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Special Contribution

2022 Update of the Drug Resistance Mutations in HIV-1

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*The 2022 edition of the IAS–USA drug resistance mutations list updates the **Figure** last published in September 2019. The mutations listed are those that have been identified by specific criteria for evidence and drugs described. The **Figure** is designed to assist practitioners to identify key mutations associated with resistance to antiretroviral drugs, and therefore, in making clinical decisions regarding antiretroviral therapy.*

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

The 2022 edition of the International Antiviral Society–USA (IAS–USA) drug resistance mutations list updates the **Figure** last published in September 2019.[1] In this update:

- Cabotegravir, fostemsavir, and ibalizumab have now been approved by regulatory agencies in many countries are all now included. The capsid inhibitor lenacapavir (GS 6207) has been added to the **Figure**.[2]
- A new section on specific drugs and details has been added to this update for information on recently approved drugs, that may not been added to the **Figure**.
- Several changes were made to drugs already on the **Figure**. Several changes were made to the **Figure Bars** of the integrase strand transfer inhibitors (InSTIs) cabotegravir and dolutegravir, the protease inhibitors atazanavir and lopinavir, and the nonnucleoside analogue reverse transcriptase (NNRTI) inhibitor doravirine.
- The user notes for tenofovir have been modified as recent clinical data suggest that the K65R plus M184V mutational profile is of less clinical relevance if tenofovir with either lamivudine or emtricitabine is prescribed in combination with a boosted protease inhibitor or one of the second generation InSTIs bictegravir or dolutegravir.
- For antiretroviral drugs that are no longer recommended, 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 significance.

Specific Drugs and Details

Cabotegravir (formerly GSK-1265744) was approved by the US Food and Drug Administration (FDA) in December 2021 in combination with rilpivirine for the treatment of HIV-1 infection in adults who are virologically suppressed on a stable antiretroviral regimen with no history of treatment

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failure and with no known or suspected resistance to either cabotegravir or rilpivirine. Cabotegravir is available for the treatment of HIV-1 infection as oral formulation or as an extended-release injectable suspension copackaged with rilpivirine.[3,4] Cabotegravir suspension was also approved as a long-acting injectable for the use of preexposure prophylaxis (PrEP).[5]

Fostemsavir (formerly GSK-3684934) was approved by the FDA in February 2020 as a first-in-class oral attachment inhibitor binding to gp120.[6] It is licensed for the treatment of HIV-1 infection in combination with other antiretroviral drugs in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection in whom their current regimen has failed due to resistance, intolerance, or safety considerations.[2,7] Fostemsavir 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.[8,9] In areas where CRF01_AE is prevalent, subtyping is recommended. No correlation between baseline resistance and treatment success has yet been established. For this reason, resistance testing for gp120 is not currently recommended. Fostemsavir-associated resistance does not cause cross-resistance to other entry or attachment inhibitors such as ibalizumab and maraviroc.[10]

Ibalizumab, a humanized monoclonal antibody and noncompetitive CD4 post-attachment inhibitor, is approved for treatment in patients with multiclass drug-resistant virus.[11] Since the mechanism of action of ibalizumab requires a previous attachment of HIV-gp120 to the CD4 receptor, ibalizumab does not interfere with the functional capacity of CD4 receptors unbound to HIV-1. Loss of N-linked glycosylation sites in the V5 loop reduce the activity of this compound by preventing HIV-1 gp120 conformational changes and gp41 rearrangements required for the virus to enter target cells.[12-14] There are no mutations depicted on the **Figure Bars** for fostemsavir, ibalizumab, or maraviroc. As such, genotypic testing to predict resistance to these drugs is not recommended in clinical practice. In rare occasions phenotypic testing may be performed, if 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 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 FDA and are generally recommended, as well as any drugs available in development with expectation of approval in the next few years 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 definitive.

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

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Table 1. 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	Tryosine	Y

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. The delineation between major and minor is often not clear-cut.

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 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 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 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 on the Figure can be used to identify transmitted drug resistance.[15]

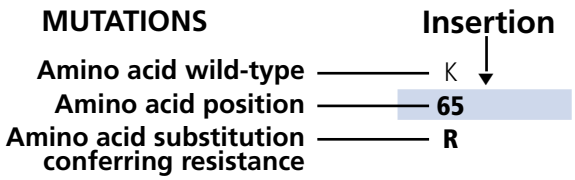

Figure 1. Display of the Figure Bar: Amino acid position, wild type, mutation conferring resistance, and indication of insertion mutation.

