Special Contribution

2017 Update of the Drug Resistance Mutations in HIV-1

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The 2017 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2015. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The figures are designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs and, therefore, in making clinical decisions regarding antiretroviral therapy.

The 2017 edition of the IAS–USA drug resistance mutations list updates the figures last published in November 2015.[1] The Q148K mutation was added to the bar for the integrase strand transfer inhibitor dolutegravir, and the bars for multinucleoside and nucleotide analogue reverse transcriptase inhibitor (nRTI) resistance were modified to indicate specifically that thymidine analogue mutations do not affect susceptibility to emtricitabine and lamivudine.

Methods

The IAS–USA Drug Resistance Mutations Group is an independent, volunteer panel of experts charged with delivering accurate, unbiased, and evidence-based information on drug resistance–associated mutations for HIV clinical practitioners. The group reviews new data on HIV drug resistance to maintain a current list of mutations associated with clinical resistance to HIV-1. 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 Food and Drug Administration as well as any drugs available in expanded access programs are included (listed in alphabetic order by drug class). User notes provide additional information as necessary. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive.

Positions in bold generally indicate that particular caution is warranted with use of a drug. For nucleoside and nucleotide reverse transcriptase inhibitors, bold mutations indicate signature mutations selected for by particular drugs that may, alone or in combination with other mutations, result in a substantial reduction in drug susceptibility and clinical outcome. For nonnucleoside reverse transcriptase inhibitors, bold mutations indicate a substantial reduction in drug susceptibility or clinical outcome and that particular drugs should be avoided if possible. For protease inhibitors, mutations at bolded positions are associated with greater reductions in drug susceptibility and virologic responses to therapy. Certain protease inhibitors, particularly ritonavir-boosted darunavir, have high genetic barriers to resistance and may still retain considerable activity despite the presence of a mutation at a bolded position. For the entry inhibitor enfuvirtide, bold mutations may indicate a significant reduction in drug susceptibility or clinical outcome and that use of the drug should be avoided if possible. For integrase strand transfer inhibitors, bold mutations indicate a substantial reduction in drug susceptibility or clinical outcome for elvitegravir and raltegravir, and these drugs should be avoided if possible. Dolutegravir may still retain considerable activity in the presence of bolded mutations if twice-daily dosing is applied.

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.

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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 emerges most commonly to lamivudine or emtricitabine or nonnucleoside analogue reverse transcriptase inhibitors).

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, 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.

For more in-depth reading and an extensive reference list, see the 2008 IAS–USA panel recommendations for resistance testing[2] and 2016 IAS–USA panel recommendations for antiretroviral therapy.[3] Updates are posted periodically at www.iasusa.org.

Comments

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

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 format or content can be made.**

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Permission will be granted only for requests to reprint or adapt the most current version of the mutations figures as they are posted at 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 IAS–USA.

Financial affiliations in the past 12 months: The authors (listed alphabetically) disclose the following affiliations with commercial organizations that may have interests related to the content of this article: Dr Calvez has served as an advisor or consultant to and has received research grants from Bristol-Myers Squibb, Gilead Sciences, Inc, Johnson and Johnson, and ViiV Healthcare, and is a founder of SkinDermic Pharma. Dr Günthard has received grants from Gilead Sciences, Inc, has served on a data and safety monitoring board for Merck & Co, Inc, and on a consulting or advisory board for Gilead Sciences, Inc, and has received travel support from Bristol-Myers Squibb, Gilead Sciences, Inc, and Janssen Therapeutics. Dr Johnson has no relevant financial affiliations to disclose. Dr Paredes has received research grants from ViiV Healthcare, and Merck, Sharp, and Dohme. Dr Pillay has no relevant financial affiliations to disclose. Dr Richman has been a consultant to Antiva Biosciences, Chimerix, Gilead Sciences, Inc, and Monogram Biosciences, Inc. Dr Shafer has served as a consultant or advisor for ViiV Healthcare and has received grants from Bristol-Myers Squibb, Gilead Sciences, Inc, Merck & Co, Inc, and Vela Diagnostics. Dr Wensing has served on advisory boards for CLJI Worldwide, Gilead Sciences, Inc, and ViiV Healthcare; has participated in the Dutch HIV Masterclass organized by Virology Education; has received travel support from Virology Education; and has received grants from Janssen Pharmaceuticals, Gilead Sciences, Inc, and ViiV Healthcare.

