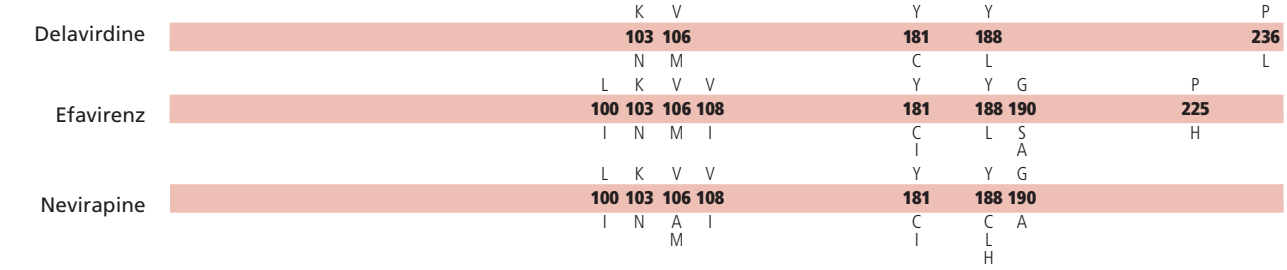
Multi-nRTI Resistance: Thymidine Analogue-associated Mutations[6,10] (TAMs; affect all nRTIs currently approved by the US FDA)

Multi-nRTI Resistance: 69 Insertion Complex[11] (affects all nRTIs currently approved by the US FDA)

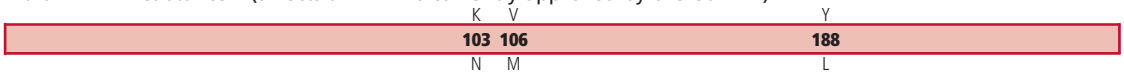


Multi-nRTI Resistance: 151 Complex[12] (affects all nRTIs currently approved by the US FDA except tenofovir)

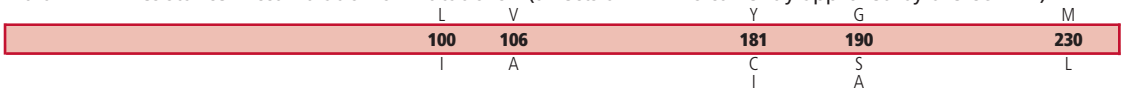
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)[1,13]



Multi-NNRTI Resistance[14] (affects all NNRTIs currently approved by the US FDA)



Multi-NNRTI Resistance: Accumulation of Mutations[15] (affects all NNRTIs currently approved by the US FDA)



Date of Revision: November 2005

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS [16,17]

Drug	Amino acid, wild-type	Position	Substitutions conferring resistance
Atazanavir[18]	L	10	I, F, V
	G	16	E
	K	20	R, M, I
	L	24	I
	V	32	I
	L	33	I, F, V
	M	36	I, L, V
	M	46	I, L
	G	48	V
	I	**50**	L
	I	54	L, V, M, T
	D	60	E
	I	62	V
	A	71	V, I, T, L
	G	73	C, S, T, A
	V	82	A, T
	I	**84**	V
	I	85	V
	N	**88**	S
	L	90	M
	I	93	L
(Fos) amprenavir	L	10	F, I, R, V
	V	32	I
	M	46	I, L
	I	47	V
	I	**50**	V
	I	54	L, V, M
	G	73	S
	V	82	A, F, S, T
	I	**84**	V
	L	90	M
Indinavir	L	10	I, R, V
	K	20	M, R
	L	24	I
	V	32	I
	M	36	I
	M	**46**	I, L
	I	54	V
	A	71	V, T
	G	73	S, A
	V	77	I
	V	**82**	A, F, T
	I	**84**	V
	L	90	M
Lopinavir/ ritonavir[19]	L	10	F, I, R, V
	K	20	M, R
	L	24	I
	V	**32**	I
	L	33	F
	M	46	I, L
	I	**47**	V, A
	I	50	V
	F	53	L
	I	54	V, L, A, M, T, S
	L	63	P
	A	71	V, T
	G	73	S
	V	**82**	A, F, T, S
	I	84	V
	L	90	M
Nelfinavir[20]	L	10	F, I
	D	**30**	N
	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
	L	**90**	M
Ritonavir	L	10	F, I, R, V
	K	20	M, R
	V	32	I
	L	33	F
	M	36	I
	M	46	I, L
	I	50	V
	I	54	V, L
	A	71	V, T
	V	77	I
	V	**82**	A, F, T, S
	I	**84**	V
	L	90	M
Saquinavir	L	10	I, R, V
	G	**48**	V
	I	54	V, L
	A	71	V, T
	G	73	S
	V	77	I
	V	82	A
	I	84	V
	L	**90**	M
Tipranavir/ ritonavir[21]	L	10	V
	I	13	V
	K	20	M, R
	L	**33**	F
	E	35	G
	M	36	I
	K	43	T
	M	46	L
	I	47	V
	I	54	A, M, V
	Q	58	E
	H	69	K
	T	74	P
	V	**82**	L, T
	N	83	D
	I	**84**	V
	L	90	M

