Special Contribution
2019 Update of the Drug Resistance Mutations in HIV-1

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The 2019 edition of the IAS–USA drug resistance mutations list updates the ***Figure*** *last published in January 2017. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The* ***Figure*** *is designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs, and therefore, in making clinical decisions regarding antiretroviral therapy.*

Keywords: HIV, antiretroviral, drug resistance, therapy, mutations

The 2019 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations list updates the **Figure** last published in January 2017.[1] In this update:

- 2 integrase strand transfer inhibitors (InSTIs), bictegravir and cabotegravir, and the nonnucleoside reverse transcriptase inhibitor (NNRTI), doravirine, were added to the **Figure**.

- Bictegravir (formerly GS-9883) was approved by the US Food and Drug Administration (FDA) in February 2018 as part of a fixed-dose combination of bictegravir/emtricitabine/tenofovir alafenamide for the treatment of HIV-infected, treatment-naive individuals or to replace an antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA below 50 copies/mL) on a stable antiretroviral regimen for at least 3 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of the fixed-dose combination.[2]

- Cabotegravir (formerly S/GSK-1265744) is an investigational drug that has been filed for approval at the FDA as part of a fixed-dose, long-acting combination of cabotegravir/rilpivirine for the treatment of HIV-infection in adults who are virologically suppressed and have no resistance to the individual components of the combination.[3]

- Doravirine (formerly MK-1439) was approved by the FDA in August 2018 for the treatment of HIV-infected, treatment-naive individuals in combination with other antiretroviral drugs.[4]

- Several changes were made to drugs already on the **Figure**. On the lopinavir/ritonavir bar, mutations at positions 50, 54, and 84 were changed to boldface to indicate recognition as major mutations rather than minor mutations.[5-7] The G118R mutation was added to the bar for the InSTI dolutegravir.[8,9]

- For antiretroviral drugs that are no longer recommended, the bars are listed at the bottom of the class and are shaded in gray.

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.

The group considers only data that have been published or have been presented at a scientific conference. Table 1 provides the list of amino acids and the abbreviations used. Drugs that have been approved by the US Food and Drug Administration and are generally recommended, as well as any drugs

Table 1. Amino acids and their abbreviations.

Alanine	A
Cysteine	C
Aspartate	D
Glutamate	E
Phenylalanine	F
Glycine	G
Histidine	H
Isoleucine	I
Lysine	K
Leucine	L
Methionine	M
Asparagine	N
Proline	P
Glutamine	Q
Arginine	R
Serine	S
Threonine	T
Valine	V
Tryptophan	W
Tryosine	Y

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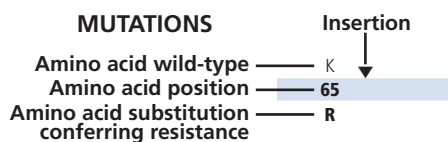
MUTATIONS   Insertion

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

Figure 1. Display of the Figure Bar: Amino acid position, wild type, mutation conferring resistance, and indication of insertion mutation.

available in expanded access programs are included (listed in alphabetic order by drug class). Drugs that are no longer recommended are listed at the bottom of the class and are shaded in gray. User notes provide additional information. 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.

The magnitude of the reduction in susceptibility conferred by drug resistance mutations varies widely, and is modulated by the genetic context of the HIV sequence in which the mutation occurs. Despite the fact that mutations result in a spectrum of degrees of resistance, mutations have been arbitrarily designated as major (bolded) or minor (not bolded) (see Figure 1). Those defined as major tend to occur earlier during treatment failure and generally confer larger reductions in susceptibility. Those defined as minor tend to accrue after the emergence of a major mutation, confer some incremental resistance, may occur as well as polymorphisms in wild-type virus, and in some cases do not reduce susceptibility but restore replication fitness to viruses with resistance mutations that impair fitness. In general, a major mutation should raise concern that a drug is at least partially compromised; a minor mutation on its own may not raise such a concern, but it should add concern in the presence of other mutations.

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 mu-

tagenesis; (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. Consequently, only some of the resistance mutations depicted on the **Figure** can be used to identify transmitted drug resistance.[10]

Clinical Context

The **Figure** is 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 history of antiretroviral therapy; (2) recognizing that in the absence of current drug treatment that is conferring 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 a first-line 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, nonnucleoside analogue reverse tran-

scriptase inhibitors, or first generation InSTIs (elvitegravir, raltegravir).

