Update of the Drug Resistance Mutations in HIV-1: 2004

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The International AIDS Society-USA (IAS-USA) Drug Resistance Mutations Group is a volunteer panel of experts in HIV-1 virology, research, and clinical care that meets regularly to review and interpret new data on HIV-1 resistance to antiretroviral drugs, and to maintain a list of mutations that may contribute to a reduced virologic response to drug.

The mutations included on the figures 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. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded-access mechanisms are included. Additional information on the mutations is provided, where necessary, in the accompanying user notes. Although the group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive, and readers are encouraged to consult the literature and experts in the field for clarification or more information about mutations not listed in the figure.

The IAS-USA drug resistance mutations figures are designed for use in identifying mutations associated with HIV-1 resistance 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 Panel[6] can be found on the IAS–USA Web site at www.iasusa.org.

This October 2004 version of the IAS-USA drug resistance mutations figures replaces the version published in this journal in October 2003.

Revisions to the Figures in the October 2004 Update

In the nucleoside and nucleotide reverse transcriptase inhibitor (nRTI) category, the vertical pink lines that represent nucleoside- or nucleotide-associated mutations (NAMs) have been added to emtricitabine (see user note 2 on NAMs). The figures had previously identified the NAMs for lamivudine but not for emtricitabine (these 2 drugs are assumed to be similar). However, based on available data, there are insufficient data to suggest any in vivo difference in NAM resistance patterns between emtricitabine and lamivudine.

In the protease inhibitor (PI) category, the I84V mutation is now listed as a major mutation for atazanavir. The mutation is associated with a reduced virologic response to atazanvir and it meets the group's criteria for a "major" mutation (see user notes 18 and 23).[7,8]

In addition, for both atazanavir and ritonavir-boosted tipranavir, the L33V mutation has been removed. The L33I/F mutations for both drugs remain, as recent studies support.[9] The L33V appears

The **IAS-USA Drug Resistance Mutations Group** was originally a subgroup of the IAS-USA HIV Resistance Testing Panel. In 2000, the Drug Resistance Mutations Group became 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.

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

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Each entry lists the codon position with the wild-type amino acid (above) and the resistance-associated substitution(s) (below).

Drug / Complex	41	44	62	65	67	69	70	74	75	77	115	116	118	151	184	210	215	219
Multi-nRTI Resistance: 151 Complex			A/V						V/I	F/L		F/Y		Q/M				
Multi-nRTI Resistance: 69 Insertion Complex[1]	M/L		A/V		D/N	▼/Insert	K/R									L/W	T/Y,F	K/Q,E
Multi-nRTI Resistance: NAMs[2]	M/L	E/D			D/N		K/R						V/I			L/W	T/Y,F	K/Q,E
Zidovudine[3,4]	M/L	E/D			D/N		K/R						V/I			L/W	T/Y,F	K/Q,E
Stavudine[3-5]	M/L	E/D		K/R	D/N		K/R						V/I			L/W	T/Y,F	K/Q,E
Didanosine[6,7]				K/R				L/V										
Zalcitabine				K/R		T/D		L/V							M/V			
Abacavir[8]				K/R				L/V			Y/F				M/V			
Lamivudine[9,10]		E/D		K/R									V/I		M/V,I,M			
Emtricitabine[10]				K/R											M/V,I			
Tenofovir[3,11]				K/R														

Nonnucleoside Reverse Transcriptase Inhibitors

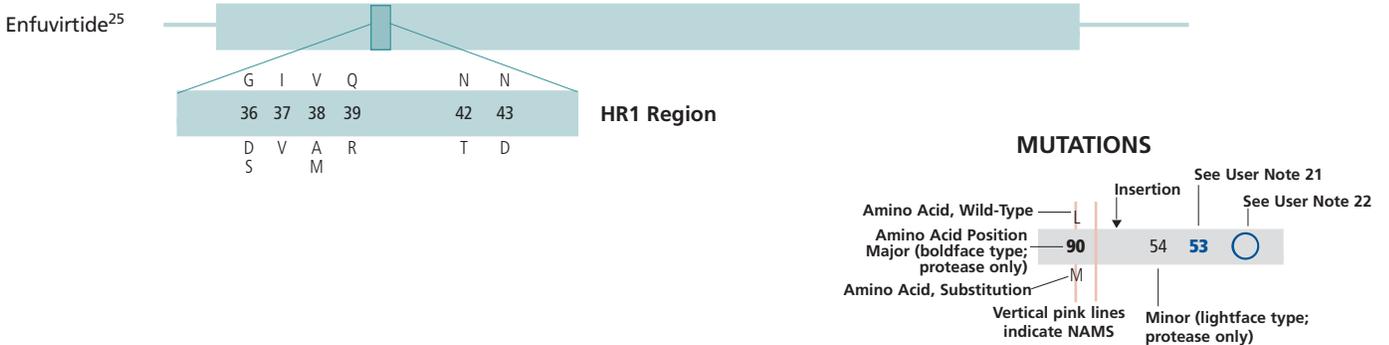| Drug / Complex	100	103	106	108	181	188	190	225	230	236
Multi-NNRTI Resistance[12,13]		K/N	V/M			Y/L				
Multi-NNRTI Resistance: Accumulation of Mutations[14]	L/I		V/A		Y/C,I		G/S,A		M/L	
Nevirapine	L/I	K/N	V/A,M	V/I	Y/C,I	Y/C,L,H	G/A			
Delavirdine[15]		K/N	V/M		Y/C	Y/L				P/L
Efavirenz[15-17]	L/I	K/N	V/M	V/I	Y/C,I	Y/L	G/S,A	P/H		

