Update of the Drug Resistance Mutations in HIV-1: December 2008

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group reviews new data on HIV-1 drug resistance that have been published or presented at recent scientific meetings to maintain a current list of mutations associated with antiretroviral drug resistance. This December 2008 version of the IAS–USA drug resistance mutations figures updates those published in this journal in March/April 2008 (Johnson VA, Brun-Vézinet F, Clotet B, et al, *Top HIV Med*, 2008;16:62-68). The compilation includes mutations that may contribute to a reduced virologic response to HIV-1 drugs. It should not be assumed that the list presented here is exhaustive. Drugs that have been approved by the US Food and Drug Administration (US FDA) as well as any drugs available in expanded access programs are included and listed in alphabetical order by drug class. The figures are designed for practitioners to use in identifying key mutations associated with viral resistance to antiretroviral drugs and in making therapeutic decisions. Updates are posted periodically at www.iasusa.org. For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing (Hirsch MS, Gunthard HF, Schapiro JM, et al, *Clin Infect Dis*, 2008:47:266-285).

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) nucleotide 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 a drug. The availability of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV-1 genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral therapy 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 analogue reverse transcriptase inhibitors [NNRTIs]). The absence of detectable viral resistance after treatment failure may result from any combination of the following factors: the presence of drug-resistant minority viral populations, nonadherence to medications, laboratory error, lack of current knowledge of the association of certain mutations with drug resistance, the occurrence of relevant mutations outside the regions targeted by routine resistance assays, 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.

Current Revision

This December 2008 update includes several changes to the list of drug resistance mutations for HIV-1, as shown on the figure bars. For etravirine, 3 new mutations were added—K101H, E138A, and M230L—and the mutations at positions L100, K101, and Y181 were changed to boldface to indicate their newer categorization as more important mutations because they are sufficient on their own to confer partial

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reduction in virologic response based on weighting factors identified through correlations with phenotype (see User Note m). Changes to the figure bar for ritonavir-boosted darunavir include the removal of G73S and addition of L74P. For ritonavir-boosted tipranavir, the representations for 3 existing mutations—at positions I47, Q58, and T74—were changed to boldface. Finally, the mutations Y143R/H/C were added to the raltegravir figure bar.

The IAS–USA Drug Resistance Mutations Group also undertook a comprehensive revision of the user notes. The information in each note was reviewed and updated as necessary. The references were updated as needed; citations to full papers replaced those to abstract presentations whenever possible.

Mutations Panel

The authors comprise the IAS–USA Drug Resistance Mutations Group, an independent, volunteer panel of experts charged with the goal of delivering accurate, unbiased, and evidence-based information on these mutations to practitioners. As for all IAS–USA panels, a rotation procedure is in place whereby 1 or 2 panel members periodically step down from panel participation and new members join. These rotations are designed to ensure that all IAS–USA expert panels remain diverse in member affiliations and areas of expertise.

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 **resistance2009''at''iasusa.org** or by fax at 415-544-9401. Please include your name and institution.

Reprint Requests

The Drug Resistance Mutations Group welcomes interest in the mutations figures as an educational resource for practitioners and encourages dissemination of the material to as broad an audience as possible. However, permission is required to reprint the figures and **no alterations in the content can be made**. If you wish to reprint the mutations figures, please send your request to the IAS–USA via e-mail or fax (see above).

To ensure the integrity of the mutations figures, IAS–USA policy is to grant permission for only minor, preapproved adaptations of the figures (eg, an adjustment in size). Minimal adaptations only will be considered; no alterations of the content of the figures or user notes will be permitted. Please note that permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted on the Web site (www.iasusa.org). Because scientific understanding of HIV drug resistance evolves rapidly and the goal of the Drug Resistance Mutations Group is to maintain the most up-to-date compilation of mutations for HIV clinicians and researchers, publication of out-of-date figures is counterproductive. If you have any questions about reprints or adaptations, please contact us.

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

Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (nRTIs)[a]

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

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

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

A	V	F	F	Q
62	**75**	**77**	**116**	**151**
V	I	L	Y	M

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

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Abacavir[f,g]

K	L	Y	M
65	**74**	**115**	**184**
R	V	F	V

Didanosine[g,h]

K	L
65	**74**
R	V

Emtricitabine

K	M
65	**184**
R	V I

Lamivudine

K	M
65	**184**
R	V I

Stavudine[d,e,i,j]

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Tenofovir[k]

K	K
65	**70**
R	E

Zidovudine[d,e,i,j]

M	D	K	L	T	K
41	**67**	**70**	**210**	**215**	**219**
L	N	R	W	Y F	Q E

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[a,l]

Efavirenz

L	K	V	V	Y	Y	G	P
100	**103**	**106**	**108**	**181**	**188**	**190**	**225**
I	N	M	I	C I	L	S A	H

Etravirine[m]