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

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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]

69 Insertion Complex[b] (affects all nRTIs currently approved by the US FDA)

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

151 Complex[c] (affects all nRTIs currently approved by the US FDA except tenofovir)

	A	V	F	F	Q
Multi-nRTI Resistance	62	75	77	116	151
	V	I	L	Y	M

Thymidine Analogue-Associated Mutations[d,e] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

	M	D	K	L	T	K
Multi-nRTI Resistance	41	67	70	210	215	219
	L	N	R	W	Y	Q
					F	E

	K	L	Y	M
Abacavir[f,g]	65	74	115	184
	R	V	F	V
	E			
	N			

	K	L
Didanosine[g,h]	65	74
	R	V
	E	
	N	

	K	M
Emtricitabine	65	184
	R	V
	E	I
	N	

	K	M
Lamivudine	65	184
	R	V
	E	I
	N	

	M	K	D	K	L	T	K
Stavudine[d,e,g,i,j,k]	41	65	67	70	210	215	219
	L	R	N	R	W	Y	Q
		E				F	E
		N					

	K	K
Tenofovir[l]	65	70
	R	E
	E	
	N	

	M	D	K	L	T	K
Zidovudine[d,e,j,k]	41	67	70	210	215	219
	L	N	R	W	Y	Q
					F	E

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

	L	K	K	V	V	Y	Y	G	P	M
Efavirenz	100	101	103	106	108	181	188	190	225	230
	I	P	N	M	I	C	L	S	H	L
			S			I		A		

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

	L	K	K	V	V	Y	Y	G	M
Nevirapine	100	101	103	106	108	181	188	190	230
	I	P	N	A	I	C	C	A	L
			S	M		I	L		
							H		

	L	K	E	V	Y	Y	H	F	M
Rilpivirine[o]	100	101	138	179	181	188	221	227	230
	I	E	A	L	C	L	Y	C	I
		P	G		I				L
			K		V				
			Q						
			R						

MUTATIONS

Insertion

Amino acid wild-type — K
Amino acid position — 65
Amino acid substitution conferring resistance — R

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 IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS[p,q,r]

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

	G	I	V	Q	Q	N	N
Enfuvirtide[x]	**36**	**37**	**38**	**39**	**40**	**42**	**43**
	D	**V**	**A**	**R**	**H**	**T**	**D**
	S		**M**				
			E				

Maraviroc[y] See User Note

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

	T	L	E	T	F	E	G	Y	S	Q	N	R
Dolutegravir[aa]					121	138	140			**148**	155	263
					Y	A	A			**H**	H	K
						K	S			**K**		
										R		
Elvitegravir[bb]	**66**		**92**	97	**121**				**147**	148	**155**	263
	I		**Q**	A	**Y**				**G**	**H**	**H**	K
	A		G							**K**		
	K									**R**		
Raltegravir[cc]		74	92	97	**121**	138	140	**143**	148	148	**155**	263
		M	Q	A	**Y**	A	A	**R**	**H**	**H**	**H**	K
						K	S	**H**	**K**	**K**		
								C	**R**	**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 nonnucleoside 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-naive 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 they have not been associated with increased rates of virologic failure of etravirine or rilpivirine in clinical trials.[8-10] K65E/N variants are increasingly reported in patients experiencing treatment failure with tenofovir, stavudine, or didanosine. K65E usually occurs in mixtures with wild type. K65N gives an approximately 4-fold decrease in susceptibility. Patient-derived viruses with K65E and site-directed mutations replicate very poorly in vitro; as such, no susceptibility testing can be performed.[11,12]

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 Food and Drug Administration (FDA) when present with 1 or more TAMs at codons 41, 210, or 215.[13] 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.[13] 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[14] except emtricitabine and lamivudine, which in fact reverse the magnitude of resistance and are recommended with tenofovir or zidovudine in the presence of TAMS. The degree to which cross-resistance is observed depends on the specific mutations and number of mutations involved.[15-18]

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.[19-21]

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.[22,23]

