Special Contribution

2025 Update of the Drug Resistance Mutations in HIV-1

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Certain mutations in HIV-1 that emerge during exposure to antiretroviral drugs may have varied impact on the effectiveness of current and subsequent treatments for HIV. This 2025 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations list updates the Figure last published in November 2022 based on new data that have become available. The mutations listed are those that have been identified by specific criteria to contribute to a reduced virologic response to currently available antiretroviral drugs. The Figure is designed to assist practitioners in identifying key mutations associated with resistance to antiretroviral drugs, and therefore, to consider when making clinical decisions regarding the components of an initial antiretroviral regimen and changing a regimen in the settings of avoiding toxicity, regimen simplification, or previous or current virologic failure.

Keywords: HIV, antiretroviral, drug resistance, TAM, therapy, mutation

Introduction

Mutations in the HIV-1 genome that emerge during exposure to antiretroviral drugs may contribute to reducing the virologic response to a drug or drugs in the same class and reduce the effectiveness of the regimen overall. This 2025 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations list updates the **Figure** last published in November 2022.[1] In this update:

- Several changes were made to drugs already on the **Figure** (see Table 1). Changes were made to the integrase strand transfer inhibitors (InSTIs) cabotegravir, dolutegravir, elvitegravir, and raltegravir, the nonnucleoside analogue reverse transcriptase inhibitor (NNRTI) doravirine, and the capsid inhibitor lenacapavir.
- **Figure Bars** and user notes were added for the entry inhibitors fostemsavir and ibalizumab.
- For antiretroviral drugs that are no longer recommended or manufactured, the associated **Figure Bars** are listed at the bottom of the drug class and are shaded in gray. Their user notes are retained for historical reference.

Specific Drugs and Details

L74I, a signature mutation in HIV-1 subtype A6 that may occur as a polymorphism in other HIV-1 subtypes

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Table 1. Summary of mutation updates to the 2025 figure bars.

Drug	Figure bar changes (mutation type)
Doravirine	Added A98G (minor)
Dolutegravir	Added S147G (minor)
Cabotegravir	Added L74I (major)[a]
Lenacapavir	Added K70H (major) Updated K70N (major) Updated L56I (major) Updated N74D (major)
Raltegravir	Added G118R (major) Added G140C (minor)
Elvitegravir	Added G118R (major) Added E138A/K (minor) Added G140A/C/S (minor)

[a]Relevant for subtype A6 only.

has no direct effect on the susceptibility to cabotegravir.[2,3] However, in subtype A6 the mutation was associated with confirmed virologic failure in clinical trials of long-acting cabotegravir and rilpivirine.[4] In vitro analysis of recombinant viruses expressing integrase of subtype A6 showed that the presence of the L74I mutation confers a greater replication capacity when present with integrase resistance mutations at positions 118, 140, 148, and 263, thereby facilitating the selection of resistance to cabotegravir. Therefore, L74I was added as a major mutation for subtype A6 only in the cabotegravir bar.[5]

The capsid inhibitor lenacapavir[6] is approved for the treatment of HIV-1 infection in combination with other antiretroviral drugs in heavily treatment-experienced adults with multidrug-resistant virus in whom their current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations.

There are no mutations depicted on the **Figure Bars** for the entry inhibitors fostemsavir, ibalizumab, and maraviroc. There is as yet no consensus on specific signature mutations that impair treatment with these drugs. As such, genotypic testing to predict resistance to these drugs is not recommended in clinical practice. On occasion phenotypic testing may be performed, if available.

The enfuvirtide bar is shaded in gray because this drug is no longer available.

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 drugs used to treat HIV-1 infection. The group considers only data that have been published or have been presented at a peer-reviewed scientific conference. Table 2 provides the list of amino acids and the abbreviations used.

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 (bold) or minor (not bold) (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

Table 2. Amino acids and their abbreviations.

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

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concern but might cause concern in the presence of other mutations. The delineation between major and minor is often not clear-cut.

Identification of Mutations

The mutations listed are those that have been identified by one or more of the following criteria: (1) in vitro passage experiments with validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) nucleotide sequencing of viruses from individuals in whom the drug is failing; and (4) association studies between genotype at baseline and virologic response in persons exposed to the drug.