V	A	L	K	V	E	V	Y	G	M
90	98	**100**	**101**	106	138	179	**181**	190	230
I	G	I	E H P	I	A	D F T	C I V	S A	L

Nevirapine

L	K	V	V	Y	Y	G
100	**103**	**106**	**108**	**181**	**188**	**190**
I	N	A M	I	C I	C L H	A

MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[n,o,p]

Atazanavir +/– ritonavir[q]

Wild-type	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Position	10	16	20	24	32	33	34	36	46	48	**50**	53	54	60	62	64	71	73	82	**84**	85	**88**	90	93
Mutation	I F V C	E	R M I T V	I	I	I F V	Q	I L V	I L	V	L	L Y	L V M T A	E	V	L M V	V I T L	C S T A	A T F I	V	V	S	M	L M

Darunavir/ ritonavir[r]

Wild-type	V	V	L	I	I	I	T	L	I	L
Position	11	32	33	47	**50**	**54**	74	**76**	**84**	89
Mutation	I	I	F	V	V	M L	P	V	V	V

Fosamprenavir/ ritonavir

Wild-type	L	V	M	I	I	I	G	L	V	I	L
Position	10	32	46	47	**50**	54	73	76	82	**84**	90
Mutation	F I R V	I	I L	V	V	L V M	S	V	A F S T	V	M

Indinavir/ ritonavir[s]

Wild-type	L	K	L	V	M	M	I	A	G	L	V	V	I	L
Position	10	20	24	32	36	**46**	54	71	73	76	77	**82**	**84**	90
Mutation	I R V	M R	I	I	I	I L	V	V T	S A	V	I	A F T	V	M

Lopinavir/ ritonavir[t]

Wild-type	L	K	L	V	L	M	I	I	F	I	L	A	G	L	V	I	L
Position	10	20	24	**32**	33	46	**47**	50	53	54	63	71	73	76	**82**	84	90
Mutation	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	V	A F T S	V	M

Nelfinavir[s,u]

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

Saquinavir/ ritonavir[s]

Wild-type	L	L	G	I	I	A	G	V	V	I	L
Position	10	24	**48**	54	62	71	73	77	82	84	**90**
Mutation	I R V	I	V	V L	V	V T	S	I	A F T S	V	M

Tipranavir/ ritonavir[v]

Wild-type	L	I	K	L	E	M	K	M	I	I	Q	H	T	V	N	I	L
Position	10	13	20	**33**	35	36	43	46	**47**	54	**58**	69	**74**	**82**	83	**84**	90
Mutation	V	V	M R	F	G	I	T	L	V	A M V	E	K	P	L T	D	V	M

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

Enfuvirtide[w]

Wild-type	G	I	V	Q	Q	N	N
Position	36	37	38	39	40	42	43
Mutation	D S	V	A M E	R	H	T	D

Maraviroc[x] See User Note

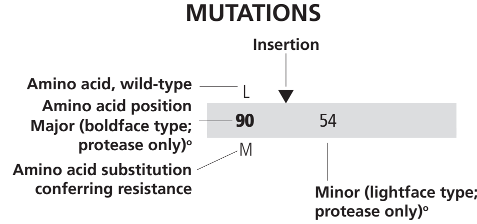
MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE INHIBITORS

Raltegravir[y]

Wild-type	Y	Q	N
Position	**143**	**148**	**155**
Mutation	R H C	H K R	H

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.

MUTATIONS



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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) nucleotide 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 a drug. The availability of more recently approved drugs that cannot be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by activity of other drug components in the background regimen. Readers are encouraged to consult the literature and experts in the field for clarification or more information about specific mutations and their clinical impact. Polymorphisms associated with impaired treatment responses that occur in wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

User Notes

a. Numerous nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like M41L, L210W, and T215Y, may lead to viral hypersusceptibility to the nonnucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,[1] in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals[2-6] or with etravirine in some NNRTI-experienced individuals.

b. 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.[7] Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

c. Tenofovir retains activity against the Q151M complex of mutations.[7]

d. Mutations known to be selected by thymidine analogues (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E, termed TAMS) also confer reduced susceptibility to all approved nRTIs.[8] The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[9-12] 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-1 drug resistance. The clinical relevance of these in vitro findings remains unclear, and there is yet no evidence that they have a substantial impact in the absence of other, established mutations. Thus, they are not depicted on the figure bars.

e. The E44D and the V118I mutations increase the level of resistance to zidovudine and stavudine in the presence of TAMs and correspondingly increase cross-resistance to other nRTIs. Their presence in the absence of other key mutations does not substantially alter resistance.[13,14] Furthermore, V118I alone does not compromise response to nRTI-containing regimens.[15]