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.[22,24,25] 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.[26] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[27]

i. K65R is selected frequently (4%–11%) in patients with some nonsubtype-B clades for whom stavudine-containing regimens are failing in the absence of tenofovir.[28,29]

j. The presence of M184V appears to delay or prevent emergence of TAMs.[30] 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-naive patients.[31,32] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[33]

l. The presence of K65R is associated with a reduced virologic response to tenofovir.[13] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[13] The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.[34-36] There are no data to indicate differences in resistance patterns between tenofovir disoproxil fumarate and tenofovir alafenamide because the active drug component in both formulations is tenofovir.

m. There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.[37]

n. Resistance to etravirine has been extensively studied only in the context of coadministration with ritonavir-boosted darunavir. 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.[38-40] The single mutations L100I, K101P, and Y181C/I/V have a high relative weight with regard to reduced susceptibility and reduced clinical response compared with other mutations.[41,42] The presence of K103N alone does not affect etravirine response.[42] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[43-45]

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).[46-48] A 16th mutation, Y188L, reduces rilpivirine susceptibility 6 fold.[48] K101P and Y181I/V reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are not commonly observed in patients receiving rilpivirine.[49-51] Mutations at position 138 (most notably 138A) may occur as natural polymorphisms, especially in non-B subtypes.[52] 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–associated mutation M184I, which alone does not reduce rilpivirine susceptibility. When M184I is combined with E138K or K101E, rilpivirine susceptibility is reduced about 7 fold and 4.5 fold, respectively.[51,53-55] The combinations of reverse transcriptase–associated mutations L100I plus K103N/S and L100I plus K103R plus V179D were strongly associated with reduced susceptibility to rilpivirine. However, for isolates harboring the K103N/R/S or V179D as single mutations, no reduction in susceptibility was detected.[48,56]

p. Often, numerous mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[57] 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 and may also be associated with reductions in virologic responses to therapy. 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. So minor mutations are present as common polymorphic changes in HIV-1 nonsubtype-B clades. Mutations in *gag* cleavage sites may

confer resistance to all PIs and may emerge before mutations in protease. A large proportion of virus samples from patients with confirmed virologic failure on a PI-containing regimen is not found to have PI resistance–associated mutations. Preliminary data from recent studies suggest that several mutations in the Gag protein[58] may be responsible for reduced PI susceptibility in a subset of these patients.

r. Ritonavir is not listed separately, as it is currently used only at low doses 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.[59]

t. HIV-1 RNA response to ritonavir-boosted darunavir correlates with baseline susceptibility and the presence of several specific PI resistance–associated 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 ritonavir-boosted darunavir were shown in 2 data sets independently.[60,61] Some of these mutations appear to have a greater effect on susceptibility than others (eg, I50V vs V11I). The presence at baseline of 2 or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.[62]

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 ritonavir-boosted lopinavir.[63,64] The product information states that accumulation of 7 or 8 mutations confers resistance to the drug.[65] However, there is emerging evidence that specific mutations, most notably I47A (and possibly I47V) and V32I, are associated with high-level resistance.[66-68] The addition of L76V to 3 PI resistance–associated mutations substantially increases resistance to ritonavir-boosted lopinavir.[59]

w. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI resistance–associated mutations.[69]

x. 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]

y. 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 CXC 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 is frequently 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 virologic failure of a CCR5 antagonist. Most of these mutations are found in the V3 loop, the major determinant of viral tropism.[73] 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[74]; the clinical significance of such mutations is not yet known.

z. In site-directed mutants and clinical isolates, the mutation F121Y has a profound effect on susceptibility to elvitegravir and raltegravir and to a lesser extent to dolutegravir. Mutation R263K can be selected in vivo during treatment with dolutegravir and raltegravir and results in a 2- to 5-fold reduction in susceptibility to dolutegravir, elvitegravir, and raltegravir.[75-80]

aa. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.[81] Cross-resistance studies with raltegravir- and elvitegravir-resistant viruses indicate that Q148H/R 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 susceptibility[82] and reduced virologic suppression in patients.[83-86]

bb. Seven elvitegravir codon mutations have been observed in integrase strand transfer inhibitor treatment–naive and –experienced patients in whom therapy is failing.[87-93] T97A, which may occur as a polymorphism,[94] results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.[92,93] The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.[92]

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.[95] The Y143R/H/C mutation is uncommon.[96-100] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (< 5 fold) cross-resistance to raltegravir.[101-103] 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.[96]

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