Clinical Context

The **Figure** is designed for practitioners to use in identifying key mutations associated with antiretroviral drug resistance and in selecting therapeutic regimens. 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; 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 of the regimen that conferred the selection pressure. 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, NNRTIs, 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 the consequence of drugs not reaching optimal levels in specific anatomic compartments.

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For more in-depth reading and an extensive reference list, see the 2018 IAS–USA panel recommendations for resistance testing[16] and 2020 IAS–USA panel recommendations for antiretroviral therapy.[17] Updates to the **Figure** 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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Top Antivir Med. 2022;30(4):559-574.

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 Resistance	**41**	**62**	**69**	**70**	**210**	**215**	**219**
	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 Resistance	**62**	**75**	**77**	**116**	**151**
	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	K	L	T	K
Multi-nRTI Resistance	**41**	**70**	**210**	**215**	**219**
	L	**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/ 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	Y
Doravirine[12]	**106**	**188**	190	225	**227**	**230**	234	**318**
	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
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				

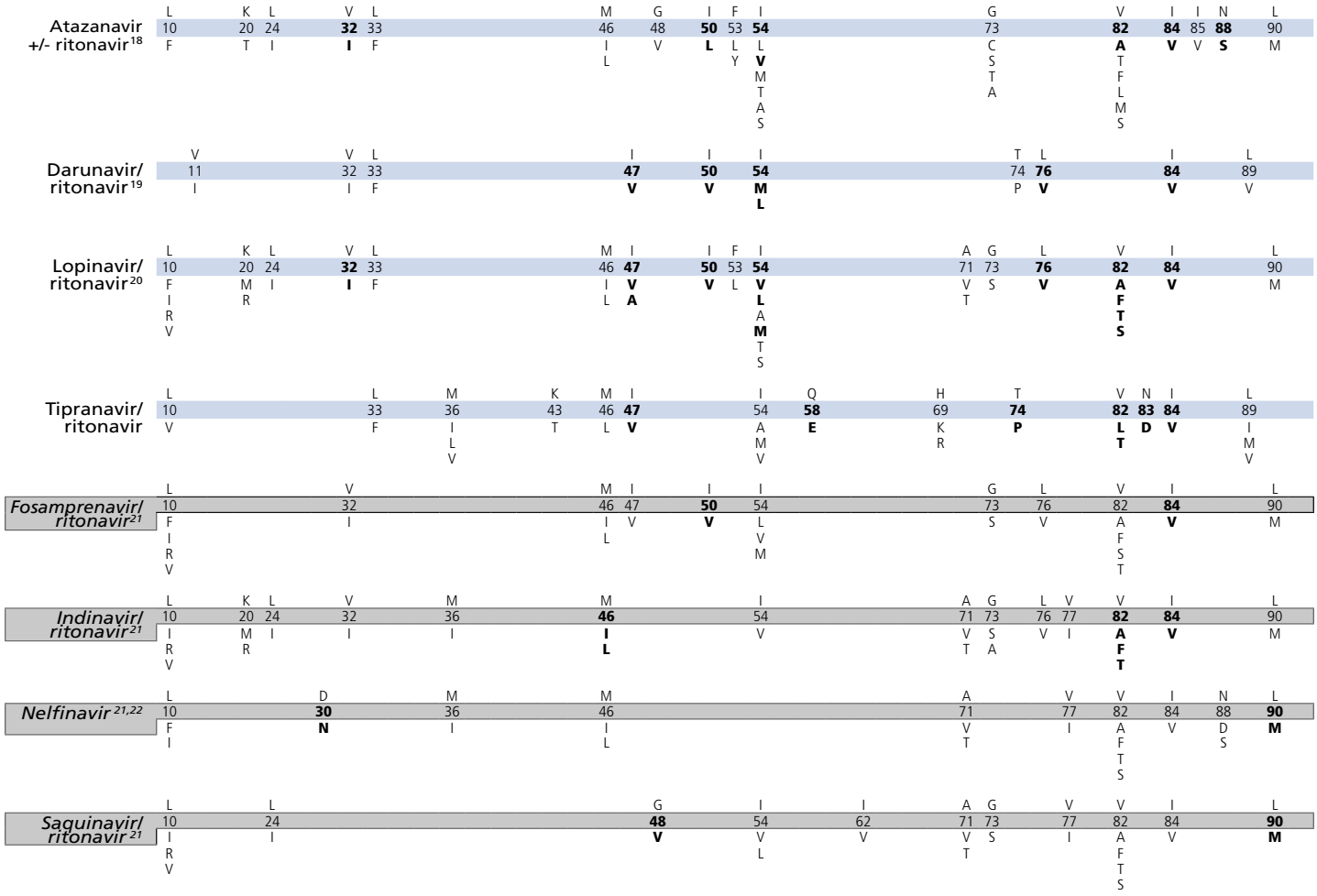
	L	K	K	V	V	Y	Y	G	M
Nevirapine	**100**	**101**	**103**	**106**	**108**	**181**	**188**	**190**	**230**
	I	**P**	**N**	**A**	**I**	**C**	**C**	**A**	**L**
			S	**M**		**I**	**L**		
							H		