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 2018 IAS–USA panel recommendations for resistance testing[11] and 2018 IAS–USA panel recommendations for antiretroviral therapy.[12] Updates are posted periodically at www.iasusa.org.

Comments

Please send your evidence-based comments, including relevant reference citations, to journal@iasusa.org.

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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)[1]

69 Insertion Complex[2] (affects all nRTIs currently approved by the US FDA)

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

151 Complex[3] (affects all nRTIs currently approved by the US FDA except tenofovir)

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

Thymidine Analogue-Associated Mutations[4,5] (TAMs; affect all nRTIs currently approved by the US FDA other than emtricitabine and lamivudine)

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

	K		L		Y		M
Abacavir[1,6]	65		74		115		184
	R		V		F		V
	E						
	N						

	K				M
Emtricitabine	65				184
	R				V
	E				I
	N				

	K				M
Lamivudine	65				184
	R				V
	E				I
	N				

	K	K
Tenofovir[1,7]	65	70
	R	E
	E	
	N	

	M		D	K						L	T	K
Zidovudine[4,5,8,9]	41		67	70						210	215	219
	L		N	R						W	Y	Q
											F	E

	K		L
Didanosine[1,10,21]	65		74
	R		V
	E		
	N		

	M	K	D	K						L	T	K
Stavudine[1,4,5,8,9]	41	65	67	70						210	215	219
	L	R	N	R						W	Y	Q
		E									F	E
		N										

Nonnucleoside Analogue Reverse Transcriptase Inhibitors (NNRTIs)[1,11]

					V			Y	G		P	F	M	L
Doravirine[12]					106			188	190		225	227	230	234
					A			C	E		H	C	L	I
					I			L				L		
					M			H				R		
					T									

	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[13]	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[14]	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 IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS (PIs) [15,16,17]

Atazanavir +/- ritonavir [18]

Pos	10	16	20	24	32	33	34	36	46	48	50	53	54	60	62	64	71	73	82	84	85	88	90	93
WT	L	G	K	L	V	L	E	M	M	G	I	F	I	D	I	I	A	G	V	I	I	N	L	I
Mut	I F V C	E	R M I T V	I	I F V	I 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 [19]

Pos	11	32	33	47	50	54	74	76	84	89
WT	V	V	L	I	I	I	T	L	I	L
Mut	I	I	F	V	V	M L	P	V	V	V

Lopinavir/ritonavir [20]

Pos	10	20	24	32	33	46	47	50	53	54	63	71	73	76	82	84	90
WT	L	K	L	V	L	M	I	I	F	I	L	A	G	L	V	I	L
Mut	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

Tipranavir/ritonavir

Pos	10	33	36	43	46	47	54	58	69	74	82	83	84	89
WT	L	L	M	K	M	I	I	Q	H	T	V	N	I	L
Mut	V	F	I L V	T	L	V	A M V	E	K R	P	L T	D	V	I M V

Fosamprenavir/ritonavir [21]

Pos	10	32	46	47	50	54	73	76	82	84	90
WT	L	V	M	I	I	I	G	L	V	I	L
Mut	F I R V	I	I L	V	V	L V M	S	V	A F S T	V	M

Indinavir/ritonavir [21]

Pos	10	20	24	32	36	46	54	71	73	76	77	82	84	90
WT	L	K	L	V	M	M	I	A	G	L	V	V	I	L
Mut	I R V	M R	I	I	I	I L	V	V T	S A	V	I	A F T	V	M

Nelfinavir [21,22]

Pos	10	30	36	46	71	77	82	84	88	90
WT	L	D	M	M	A	V	V	I	N	L
Mut	F I	N	I	I L	V T	I	A F T S	V	D S	M

Saquinavir/ritonavir [21]

Pos	10	24	48	54	62	71	73	77	82	84	90
WT	L	L	G	I	I	A	G	V	V	I	L
Mut	I R V	I	V	V L	V	V T	S	I	A F T S	V	M

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

Enfuvirtide [23]

Pos	36	37	38	39	40	42	43
WT	G	I	V	Q	Q	N	N
Mut	D S	V	A M E	R	H	T	D

Maraviroc [24] See User Note

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS [25]