The development of more recently approved drugs that cannot always be tested as monotherapy precludes assessment of the impact of resistance on antiretroviral activity that is not seriously confounded by the 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 in the **Figure** can be used to identify transmitted drug resistance.[6]

Drugs that have been approved by the US Food and Drug Administration and that are generally recommended, as well as specific drugs available in development with expectation of approval in the next few years, are included. All drugs are listed in alphabetical order by drug class. User notes provide additional information. Although the Drug Resistance Mutations Group works to maintain a complete and current list of these mutations, the data are constantly evolving, and it cannot be assumed that the list presented here is definitive. Consultation with an expert in HIV resistance is advisable in certain situations.

Clinical Context

The **Figure** identifies key mutations associated with antiretroviral drug resistance for clinicians to consider

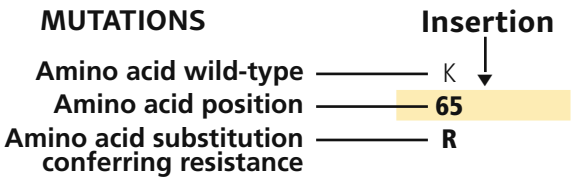

Figure 1. Figure Bar Key. Amino acid position, wild type, mutation conferring resistance, and indication of insertion mutation.

for selecting initial and subsequent therapeutic regimens. In the context of selecting an antiretroviral regimen, 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; and (2) recognizing that resistant strains may be present at levels below the limit of detection of the test after discontinuation or during poor adherence to the regimen that conferred the selection pressure. Analyzing stored samples collected under the selection pressure of treatment could be useful in this setting; and (3) recognizing that initial virologic failure typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen if the failing regimen is not continued for a prolonged period after failure.

The absence of detectable viral resistance after treatment failure may result from several factors: the presence of drug-resistant minority viral populations below the threshold of the applied resistance test; 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 the consequence of drugs not reaching optimal levels in specific anatomic compartments.

For more in-depth reading and an extensive reference list, see the 2018 IAS–USA panel recommendations for resistance testing and the 2024 IAS–USA panel recommendations for antiretroviral therapy.[7,8] Updates to the **Figure** are posted periodically at www.iasusa.org.

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Comments

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Financial relationships with ineligible companies within the past 24 months: Dr Calvez reported serving as a board member, advisor, or consultant to, and receiving research grants to his institution from Moderna, Merck Sharp & Dohme, Inc, ViiV Healthcare, and Gilead Sciences, Inc. (Updated March 5, 2025) *Dr Ceccherini-Silberstein reported consulting for ViiV Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc, and receiving research grants from ViiV Healthcare, Gilead Sciences, Inc, and Merck Sharp & Dohme, Inc.* (Updated November 7, 2024) *Dr Charpentier reported serving as an advisor to ViiV Healthcare, Gilead Sciences, Inc, Janssen Therapeutics, Theratechnologies, and Merck Sharp & Dohme, Inc, and receiving research grants from ViiV Healthcare.* (Updated November 11, 2024) *Dr Günthard reported serving as a consultant to Merck & Co, Inc, ViiV Healthcare, GlaxoSmithKline, Novartis, Johnson andJohnson, Inc, and Gilead Sciences, Inc, and receiving research grants from Gilead Sciences, Inc.* (Updated November 7, 2024) *Dr Paredes reported receiving research grants from ViiV Healthcare and Merck Sharp & Dohme, Inc, and serving as a consultant to Gilead Sciences, Inc, ViiV Healthcare, Pfizer, Inc, Theratechnologies, Inc, and Eli Lilly and Company.* (Updated November 11, 2024) *Dr Richman reported serving as a consultant to Antiva Biosciences, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and serving as Chair of the Data Management Committee of Gilead Sciences, Inc.* (Updated March 4, 2025) *Dr Shafer reported receiving research grants from Janssen Therapeutics, Vela Diagnostics, and InSilixa, Inc, and receiving personal consulting fees from Abbott Diagnostics.* (Updated November 8, 2024) *Dr Wensing reported serving on advisory boards for ViiV Healthcare, Glaxo-Smith Kline, Janssen Therapeutics, and Gilead Sciences, Inc, and receiving investigator-initiated research grants from Gilead Sciences, Inc.* (Updated November 8, 2024) *Ms Jacobsen reported no relevant financial relationships with ineligible companies.* (Updated March 4, 2025) *All relevant financial relationships with ineligible companies have been mitigated.*