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

Protease Inhibitors[18]

Multi-PI Resistance: Accumulation of Mutations[19]

	10	32	46	54	82	84	90
Wild-type	L	V	M	I	V	I	L
Substitution	F, I, R, V	I	I, L	V, M, L	A, F, T, S	V, A, C	M

Indinavir[20]

	10	20	24	32	36	46	54	71	73	77	82	84	90
Wild-type	L	K	L	V	M	M	I	A	G	V	V	I	L
Substitution	I, R, V	M, R	I	I	I	I, L	V	V, T	S, A	I	A, F, T	V	M

Ritonavir

	10	20	32	33	36	46	54	71	77	82	84	90
Wild-type	L	K	V	L	M	M	I	A	V	V	I	L
Substitution	F, I, R, V	M, R	I	F	I	I, L	V, L	V, T	I	A, F, T, S	V	M

Saquinavir

	10	48	54	71	73	77	82	84	90
Wild-type	L	G	I	A	G	V	V	I	L
Substitution	I, R, V	V	V, L	V, T	S	I	A	V	M

Nelfinavir

	10	30	36	46	71	77	82	84	88	90
Wild-type	L	D	M	M	A	V	V	I	N	L
Substitution	F, I	N	I	I, L	V, T	I	A, F, T, S	V	D, S	M

(Fos)amprenavir

	10	32	46	47	50	54	73	84	90
Wild-type	L	V	M	I	I	I	G	I	L
Substitution	F, I, R, V	I	I, L	V	V	L, V, M	S	V	M

Lopinavir/Ritonavir[21,22]

	10	20	24	32	33	46	47	50	53	54	(63)	71	73	82	84	90
Wild-type	L	K	L	V	L	M	I	I	F	I	L	A	G	V	I	L
Substitution	F, I, R, V	M, R	I	I	F	I, L	V, A	V	L	V, L, A, M, T, S	P	V, T	S	A, F, T, S	V	M

Atazanavir[23]

	10	20	24	32	33	36	46	48	50	54	71	73	82	84	88	90
Wild-type	L	K	L	V	L	M	M	G	I	I	A	G	V	I	N	L
Substitution	I, F, V	R, M, I	I	I	I, F	I, L, V	I	V	L	L	V	C, S, T, A	A	V	S	M

Tipranavir/Ritonavir (expanded access)[24]

	10	20	33	46	54	82	84	90
Wild-type	L	K	L	M	I	V	I	L
Substitution	I, V	M, L, T	I, F	I	V	A, F, L, T	V	M

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

Enfuvirtide[25]

HR1 Region

	36	37	38	39	42	43
Wild-type	G	I	V	Q	N	N
Substitution	D, S	V	A, M	R	T	D

MUTATIONS

Amino Acid, Wild-Type — L

Amino Acid Position — Major (boldface type; protease only) — **90**

Amino Acid, Substitution — M

Vertical pink lines indicate NAMS

Insertion

Minor (lightface type; protease only) — 54

53 ⃝

See User Note 21

See User Note 22

User Notes

The IAS–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. These mutations 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. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through-expanded access protocols are included. Additional information on the mutations is provided, where necessary, in these user notes.

1. 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, or others), is associated with resistance to all FDA-approved nRTIs. The 69 insertion complex 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.

2. The nRTI-associated mutations (NAMs), including M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, and K219Q/E, are associated with cross-resistance to nRTIs and are represented by vertical pink lines. Zidovudine and stavudine select for these mutations, and as such, the positions and mutations are indicated on the bars along with the pink lines. For other nRTIs, the NAMs are not commonly selected by those drugs, but the presence of the NAMs confers cross-resistance to the drugs. This is represented by pink lines only at the positions.