Bictegravir [26]

Pos	118	138	140	148	263
WT	G	E	G	Q	R
Mut	R	K	S	H	K

Cabotegravir [27]

Pos	66	118	138	140	148	153	155	263
WT	T	G	E	G	Q	S	N	R
Mut	K	R	A K T	A C R S	H K R	F Y	H	K

Dolutegravir [28]

Pos	118	121	138	140	148	155	263
WT	G	F	E	G	Q	N	R
Mut	R	Y	A K T	A S	H K R	H	K

Elvitegravir [29]

Pos	66	92	97	121	147	148	155	263
WT	T	E	T	F	S	Q	N	R
Mut	I A K	Q	A G	Y	G	H K R	H	K

Raltegravir [30]

Pos	74	92	97	121	138	140	143	148	155	263
WT	L	E	T	F	E	G	Y	Q	N	R
Mut	M	Q	A	Y	A K	A S	R H C	H K R	H	K

v

User Notes

1. Mutations at the C-terminal reverse transcriptase domains (amino acids 293-560) outside of regions depicted on the **Figure Bar** may contribute to nucleoside (or nucleotide) analogue reverse transcriptase inhibitor (nRTI) and nonnucleoside analogue reverse transcriptase inhibitors (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.[1-3] K65E/N/R variants are reported in patients experiencing treatment failure with tenofovir (meaning tenofovir disoproxil fumarate [TDF] or tenofovir alafenamide [TAF]) stavudine, or didanosine. The K65R/N variants may be selected by tenofovir, didanosine, abacavir, or stavudine and are associated with decreased viral susceptibility to these drugs.[4-8] 65R may be more easily selected in subtype C clades.[9] K65E usually occurs in mixtures with wild-type virus. Patient-derived viruses with K65E and site-directed mutations replicate very poorly in vitro; as such, no susceptibility testing can be performed.[10,11] Some nRTI mutations, like T215Y and H208Y,[12] may lead to viral hypersusceptibility to nonnucleoside reverse transcriptase inhibitors (NNRTIs), including etravirine,[13] 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,[14-18] although no clinical data exist for improved response to etravirine in NNRTI-experienced individuals.

2. 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.[4] Some other amino acid changes from the wild-type T at codon 69 without the insertion may be associated with broad nRTI resistance.

3. Tenofovir retains activity against the Q151M complex of mutations.[4] 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). Since no differences in resistance patterns have been observed between TDF and TAF, both drugs are referred to as "tenofovir" on the **Figure Bar**.[19]

4. 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[20] 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.[21-24]

5. 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.[25-27]

6. 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.[5,28]

7. The presence of K65R is associated with a reduced virologic response to tenofovir.[4] A reduced response also occurs in the presence of 3 or more TAMs inclusive of either M41L or L210W.[4] The presence of TAMs or combined treatment with zidovudine prevents the emergence of K65R in the presence of tenofovir.[29-31]

8. The presence of M184V appears to delay or prevent emergence of TAMs.[32] This effect may be overcome by an accumulation of TAMs or other mutations.

9. 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.[33,34] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[35]

10. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[36] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[37] However, 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.

11. There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI resistance.[38]

12. Doravirine is active in vitro against variants containing the common NNRTI mutations K103N, E138K, Y181C, and G190A.[39,40] Doravirine selects for mutations at positions 106, 108, 227, and 234, with more than 1 mutation usually required for substantial levels of resistance.[41] Mutations V106A, Y188L, and M230L are associated with a 10- or greater fold reduced susceptibility to doravirine. V106A and Y188L have also been selected in vivo.[42,43] In 1 clinical isolate, G190E was associated with about 20-fold reduced susceptibility to doravirine.[40] Furthermore, the double and triple mutants V106A and F227L; V106A and L234I; V106A and F227L and L234I; and V106A and 190A and F227L, are all associated with substantial resistance to doravirine.[39,41,44]

13. Resistance to etravirine has been extensively studied only in the context of co-administration with ritonavir-boosted darunavir. There, mutations associated with virologic outcome were assessed and their relative weights (or magnitudes of impact) assigned. In addition, phenotypic cutoff values were calculated, and assessments 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.[45-47] The single mutations L100I, K101P, and Y181C/I/V have high relative weights with regard to reduced susceptibility and reduced clinical response compared with other mutations.[48,49] The presence of K103N alone does not affect etravirine response.[49] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[50-52]

