

Special Contribution

Update of the Drug Resistance Mutations in HIV-1: March 2013

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This March 2013 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2011.¹

In this update, 2 integrase strand transfer inhibitors (InSTIs), elvitegravir and dolutegravir, have become available and were added to the figure. Elvitegravir was approved by the US Food and Drug Administration (FDA) in August 2012 for HIV-1 treatment-naïve patients as part of a fixed-dose combination of elvitegravir/cobicistat/tenofovir/emtricitabine.^{2,3} Dolutegravir is being evaluated in clinical trials for both initial HIV therapy and for use by treatment-experienced patients. It is available in an expanded access program and has been designated for priority review by the US FDA for treatment-experienced patients with detectable viral load who have documented HIV-1 resistance to raltegravir or elvitegravir. Relevant elvitegravir and dolutegravir mutations that have been identified to date are listed on the figure.

The following mutations have been added to existing classes or drugs: M230L has been added to the bars for the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs) efavirenz and nevirapine;^{4,5} Y188L has been added to the NNRTI rilpivirine bar; the asterisk was removed from E138K (see revised user note).^{6,7} L74M, T97A, E138A/K, and G140A/S have been added to the InSTI raltegravir bar; E92Q was unbolded.

Methods

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer pa-

nel of experts charged with delivering accurate, unbiased, and evidence-based information on these mutations to HIV clinical practitioners. As with all IAS–USA volunteer panels, members are rotated on a structured, planned basis. The group reviews new data on HIV drug resistance 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.

In addition, the group considers only data that have been published or have been presented at a scientific conference. Drugs that have been approved by the US FDA as well as any drugs available in expanded access programs 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.

Identification of Mutations

The mutations listed are those that 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) association studies between genotype at baseline and virologic response in patients exposed to the drug.

The development 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 otherwise wild-type viruses should not be used in epidemiologic analyses to identify transmitted HIV-1 drug resistance.

Clinical Context

The figures are designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in making therapeutic decisions. 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 develops most commonly to lamivu-

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dine or emtricitabine 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, a prolonged interval between the time of antiretroviral drug discontinuation and genotypic testing, non-adherence 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 sub-therapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing⁸ and 2012 IAS–USA panel recommendations for antiretroviral therapy.⁹ Updates are posted periodically at www.iasusa.org.

Comments


Please send your evidence-based comments, including relevant reference citations, to the journal “at” iasusa.org or by fax at 415-544-9401.

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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 format or the content can be made.**

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Financial Disclosures: The authors (listed alphabetically) disclose the following affiliations with commercial organizations that may have interests related to the content of this article (previous 12 months): Dr Calvez has served on advisory boards for Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc, Roche, and ViiV Healthcare. Dr Günthard has served as a medical advisor and/or consultant for Abbott Laboratories, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Janssen-Cilag, Pfizer Inc, Tibotec Therapeutics, and ViiV Healthcare, with all compensation going to his institution, University Hospital of Zurich. He has received unrestricted research and educational grants to his institution from Abbott Laboratories, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck Sharp & Dohme, Pfizer Inc, and Tibotec Therapeutics. Dr Johnson has received research support from Abbott Molecular, Roche Molecular Diagnostics, and Siemens Healthcare Diagnostics Inc. Dr Paredes has served as a consultant or medical advisor for Roche Diagnostics and ViiV Healthcare, and has received research grants awarded to IrsiCaixa and Lluita Contra la SIDA Foundations from Merck Sharp & Dohme Corp and ViiV Healthcare. Dr Pillay received laboratory support for University College London from ViiV Healthcare. Dr Richman has been a consultant to Biota, Bristol-Myers Squibb, Chimerix, GenProbe Inc, Gilead Sciences, Inc, Merck & Co, Inc, Monogram Biosciences, Inc, and Tobira Therapeutics. He has held stock options for Chimerix. Dr Shafer has served as a consultant or medical

advisor for Celera and Siemens Healthcare and has received grants from F. Hoffmann-La Roche Ltd, and Gilead Sciences, Inc. Dr Wensing has served as a consultant or medical advisor for Gilead Sciences, Inc, and ViiV Healthcare; has received grants from Merck & Co, Inc, and ViiV Healthcare; and has received travel, accommodations, or meeting expenses from Bristol-Myers Squibb, Gilead Sciences, Inc, Janssen Pharmaceutics, Inc, and Virology Education.

Funding/Support: This work was funded by the IAS–USA. No private sector or government funding was used to support the effort. Panel members are not compensated.