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Top Antivir Med. 2025 March 4 (Ahead of Issue)

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 Food and Drug Administration)

	M	A	▼	K	L	T	K
	41	62	69	70	210	215	219
Multi-nRTI 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	Q
	62	75	116	151
Multi-nRTI Resistance	V	I	Y	M
		L		

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

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

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

	K	M
	65	184
Emtricitabine/ Lamivudine	R	V
	E	I
	N	

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

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

	K	L
	65	74
Didanosine[1,10,22]	R	V
	E	
	N	

	M	K	D	K	L	T	K
	41	65	67	70	210	215	219
Stavudine[1,4,5,8,9,22]	L	R	N	R	W	Y	Q
		E				F	E
		N					

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

	A	V	Y	G	P	F	M	L	Y
	98	106	188	190	225	227	230	234	318
Doravirine[12]	G	A	L	E	H	C	L	I	F
		I				I			
		M				L			
		T				R			
						V			

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

	V	A	L	K	V	E	V	Y	G	M
	90	98	100	101	106	138	179	181	190	230
Etravirine[13]	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
	100	101	103	106	108	181	188	190	230
Nevirapine	I	P	N	A	I	C	C	A	L
			S	M		I	L		
						V	H		

	L	K	E	V	Y	Y	H	F	M
	100	101	138	179	181	188	221	227	230
Rilpivirine[14]	I	E	A	L	C	L	Y	C	I
		P	G		I				L
			K		V				
			Q						
			R						

MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

	L	M	Q	K	N	A	T
	56	66	67	70	74	105	107
Lenacapavir[15]	I	I	H	H	D	T	N
				N	S		
				S			
				R			

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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS (PIs)[16,17,18]

	L 10	K 20	L 24	V 32	L 33	M 46	G 48	I 50	F 53	I 54	G 73	V 82	I 84	I 85	N 88	L 90
Atazanavir +/- ritonavir[19]	F	T	I	**I**	F	I L	V	**L**	L Y	**V** M T A S	C S T A	**A** T F L M S	**V**	V	**S**	M
Darunavir/ ritonavir[20]	V 11 I			V 32 I	L 33 F		I **47 V**	I **50 V**		I **54 M L**	T 74 P	L **76 V**	I **84 V**			L 89 V
Lopinavir/ ritonavir[21]	L 10 F I R V	K 20 M R	L 24 I	V **32 I**	L 33 F	M 46 I L	I **47 V A**	I **50 V**	F 53 L	I **54 V L A M** T S	A 71 V T	G 73 S	L **76 V**	V **82 A F T S**	I **84 V**		L 90 M
Tipranavir/ ritonavir	L 10 V			L 33 F	M 36 I L V	K 43 T	M 46 L I **47 V**			I 54 A M V	Q **58 E**	H 69 K R	T **74 P**	V **82 L T**	N **83 D** I **84 V**	L 89 I M V	
Fosamprenavir/ ritonavir[22]	L 10 F I R V			V 32 I			M 46 I L I 47 V	I **50 V**		I 54 L V M		G 73 S	L 76 V	V 82 A F S T	I **84 V**		L 90 M
Indinavir/ ritonavir[22]	L 10 I R V	K 20 M R	L 24 I	V 32 I	M 36 I	M **46 I L**		I 54 V			A 71 V T	G 73 S A	L 76 V	V 77 I	V **82 A F T**	I **84 V**		L 90 M
Nelfinavir[22,23]	L 10 F I			D **30 N**	M 36 I	M 46 I L					A 71 V T		V 77 I	V 82 A F T S	I 84 V	N 88 D S		L **90 M**
Saquinavir/ ritonavir[22]	L 10 I R V		L 24 I				G **48 V**	I 54 V L		I 62 V	A 71 V T	G 73 S	V 77 I	V 82 A F T S	I 84 V			L **90 M**

MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS

Fostemsavir[24]

Ibalizumab[25]