The E44D and V118I mutations are listed as NAMs. In a recent study, the E44D and V118I mutations were more common in virus from patients who had been on zidovudine and lamivudine, and were associated with higher-level resistance to zidovudine (Stoeckli et al, *Antimicrob Agents Chemother,* 2002). When present together with other NAMs, the E44D and V118I mutations confer resistance to lamivudine. Analysis from the AIDS Clinical Trials Group (ACTG) study 136 has shown that the V118I mutation is commonly selected by a zidovudine/didanosine regimen (Shafer et al, *J Infect Dis,* 1995). Findings from ACTG study

241 have shown that the E44D mutation is commonly selected by zidovudine/didanosine (Hanna et al, *J Infect Dis,* 2002) and that the E44D mutation is associated with a significantly worse response to treatment with zidovudine and didanosine, with or without nevirapine (Precious et al, *AIDS,* 2000). 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 M184V mutation may enhance susceptibility to zidovudine, stavudine, or tenofovir. This effect may be overcome by an accumulation of NAMs or other mutations. The clinical significance of this effect is not known.

4. Data on revertant mutations in codon 215 indicate that the T215D/C/S/E/N/A/V substitutions confer increased risk of virologic failure of zidovudine and stavudine in antiretroviral-naive adults starting therapy with these drugs (Riva et al, *Antivir Ther,* 2002). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *Proc Natl Acad Sci USA,* 2001; Lanier et al, *Antivir Ther,* 2002; Riva et al, *Antivir Ther,* 2002).

5. Mutations at codon 75 (V75T/M/S/A) have been observed in vitro and may confer a low-level change in susceptibility to stavudine (Lacey et al, *Antimicrob Agents Chemother,* 1994).

6. The K65R mutation or the L74V mutation, alone or in combination with the NAMs or T69D/N can lead to didanosine resistance.

7. Based on preliminary, yet-unpublished data, the M184V mutation does not appear to have a negative impact on in vivo responses to didanosine, even though the mutation reduces susceptibility in vitro (Winters et al, *Antivir Ther,* 2002; Eron et al, *Antivir Ther,* 2002; Pozniak et al, *Antivir Ther*, 2002).

8. When present with NAMs, the M184V mutation contributes to reduced susceptibility to abacavir and is associated with impaired response in vivo. However, when present alone, the M184V mutation does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis,* 2000).

9. The E44D and V118I mutations were

reported to confer low-level resistance to lamivudine when accompanied by several other nRTI-associated mutations (M41L, D67N, L210W, T215Y/F, K219Q/E) in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother,* 2000). Data presented but not yet published (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. (See also user note 2.)

10. Emtricitabine and lamivudine have similar reverse transcriptase M184V/I patterns (Quinn et al, *ICAAC,* 2003). In addition, the K65R mutation can confer cross-resistance to emtricitabine and lamivudine (Miller et al, *ICAAC,* 2003; Miller et al, *Antivir Ther*, 2003; Miller et al, 10th CROI, 2003; Parikh et al, *Antivir Ther*, 2003; Ruane et al, *Antivir Ther*, 2003; McArthur et al, *Antivir Ther*, 2003). Additional mutations that confer resistance or cross-resistance to emtricitabine are possible, but are yet to be described.

11. The accumulation of NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E [note: data here do not include E44D and V118I]) increases resistance to tenofovir. Mutations M41L and L210W contribute more than others. Therefore, the number and type of NAMs will determine the degree of reduced response. T69D/N/S may also contribute to a reduced response to tenofovir (Miller et al, *Antivir Ther,* 2002; Lu et al, *Antivir Ther,* 2002; Masquelier et al, *Antivir Ther,* 2002).

12. The K103N or Y188L mutation alone can substantially reduce the clinical utility of all currently approved NNRTIs.

13. The V106M mutation confers high-level resistance in vitro to nevirapine, delavirdine, and efavirenz (Brenner et al, *AIDS,* 2003). This mutation has been observed only in HIV clade C clinical isolates, although site-directed mutagenesis indicates that V106M confers cross-resistance to all NNRTIs in HIV clade B virus.

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

15. The prevalence of the Y318F mutation in clinical isolates along with mutations K103N, Y181C, or P236L was approximately 5%, 2%, and 15%, respectively (Kemp et al, *Antivir Ther,* 2001). In vitro this mutation confers resistance to nevirapine, delavirdine, and efavirenz.