14. 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).[53-55] A 16th mutation, Y188L, reduces rilpivirine susceptibility 6 fold. The K101P and Y181I/V mutations reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but are not commonly observed in patients receiving rilpivirine.[56-58] Mutations at position 138 (most notably E138A) may occur as natural polymorphisms, especially in non-B subtype virus.[59] The K101E, E138K, and Y181C mutations, 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.[58,60-62] 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.[55,63]

15. Often, several mutations are necessary to substantially impact virologic response to a ritonavir-boosted protease inhibitor (PI).[64]

16. Mutations in Gag cleavage sites may confer or contribute to resistance to PIs and may even emerge before mutations in protease.[65] 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.

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

18. Several mutations are associated with atazanavir resistance. Their impacts differ, with I50L, I84V, and N88S having the greatest effect. Mutations that are selected during unboosted atazanavir are not different from those selected during boosted atazanavir, but the relative frequency of mutations may differ. 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.[66]

19. Virologic 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 on 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 independently in 2 data sets.[67,68] 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/M, T74P, L76V, I84V, or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.[69]

20. Virologic response to ritonavir-boosted lopinavir is affected by the presence of 3 or more of the following amino acid substitutions in protease at baseline: L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54L/T/V, V82A/C/F/S/T, and I84V. In addition, the combination of 47A/V with V32I is associated with high-level resistance.[66,70-76] I50V is only occasionally selected in vivo but has a clear impact on susceptibility.[77-79] Subtype C patterns with M46L, I54V, L76V, and V82A are frequently observed in patients receiving ritonavir-boosted lopinavir.

21. 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.

22. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI resistance–associated mutations.[80]

23. 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 *env* (eg, the HR2 region or those yet to be identified), as well as coreceptor usage and density, may affect susceptibility to enfuvirtide.[81-83]

24. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with virus that use 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.[84] There is as yet no consensus on specific signature mutations for CCR5 antagonist resistance, so they are not depicted on the **Figure Bar**. Some CCR5 antagonist–resistant viruses selected in vitro have shown mutations in gp41 without mutations in V3;[85] the clinical significance of such mutations is not yet known.

25. 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. 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.[86-91] 263K has been selected in vitro under pressure with bictegravir and cabotegravir.[92]

26. Bictegravir is a second-generation integrase strand transfer inhibitor (InSTI), like dolutegravir, with higher genetic barrier to resistance than raltegravir and elvitegravir. Bictegravir has only been studied in detail in treatment-naive individuals and those with suppressed viremia (<50 HIV-RNA copies/mL) who have been on stable antiretroviral therapy for at least 3 months without a history of treatment failure and without relevant resistance to bictegravir or its coformulated drugs. Susceptibility studies in vitro and in animal models[93] show that mutations G118R and R263K confer 14-fold and 6-fold increases in 50% effective concentration (EC_{50}), whereas the G140S and Q148H combination of mutations decreases HIV-1 susceptibility to bictegravir 4.8 fold. Bictegravir dose-escalation tissue culture experiments also showed the selection of the M50I and R263K mutations. In combination with Q148 and G140A mutations, E138K reduces bictegravir susceptibility 10 fold.[94] Bictegravir is coformulated with TAF/emtricitabine, which may protect the drug from mutations such as those observed during virologic failure of dolutegravir monotherapy.[93-97]

27. Cabotegravir is an investigational, long-acting InSTI. In clinical trials, Q148R (fold changes, 5.2-9.4) and G140R (fold change, 6.7) have been observed particularly in HIV-1 A1 subtype harboring the L74I integrase polymorphism.[93,98-101] The G118R mutation has been selected in macaques receiving cabotegravir (long-acting) for pre-exposure prophylaxis during acute simian/human immunodeficiency virus infection.[102]

28. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.[103] 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[104] and reduced virologic suppression in patients.[105-108]

29. Seven elvitegravir codon mutations have been observed in InSTI treatment–naive and –experienced patients in whom therapy is failing.[109-115] T97A, which may occur as a polymorphism,[116] results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.[114,115] The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.[114]

30. 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 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.[117] The Y143R/H/C mutation is uncommon.[118-122] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (<5 fold) cross-resistance to raltegravir.[123-125] 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.

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