Maraviroc[26]

	G 36	I 37	V 38	Q 39	Q 40	N 42	N 43
Enfuvirtide[22,27]	**D S**	**V**	**A M E**	**R**	**H**	**T**	**D**

MUTATIONS IN THE INTEGRASE GENE ASSOCIATED WITH RESISTANCE TO INTEGRASE STRAND TRANSFER INHIBITORS (InSTIs)[28]

	T 66	L 74	E 92	T 97	G 118	F 121	E 138	G 140	Y 143	S 147	Q 148	N 155	R 263
Bictegravir[29]					R		A K T	A C R S			H K R		**K**
Cabotegravir[30]	K	**I***		A	**R**		A K T	A C **R** S			**H K R**	**H**	**K**
Dolutegravir[29,31]					**R**		A K T	A C **R** S		G	**H K R**	H	**K**
Elvitegravir[32]	**I** A K		**Q** G	A	**R**	**Y**	A K	A C S		**G**	**H K R**	**H**	**K**
Raltegravir[33]		M	Q	A	**R**	**Y**	A K	A C S	**R H C**		**H K R**	**H**	**K**

*Relevant to subtype A6 only

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User Notes

1. Mutations in the C-terminal reverse transcriptase domains (amino acids 293-560) that are outside of regions depicted on the **Figure Bar** may contribute to 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.[1-3] K65E/N/R variants are reported in patients experiencing treatment failure of tenofovir (ie, 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] The K65R 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 RT mutations, like T215Y and H208Y,[12] may lead to viral hypersusceptibility to NNRTIs. The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals;[13-17] no clinical data exist for improved response to other NNRTIs.

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. Since no differences in resistance patterns have been observed between TDF and TAF, both drugs are referred to as "tenofovir" on the **Figure Bar**.[18] 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 multinucleoside resistance).

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[19] 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.[20-23]

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.[24-26]

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.[5,27]

7. If resistance emerges specifically to tenofovir, the most common drug resistance mutation to emerge is K65R. It is associated with about 2-fold reduced tenofovir susceptibility, which is clinically significant. However, when K65R occurs in combination with the lamivudine/emtricitabine resistance mutation M184V/I, the reduction in tenofovir susceptibility is less than 1.5 fold, a reduction in susceptibility that is less clinically significant. It does not appear to compromise switching to second-generation InSTI regimens including tenofovir and lamivudine or emtricitabine in fully suppressed subjects; however, success is diminished in those switching while still viremic.[28] This is particularly the case in patients who are treated with the combination of tenofovir, a cytosine analogue, and a highly potent third drug such as the InSTIs bictegravir and dolutegravir or a boosted protease inhibitor (PI).[29,30]

A reduced response to tenofovir 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.[31-33]

8. The presence of M184V appears to delay or prevent emergence of TAMs.[34] This effect may be overcome by an accumulation of TAMs.

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.[35] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine, because it has been archived in the latent reservoir.[36]

10. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[37] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[38]

11. There is no evidence for the utility of efavirenz, nevirapine, or rilpivirine in patients with NNRTI-resistant virus.[39]

12. Doravirine is active in vitro against variants containing the common NNRTI mutations K103N, E138K, Y181C, and G190A.[40,41] Doravirine selects for mutations at positions 106, 108, 227, and 234, with more than 1 mutation usually required for substantial levels of resistance.[42] Mutations V106A, Y188L, and M230L are associated with a 10- or greater-fold reduced susceptibility to doravirine. V106A, Y188L, H227C, and Y318F have also been

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selected in vivo (eg, DRIVE-FORWARD and DRIVE-AHEAD studies).[43-46] The A98G mutation was also selected in vivo and site-directed mutants conferred a 5.8-fold reduction in susceptibility to doravirine.[46] In 1 clinical isolate, G190E was associated with about 20-fold reduced susceptibility to doravirine.[41] Furthermore, the double and triple mutants V106A and F227L; V106A and L234I; V106A and F227L and L234I; and V106A and G190A and F227L, are all associated with substantial resistance to doravirine.[40,42,47]