16. The Y181C/I mutation is not selected by efavirenz, but its presence contributes to low-level cross-resistance to the drug. Clinical impact of this mutation may be overcome with a fully active antiretroviral combination regimen, although no clinical trial data yet address this question.

17. V108I and P225H each contribute to efavirenz resistance when present in combination with other NNRTI-associated 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.

18. Resistance mutations in the protease gene are classified as either "major" or "minor" (if known).

Major: In general, major mutations are either (1) selected first in the presence of the drug; or (2) 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 do not have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus carrying major mutations.

19. Accumulation of 4 or more of these mutations is likely to cause multi-PI resistance (Palmer et al, *AIDS,* 1999; Shafer et al, *Ann Intern Med,* 1998).

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

21. Major and minor mutations have not been designated for lopinavir/ritonavir-associated resistance since currently there are 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 accumulation of 7 or 8 mutations confers resistance to the drug. However, recent data suggest as few as 4 mutations can be associated with such high-level resistance (Prado et al, *AIDS,* 2002). Further clinical experience and research are needed to better define the mutations that affect the clinical effectiveness of lopinavir/ritonavir. It is reasonable to consider phenotyping to assess this in individual cases.

22. Protease mutation L63P is common in viruses that have never been exposed to PIs (Kozal et al, *Nat Med,* 1996) and may be more prevalent in viruses from patients in whom a PI-containing regimen has failed. However, by itself, L63P does not cause any appreciable increase in the IC_{50} for any PI.

L63P is listed for lopinavir/ritonavir (and not any other PI) because studies have shown that this mutation, when present with multiple other mutations, is associated with clinical failure.

23. When administered to patients as the initial PI, atazanavir selects for the mutations I50L and A71V (Colonno et al, *Antivir Ther,* 2002). When used as a subsequent PI in combination with saquinavir, atazanavir selects for I54L and I84V (Colonno et al, *Antivir Ther,* 2002). In vitro, atazanavir selects for V32I, M46I, I84V, and N88S (Gong et al, *Antimicrob Agents Chemother,* 2000). Although other mutations, such as V82A and L90M, have not been selected for by atazanavir either in vitro or in vivo, these mutations have been shown to confer cross-resistance to atazanavir, particularly when present in combination with each other or with other known PI resistance mutations (Colonno et al, *Antivir Ther*, 2000). Recent data show the high impact of I84V (7- to 9-fold increase in IC_{50}) when in the background of A71V (Weinheimer at al, 11th CROI, 2004).

24. Tipranavir/ritonavir is currently available through an expanded-access protocol and is not approved by the FDA.

25. To date, resistance mutations in the gp41 envelope gene have been identified primarily at positions 36 to 45 of the first heptad repeat (HR1) region. These mutations have been identified in viruses from patients having been on enfuvirtide and have been shown to confer resistance or reduced susceptibility (Wei et al, *Antimicrob Agents Chemother,* 2002; Sista et al, *Antivir Ther,* 2002; Mink et al, *Antivir Ther,* 2002). It is important to note that wild-type viruses lacking any mutations in the depicted HR1 region vary 500-fold in susceptibility and such pretreatment susceptibility differences were not associated with differences in clinical response (Labrosse et al, *J Virol,* 2003; Greenberg et al, 10th CROI, 2003, Ab 141). Furthermore, it is possible that mutations and/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, *PNAS*, 2002). Further research is needed to define the full spectrum of clinically relevant mutations conferring enfuvirtide resistance. Testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure of regimens including enfuvirtide and must be interpreted in the context of resistance testing results for all other components of the regimen.

Figure legend. 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; NAMs indicates nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor.

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.

to be a natural polymorphism; there has been no evidence of an increase in the prevalence of this mutation in isolates from drug-experienced patients in whom therapy with trial agents has failed.

Also in the PI category, the name of the bar representing "amprenavir" has been changed to "(fos) amprenavir" to indicate that the mutations listed are relevant to the prodrug of this agent.

Future Revisions of the Figures

The Drug Resistance Mutations Group is currently revising the figure, including redeveloping the user notes to focus on the most current clinical information. The new figure and user notes will include any new data from upcoming scientific conferences and publications and will be available in early 2005.

The group is discussing the HIV-1 resistance mutations that are associated with non-subtype B virus and plans to introduce current data into the figures. Other topics under consideration include mutations in gag cleavage sites, transmitted drug resistance, drug hypersusceptibility, and emerging classes of drugs (eg, RNase H inhibitors).

Acknowledgements

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 resistance2004"at"iasusa.org or by fax at (415) 544-9401. Please include your name and institution.

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