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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS^{p,q,r}

Atazanavir +/- ritonavir ^s	L 10	G 16	K 20	L 24	V 32	L 33	E 34	M 36	M 46	G 48	I 50	F 53	I 54	D 60	I 62	I 64	A 71	G 73	V 82	I 84	I 85	N 88	L 90	I 93
	I	E	R	I	I	I	Q	I	I	V	L	L	L	E	V	L	V	C	A	V	V	S	M	L
	F	M			F			L			Y	V				M	I	S	T				M	
	V				V			V				M				V	T	T	F					
	C											T					L	A	I					
				V																				
Darunavir/ ritonavir ^t	V 11				V 32	L 33			I 47	I 50	I 54						T 74	L 76	I 84			L 89		
	I				I	F		V	V	M	L						P	V	V			V		
Fosamprenavir/ ritonavir	L 10				V 32				M 46	I 47	I 50	I 54					G 73	L 76	V 82	I 84		L 90		
	F				I			I	V	V	L						S	V	A	V		M		
	I																		F					
	R																		A					
	V																		S					
Indinavir/ ritonavir ^u	L 10	K 20	L 24	V 32				M 36	M 46			I 54					A 71	G 73	L 76	V 77	V 82	I 84	L 90	
	I	M	I	I				I			V						V	S	V	I	A	V	M	
	R	R							L								T	A			F			
	V																				T			
Lopinavir/ ritonavir ^v	L 10	K 20	L 24	V 32	L 33				M 46	I 47	I 50	F 53	I 54			L 63	A 71	G 73	L 76	V 77	V 82	I 84	L 90	
	F	M	I	I	F				I	V	V	L	V		P	V	S	V	V	A	V		M	
	I								L	A										T				
	R																				F			
	V																				T			
																					S			
Nelfinavir ^{u,w}	L 10			D 30				M 36	M 46								A 71		V 77	V 82	I 84	N 88	L 90	
	F			N				I	I								V		I	A	V	D	M	
	I								L								T			F		S		
																				T				
																				S				
Saquinavir/ ritonavir ^u	L 10	L 24							G 48		I 54			I 62			A 71	G 73	V 77	V 82	I 84	L 90		
	I	I							V		V			V			V	S	I	A	V	M		
	R																			F				
	V																			T				
																					S			
Tipranavir/ ritonavir ^x	L 10			L 33	M 36	K 43	M 46	I 47	I 54	Q 58				H 69	T 74				V 82	N 83	I 84	L 89		
	V			F	I	T	L	V	A	E				K	P				L	D	V	I		
					L				M					R					T			M		
					V				V													V		

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

Enfuvirtide ^y	G 36	I 37	V 38	Q 39	Q 40	N 42	N 43
	D	V	A	R	H	T	D
	S		M				
			E				
Maraviroc ^z	See User Note						

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS

Dolutegravir ^{aa}						E 138	G 140	Q 148			
						A	S	H			
						K	A				
Elvitegravir ^{bb}		T 66			E 92	T 97		S 147	Q 148	N 155	
		I			Q	A		G	R	H	
		A			G			H			
		K						K			
Raltegravir ^{cc}			L 74		E 92	T 97	E 138	G 140	Y 143	Q 148	N 155
			M		Q	A	A	A	R	H	
							K	S	H	K	
									C	R	

User Notes

a. Some nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) mutations, like T215Y and H208Y,¹ may lead to viral hypersusceptibility to the non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), including etravirine,² in nRTI-treated individuals. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naïve individuals,³⁻⁷ although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals. 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 nRTI and NNRTI HIV-1 drug resistance. The clinical relevance of these connection domain mutations arises mostly in conjunction with thymidine analogue-associated mutations (TAMs) and M184V and have not been associated with increased rates of virologic failure of etravirine or rilpivirine in clinical trials.⁸⁻¹⁰

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 TAMs at codons 41, 210, or 215.¹¹ 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.¹¹ Q151M is the most important mutation in the complex (ie, the other mutations in the complex [A62V, V75I, F77L, and F116Y] in isolation may not reflect multidrug resistance).

d. Mutations known to be selected by TAMs (ie, M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E) also confer reduced susceptibility to all currently approved nRTIs.¹² The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.¹³⁻¹⁶

e. Although reverse transcriptase changes associated with the E44D and V118I mutations may have an accessory role in increased resistance to nRTIs in the presence of TAMs, their clinical relevance is very limited.¹⁷⁻¹⁹

f. The M184V mutation alone does not appear to be associated with a reduced virologic response to abacavir in vivo. When associated with TAMs, M184V increases abacavir resistance.^{20,21}

g. As with tenofovir, the K65R mutation may be selected by didanosine, abacavir, or stavudine (particularly in patients with

nonsubtype-B clades) and is associated with decreased viral susceptibility to these drugs.^{20,22,23} Data are lacking on the potential negative impact of K65R on clinical response to didanosine.

h. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.²⁴ The presence of K70R or M184V alone does not decrease virologic response to didanosine.²⁵

i. K65R is selected frequently (4% – 11%) in patients with nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.^{26,27}

j. The presence of M184V appears to delay or prevent emergence of TAMs.²⁸ This effect may be overcome by an accumulation of TAMs or other mutations.