13. Resistance to etravirine has been extensively studied only in the context of coadministration with ritonavir-boosted darunavir. Mutations associated with virologic outcome were assessed and their relative weights (or magnitudes of impact) assigned. Phenotypic cutoff values were calculated, and assessments of genotype-phenotype correlations from a large clinical database have determined the relative importance of the various mutations. These 2 approaches are in agreement for many, but not all, mutations and weights.[48,49] 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.[50,51] The presence of K103N alone does not affect etravirine response.[51] Accumulation of several mutations results in greater reductions in susceptibility and virologic response than do single mutations.[52-54]

14. Sixteen mutations have been associated with decreased rilpivirine susceptibility (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, and M230I/L).[55-57] The K101P and Y181I/V mutations reduce rilpivirine susceptibility approximately 50 fold and 15 fold, respectively, but do not commonly emerge during treatment failure with rilpivirine.[58-60] Mutations at position 138 (most notably E138A) may occur as natural polymorphisms, especially in non-B subtype virus.[61] The K101E, E138K, and Y181C mutations, each of which reduces rilpivirine susceptibility 2.5 fold to 3 fold, occur commonly in individuals in whom rilpivirine is failing. E138K and, to a lesser extent, K101E, usually occurs 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.[60,62-64] 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.[57,65]

15. The emergence of resistance with lenacapavir was characterized with in vitro selection, which identified several variants in the capsid (CA) portion of Gag (L56I, M66I, Q67H, K70N, N74D/S, and T107N), with 20-fold to 1000-fold reduced susceptibility in vitro with Q67H plus N74S, Q67H plus T107N, L56I (204), Q67H plus M66I, Q67H plus N74D, M66I (>2700), and reduced replication capacity for most mutant viruses.[66-68]

None of these mutations was found to be polymorphic, suggesting that there is no need for resistance testing before treatment with lenacapavir.[69] In a phase Ib study, analyses after monotherapy revealed the emergence of mutation Q67H at the lowest lenacapavir doses.[67,70] In highly treatment-experienced patients with lenacapavir failure, M66I was observed alone or in combination with other mutations. In all cases, the failures were initially associated with the selection of M66I.[30]

In highly treatment-experienced individals experiencing treatment failure in the CAPELLA study, the M66I mutation was most frequently observed.[70] In treatment-naive individuals in the CALIBRATE trial, mutations Q67H (7-fold change) and K70R were selected.[71]

16. Often, several mutations are necessary to substantially impact virologic response to a ritonavir-boosted PI.[72]

17. Mutations in Gag cleavage sites may confer or contribute to resistance to PIs and may even emerge before mutations in protease.[73] PI resistance-associated mutations are not found in a large proportion of virus samples from patients with confirmed virologic failure on a boosted PI-containing regimen; this is attributable to poor adherence.

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

19. 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.[74]

20. 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 mutations indicated on the **Figure Bar**. A negative impact of the protease mutations I47V, I54M, T74P, and I84V and a positive impact of the protease mutation V82A on virologic response to ritonavir-boosted darunavir was assessed.[75] 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,

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L76V, I84V, or L89V was associated with a decreased virologic response to ritonavir-boosted darunavir.[76]

21. 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 I47A/V with V32I is associated with high-level resistance.[74,77-82] I50V is only occasionally selected in vivo but has a clear impact on susceptibility.[12,83-85] Subtype C patterns with M46L, I54V, L76V, and V82A are frequently observed in patients receiving ritonavir-boosted lopinavir.

22. The mutations depicted on the **Figure Bar** cannot be considered comprehensive because this drug is not available anymore and as such limited relevant research has been reported in recent years to update the resistance and cross-resistance patterns for this drug. The bar and notes are retained for historical reference.

23. In some nonsubtype-B HIV-1, D30N is selected less frequently than are other PI-resistance associated mutations.[86]

24. Fostemsavir is an attachment inhibitor that binds to gp120.[87] Fostemsavir-associated resistance does not cause cross-resistance to other entry or attachment inhibitors such as ibalizumab and maraviroc. It shows high variation of in vitro susceptibility, but susceptibility is not dependent on tropism or on subtype, with the exception of CRF01_AE, which shows intrinsic resistance. In areas where CRF01_AE is prevalent, subtyping is recommended. Insufficient correlation between baseline resistance and treatment success has been established.