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

Enfuvirtide[22]

First heptad repeat (HR1) region

Amino acid, wild-type	G	I	V	Q	Q	N	N
Position	36	37	38	39	40	42	43
Substitutions	D, S	V	A, M, E	R	H	T	D

MUTATIONS

Key:
- Insertion
- Amino acid, wild-type (L)
- Amino acid position (**90**)
- Major (boldface type; protease only)[17] (**90**)
- Amino acid substitution conferring resistance (M)
- Minor (lightface type; protease only)[17] (54)

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 (listed in alphabetical 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-naive 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. 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 thymidine analogue-associated mutations (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).

3. 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.

4. 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).

5. 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.

6.The E44D and the V118I 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, and therefore these mutations are not in bold type on the figure (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

7. 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.

8. 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-naive 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).

9. 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).

10. 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).

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 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).

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 K20I/R and M36I in protease.

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, *Antivir Ther* 2005).

19. 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*, 2001; Friend et al, *AIDS* 2004; Kagen et al, *Protein Sci*, 2005).

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

21. In PI-experienced patients, early studies of tipranavir/ritonavir suggested an 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 an independent role for L90M in tipranavir resistance. Subsequent analyses of data from phase II and III studies in PI-experienced patients identified mutations associated with reduced susceptibility or reduced 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 leads to reduced tipranavir response. These data must be considered preliminary, and 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; Valdez, *Antivir Ther*, 2005; Muzammil, *Antivir Ther*, 2005).

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 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 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.

(continued from page 125)

Fusion Inhibitors

The E substitution at position 38 and the Q40H have been added to the list of mutations conferring resistance to enfuvirtide.[12]

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 investigational drugs for which phase II trial data are available.

Acknowledgments

The IAS–USA Drug Resistance Mutations Group wishes to thank Jennifer Ham, MPH, for her coordination of the group's efforts.

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"at"iasusa** (this will change to **resistance2006"at"iasusa** as of January 1, 2006) or by fax at 415-544-9401. Please include your name and institution.

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Financial Disclosures: The authors disclose the following affiliations with commercial supporters that may have interests related to the content of this article: Dr Brun-Vézinet has received grant support from Bayer, bioMérieux, Bristol-Myers Squibb, GlaxoSmithKline, and PE Biosystems and has served as a consultant to Bayer, Glaxo SmithKline, Gilead, and Roche; Dr Clotet has served as a consultant and received grant support from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Pfizer, and Roche; Dr Conway has received research support from Boehringer Ingelheim and research funding from Abbott, Agouron, Bristol-Myers Squibb, Schering, and Triangle; Dr Johnson has served as a consultant to GlaxoSmithKline, Bristol-Myers Squibb, Virco, and ViroLogic and as a speaker or on a speakers bureau for Abbott, Bayer, Boehringer Ingelheim/ Roxanne, Bristol-Myers Squibb, Chiron, GlaxoSmithKline, Merck, Roche, Vertex, and ViroLogic, and has received grant support from Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, and Bayer; Dr Kuritzkes has served as a consultant to Abbott, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Ortho Biotech, Roche, Shire, Trimeris, and ViroLogic, and has received honoraria from Abbott, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, and ViroLogic and grant support from Abbott, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Roche, and Tanox; Dr Pillay has served as a consultant to and has received research grants from GlaxoSmithKline, Gilead, Bristol-Myers Squibb, Roche, and Tibotec-Virco; Dr Richman has served as a consultant to Abbott, Achillion, Bristol-Myers Squibb, Chiron, Gilead, GlaxoSmithKline, Merck, Novirio, Pfizer, Roche, Tibotec-Virco, Triangle, and ViroLogic; Dr Schapiro has served as a scientific advisor to Bayer and Roche and on the speakers bureau for Abbott, Bristol-Myers Squibb, and Roche, and has received other financial support from GlaxoSmithKline and Virology Education; Dr Telenti has no affiliations to disclose.

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