k. 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-naïve patients.^{29,30} The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.³¹

l. The presence of K65R is associated with a reduced virologic response to tenofovir.¹¹ A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.¹¹ The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.³²⁻³⁴

m. The sequential use of nevirapine and efavirenz (in either order) is not recommended because of cross-resistance between these drugs.³⁵

n. 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.³⁶⁻³⁸ Asterisks (*) are used to emphasize higher relative weights with regard to reduced susceptibility and reduced clinical response compared with other etravirine mutations.³⁹ The single mutations L100I*, K101P*, and Y181C*/I*/V* reduce clinical utility. The presence of K103N alone does not affect etravirine response.⁴⁰ Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.⁴¹⁻⁴³

o. Fifteen mutations have been associated

with decreased rilpivirine susceptibility (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, H221Y, F227C, and M230I/L).⁴⁴⁻⁴⁶ A 16th mutation, Y188L, reduces rilpivirine susceptibility 6 fold.⁴⁷ K101P and Y181I/V reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are uncommonly observed in patients receiving rilpivirine.⁴⁸⁻⁵⁰ K101E, E138K, and Y181C, each of which reduces rilpivirine susceptibility 2.5 fold to 3 fold, occur commonly in patients receiving rilpivirine. E138K and to a lesser extent K101E usually occur in combination with the nRTI resistance mutation M184I, which alone does not reduce rilpivirine susceptibility. When M184I is combined with E138K or K101E, rilpivirine susceptibility is reduced approximately 7 fold and 4.5 fold, respectively.⁵⁰⁻⁵³

p. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).⁵⁴ In some specific circumstances, atazanavir might be used unboosted. In such cases, the mutations that are selected are the same as with ritonavir-boosted atazanavir, but the relative frequency of mutations may differ.

q. Resistance mutations in the protease gene are classified as “major” or “minor.”

Major mutations in the protease gene (positions in **bold** type) 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.

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

s. 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 plus L76V might increase susceptibility to atazanavir when no other related mutations are present.⁵⁵

t. HIV-1 RNA response to 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. The negative impact of the protease mutations I47V, I54M, T74P, and I84V and the positive impact of

the protease mutation V82A on virologic response to darunavir/ritonavir were shown in 2 data sets independently.^{56,57} 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 darunavir⁵⁸ and is associated with a diminished virologic response.⁵⁹

u. 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.

v. 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.^{60,61} The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.⁶² However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.⁶³⁻⁶⁵ The addition of L76V to 3 PI resistance-associated mutations substantially increases resistance to lopinavir/ritonavir.⁵⁵

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI mutations.⁶⁶

x. Clinical correlates of resistance to tipranavir are limited by the paucity of clinical trials and observational studies of the drug. The available genotypic scores have not been validated on large, diverse patient populations. The presence of mutations L24I, I50L/V, F53Y/L/W, I54L, and L76V have been associated with improved virologic response to tipranavir in some studies.⁶⁷⁻⁶⁹

y. 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.⁷⁰⁻⁷²

z. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that uses only CCR5 for entry (R5 virus). Viruses that use both CCR5 and CXCR4 chemokine receptor 4 (CXCR4; termed dual/mixed [D/M] virus) or only CXCR4 (X4 virus) do not respond to treatment with CCR5 antagonists. Virologic failure of these drugs frequently is associated with outgrowth of D/M or X4 virus from a preexisting minority population present at levels below the limit of assay detection. Mutations in HIV-1 gp120 that allow the virus to bind to the drug-bound form of CCR5 have been described in viruses from some patients whose virus remained R5 after vi-

rologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism. There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted in the figure. Some CCR5 antagonist-resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3,⁷³ the clinical significance of such mutations is not yet known.

aa. Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses in vitro indicate that Q148H and G140S in combination with mutations L74I/M, E92Q, T97A, E138A/K, G140A, or N155H are associated with 5-fold to 20-fold reduced dolutegravir susceptibility⁷⁴ and reduced virologic suppression in patients.⁷⁵⁻⁸¹ Results of the phase III dolutegravir study in antiretroviral treatment-naïve patients are expected to provide additional resistance information.

bb. Six elvitegravir codon mutations have been observed in integrase strand transfer inhibitor treatment-naïve and -experienced patients in whom therapy is failing.⁸²⁻⁸⁸ T97A results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.^{85,86} The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.⁸⁵

cc. Raltegravir failure is associated with integrase mutations in at least 3 distinct, but not exclusive, 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 plus E138A, E138K, or G140S. The most common mutational pattern in this pathway is Q148H plus 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 plus T97A, Y143H, G163K/R, V151I, or D232N.⁸⁹ The Y143R/H/C mutation is uncommon.⁹⁰⁻⁹⁴ E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (<5 fold) cross resistance to raltegravir.^{84,95-97} N155H mutants tend to predominate early in the course of raltegravir failure but are gradually replaced by viruses with higher resistance, often bearing mutations G140S plus Q148H/R/K, with continuing raltegravir treatment.⁹⁰

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