25. Loss of N-linked glycosylation sites in the V5 loop reduces the activity of ibaluzimab by preventing HIV-1 gp120 conformational changes and gp41 rearrangements required for the virus to enter target cells. There are no consensus mutations identified correlating with loss of efficacy.[88-91]

26. The activity of CC chemokine receptor 5 (CCR5) antagonists is limited to patients with viruses 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.[92] 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;[93] the clinical significance of such mutations is not yet known.

27. 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.[94-96]

28. With their low genetic barrier to resistance and the high level of cross-resistance, the InSTIs elvitegravir and raltegravir are no longer recommended in an initial regimen for most people with HIV.[97] A second-generation InSTI (dolutegravir, bictegravir, and cabotegravir) is recommended for most treatment situations.

29. In vitro susceptibility data indicate relatively small quantitative reductions in most cases for dolutegravir and bictegravir for single mutations in integrase.[98-100] The resistance profiles of dolutegravir and bictegravir are largely superimposable. Minor differences may derive from minor molecular variations of each drug, but the mutations depicted in the **Figure Bar** reflect results acquired from clinical studies. Dolutegravir mutations are most often observed in individuals with therapy failure after first-generation InSTI regimens or during dolutegravir monotherapy trials.[101-103] In contrast, bictegravir is only registered as a fixed-dose formulation with tenofovir alafenamide and emtricitabine for individuals with no known InSTI resistance.[104] Failure of bictegravir with the emergence of resistance is rarely observed.[102] Treatment of individuals with dolutegravir is less effective in individuals who harbor Q148K with 2 or more additional mutations in integrase, even with double dolutegravir doses combined with an optimized background regimen.[105] In vitro data suggest that these double mutants also compromise the efficacy of bictegravir in one study but not another.[99,100] Clinical outcomes data are limited because bictegravir is not approved for individuals with integrase resistance.

30. Cabotegravir is a long-acting InSTI.[106-110] In clinical trials and cohorts of individuals receiving HIV treatment or preexposure prophylaxis, several resistance mutations were observed in integrase associated with in vitro cabotegravir resistance.[111-114] A multivariate analysis showed that the presence of at least 2 factors among archived rilpivirine resistance-associated mutations at baseline, HIV-1 subtype A6, or body mass index of at least 30 kg/m^2, was associated with an increased risk of confirmed virologic failure.[115] The A6/A1 subtype frequently harbors the L74I polymorphism. A recent study showed that L74I conferred greater replication capacity to recombinant viruses

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expressing HIV-1 A6 integrase when present together with InSTI resistance mutations at positions 118, 140, 148, and 263. This finding may partially explain the association of this subtype with virologic failure of long-acting cabotegravir/rilpivirine.[116]

Although knowledge from clinical studies thus far is limited, in vitro studies indicate that multiple integrase substitutions including compensatory mutations enhance resistance to cabotegravir.[117]

31. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.[101,117] 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[118] and reduced virologic suppression in patients.[119-122] S147G is frequently observed with dolutegravir failure, mostly associated with other integrase resistance mutations, such as T97A, N155H, E138K, L74I/M, and Q148R.[123-125] On its own, S147G has no substantial impact on susceptibility to dolutegravir.[126]

32. The following 6 elvitegravir codon mutations have been observed in InSTI treatment-naive and treatment-experienced individuals in whom therapy is failing: T66I/A/K, E92Q, F121Y, S147G, Q148H/K/R, and N155H.[127-132] All these mutations have a profound effect on susceptibility in vitro, whereas T97A, which may occur as a polymorphism,[133] results in only a 2-fold change in elvitegravir susceptibility, and may require additional mutations for resistance.[131,132] R263K is less frequently observed and reduced elvitegravir susceptibility about 4.5 fold.[126] The sequential use of elvitegravir and ralte gravir (in either order) is not recommended because of cross-resistance between these drugs.[131]

33. 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.[134] Y143R/H/C mutation is uncommon.[134-138] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (<5-fold) cross-resistance to raltegravir.[139-141] N155H mutants tend to predominate early in the course of raltegravir failure, but are gradually replaced with continuing raltegravir treatment by viruses with higher resistance, often bearing mutations G140S plus Q148H/R/K.

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