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo.[16,17] When present with 2 or 3 TAMs, M184V contributes to reduced susceptibility to abacavir and is associated with impaired virologic response in vivo.[17] The M184V mutation plus 4 or more TAMs results in no virologic response to abacavir in vivo.[17] Slightly increased treatment responses to tenofovir are observed if M184V is present.[7]

g. The K65R mutation may be selected by didanosine or abacavir and is associated with decreased susceptibility to these drugs.[16,18,19] The impact of K65R on clinical response to didanosine-containing triple-drug regimens remains unclear.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[20] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[21]

i. The presence of M184V appears to delay or prevent emergence of TAMs.[22] This effect may be overcome by an accumulation of TAMs or other mutations.

j. The T215A/C/D/E/G/H/I/L/N/S/V substitutions are revertant mutations at codon 215 that confer increased risk of virologic failure of zidovudine or stavudine in antiretroviral-naive patients.[23-25] The T215Y mutant may emerge quickly from 1 of these mutations in the presence of zidovudine or stavudine.[26,27]

k. The presence of K65R is associated with a reduced virologic response to tenofovir.[7] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[7] Slightly increased treatment responses to tenofovir are observed when M184V is present.[7]

l. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.[28]

m. Resistance to etravirine has been extensively studied only in the context of coadministration with darunavir/ritonavir. In this context, mutations associated with virologic outcome have been assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values have been calculated, and assessment of genotype-phenotype correlations from a large clinical database have determined relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.[29-31] The single mutations Y181C/I/V, K101P, and L100I reduce but do not preclude clinical utility. The presence of K103N does not affect etravirine response.[32] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[33]

n. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[34] When used as unboosted

agents, atazanavir, fosamprenavir, and saquinavir generally select the same mutations as the ritonavir-boosted drug regimen, although the relative frequency of mutations may differ.

o. Resistance mutations in the protease gene are classified as "major" or "minor."

> Major mutations in the protease gene are defined as those selected first in the presence of the drug or those substantially reducing drug susceptibility. 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 substantial effect on phenotype. They may improve replication of viruses containing major mutations. Some minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades.

p. Ritonavir is not listed separately, as it is currently used only at low dose as a pharmacologic booster of other PIs.

q. Many mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Higher atazanavir levels obtained with ritonavir boosting increase the number of mutations required for loss of activity. The presence of M46I + L76V might increase susceptibility to atazanavir.[35]

r. Ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI mutations. Reductions in response are associated with increasing numbers of the mutations indicated in the figure bar. Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). A median darunavir phenotypic fold-change greater than 10 (low clinical cutoff) occurs with 3 or more of the 2007 IAS–USA mutations listed for darunavir[36] and is associated with a diminished virologic response.[37]

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

t. In PI-experienced patients, the accumulation of 6 or more of the mutations indicated on the figure bar is associated with a reduced virologic response to lopinavir/ritonavir.[38,39] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[40] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[41-43] The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to lopinavir/ritonavir.[35]

u. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.[44]

v. Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. Lists of mutations associated with accumulating resistance have been presented, with some conflicting results. In vitro studies and initial analysis of clinical data show mutations L33F, V82L/T, and I84V as having substantial contributions. Confirmatory studies are pending. A number of mutations (L24I, I50L/V, I54L, and L76V) are associated with decreased resistance in vitro and improved short-term virologic response if 2 or more are present.

w. Resistance to enfuvirtide is associated primarily with mutations in the first heptad repeat (HR1) region of the gp41 envelope gene. However, mutations or polymorphisms in other regions of the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide.[45-47]

x. Maraviroc activity is limited to patients with virus that uses only the CC chemokine receptor 5 (CCR5) for entry (R5 virus); viruses that use both CCR5 and the CXC chemokine receptor 4 (CXCR4) (termed dual/mixed or D/M) or only CXCR4 (X4) do not respond to maraviroc treatment. Virologic failure with maraviroc therapy frequently is associated with outgrowth of X4 virus that preexisted as a minority population below the level of assay detection. Mutations in the HIV-1 gp120 molecule that allow the virus to bind to the maraviroc-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 at the time of virologic failure. The resistance profile for maraviroc is too complex to be depicted on the figure bar. The frequency and rate at which maraviroc resistance mutations emerge are not yet known.

y. Raltegravir failure is associated with integrase mutations in at least 3 distinct genetic pathways defined by 2 or more mutations including (1) a signature (major) mutation at Q148H/K/R, N155H, or Y143R/H/C; and (2) 1 or more additional minor mutations. Minor mutations described in the Q148H/K/R pathway include L74M + E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H + G140S, which also confers the greatest loss of drug susceptibility. Mutations described in the N155H pathway include this major mutation plus either L74M, E92Q, T97A, E92Q + T97A, Y143H, G163K/R, V151I, or D232N.[48] The Y143R/H/C mutation is uncommon.[49-53]

References to the User Notes

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