	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						

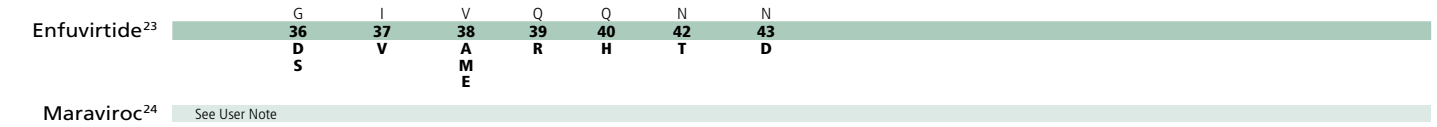
MUTATIONS IN THE CAPSID GENE ASSOCIATED WITH RESISTANCE TO CAPSID INHIBITORS

	L	M	Q	K	N	A	T
Lenacapavir[31]	56	**66**	**67**	70	74	105	107
	I	**I**	**H**	N	D	T	N
				S	S		
				R			

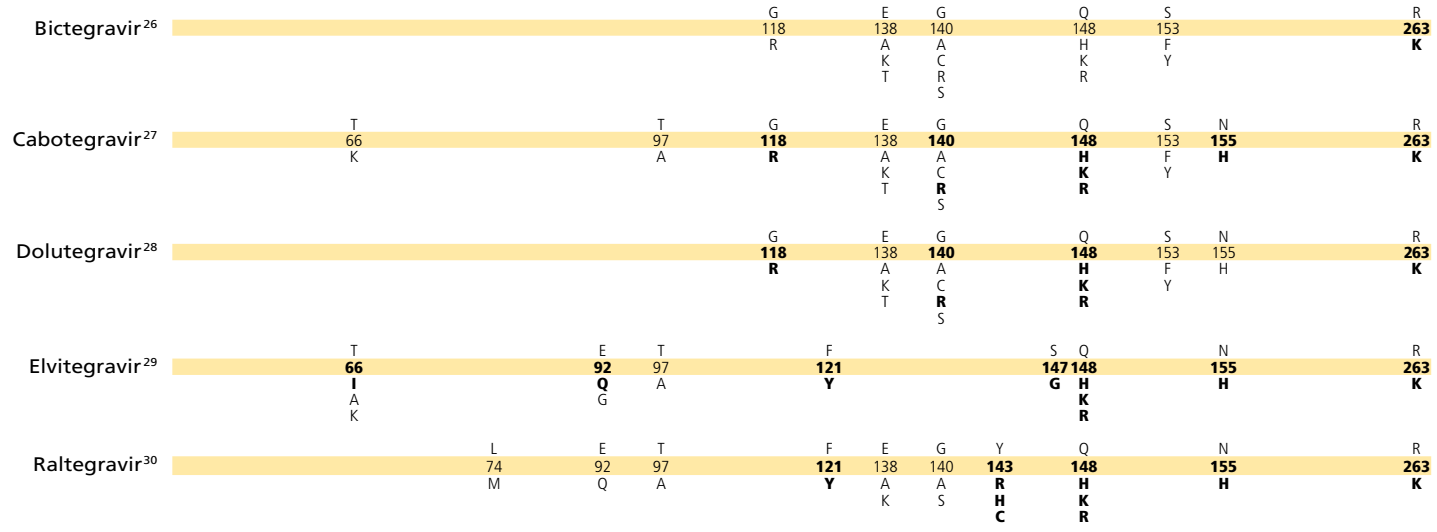
MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS (PIs)[15,16,17]



MUTATIONS IN THE ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



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



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 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 nRTI mutations, like T215Y and H208Y,[12] may lead to viral hypersusceptibility to NNRTIs, including etravirine.[13] The presence of these mutations may improve subsequent virologic response to NNRTI-containing regimens (nevirapine or efavirenz) in NNRTI-naive individuals;[14-18] 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. 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] 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 multi-nucleoside 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[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. K65R is the most common drug resistance mutation to emerge in patients with virologic failure on a tenofovir-containing regimen. 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. 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 integrase strand transfer inhibitors (InSTIs) bictegravir and dolutegravir or a boosted protease inhibitor (PI).[29,30]

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.[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.[35,36] The T215Y mutant may emerge quickly from one of these mutations in the presence of zidovudine or stavudine.[37]

10. The presence of 3 of the following mutations—M41L, D67N, L210W, T215Y/F, K219Q/E—is associated with resistance to didanosine.[38] The presence of K70R or M184V alone does not decrease virologic response to didanosine.[39] 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 resistant virus.[40]

12. Doravirine is active in vitro against variants containing the common NNRTI mutations K103N, E138K, Y181C, and G190A.[41,42] Doravirine selects for mutations at positions 106, 108, 227, and 234, with more than 1 mutation usually required for substantial levels of resistance.[43] 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.[44,45] In 1 clinical isolate, G190E was associated with about 20-fold reduced susceptibility to

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doravirine.[42] 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.[41,43,46]

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.[47-49] 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 are not commonly observed in patients receiving 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 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.[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. Often, several mutations are necessary to substantially impact virologic response to a ritonavir-boosted PI.[66]

16. Mutations in Gag cleavage sites may confer or contribute to resistance to PIs and may even emerge before mutations in protease.[67] 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, attributable to poor adherence.

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.[68]

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.[69,70] 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.[71]

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.[68,72-78] I50V is only occasionally selected in vivo but has a clear impact on susceptibility.[12,79-81] 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.[82]

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.[83-85]

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

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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.[86] 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;[87] the clinical significance of such mutations is not yet known.

25. With their low genetic barrier to resistance and the high level of cross-resistance, the InSTIs elvitegravir and raltegravir are no longer generally recommended in an initial therapy for most people with HIV.[88] A second-generation InSTIs (dolutegravir, bictegravir, and cabotegravir) is recommended for most treatment situations.

26. In vitro susceptibility data indicate relatively small quantitative reductions in most cases for dolutegravir and bictegravir for single mutations in integrase.[89-91] Consequently, the **Figure Bar** listing the mutations or indicating them as bold is somewhat arbitrary in the absence of clinical data. The listing of mutations is based in most cases on in vitro selection data and testing single mutations seen mostly with first-generation InSTI failure in vitro. Several mutations were selected by dolutegravir, primarily during monotherapy trials or as add-on therapy to failing regimens.[92] Failure with the emergence of resistance to bictegravir, which is only available as a fixed-dose formulation with TAF and emtricitabine for individuals with no known InSTI resistance, has not been well documented. The only clinical data for treatment of individuals with InSTI resistance comes from the VIKING Study, in which even double doses of dolutegravir combined with the best available background regimen had higher failure rates against Q148K with 2 or more additional mutations in integrase.[93] Failure with emergence of resistance to bictegravir in a first-line regimen has been very rarely observed.[94] In vitro data suggest that these double mutants might have compromised the efficacy of bictegravir in one study but not another.[90,91] Multiple mutations are not displayed in the **Figure Bar**.

27. Cabotegravir is a long-acting InSTI. In clinical trials in individuals receiving HIV treatement or PrEP, several resistance mutations were observed in integrase associated with in vitro cabotegravir resistance.[95-97] A multivariate analysis showed that the presence of at least 2 factors among archived rilpivirine resistance-associated mutations at baseline, HIV-1 subtype A6/A1, or body mass index of at least 30 kg/m^2, was associated with increased risk of confirmed virologic failure.[98] The A6/A1 subtype frequently harbors the L74I polymorphism. A recent study showed that L74I conferred greater replication capacity to recombinant viruses expressing HIV-1 A6 integrase when present together with InSTI resistance mutations at positions 118, 140, 148, and 263. This finding may explain in part the association of this subtype to virologic failures of long-acting cabotegravir/rilpivirine.[99]

Although knowledge from clinical studies thus far is limited, in vitro studies indicate that multiple integrase substitutions including compensatory mutations enhance resistance to cabotegravir.[100]

28. Several mutations are required in HIV integrase to confer high-level resistance to dolutegravir.[100,101] 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[102] and reduced virologic suppression in patients.[103-106]

29. Seven elvitegravir codon mutations have been observed in InSTI treatment–naive and –experienced patients in whom therapy is failing.[107-113] T97A, which may occur as a polymorphism,[114] results in only a 2-fold change in elvitegravir susceptibility and may require additional mutations for resistance.[112,113] The sequential use of elvitegravir and raltegravir (in either order) is not recommended because of cross-resistance between these drugs.[112]

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.[115] The Y143R/H/C mutation is uncommon.[116-120] E92Q alone reduces susceptibility to elvitegravir more than 20 fold and causes limited (<5 fold) cross-resistance to raltegravir.[121-123] 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.

31. 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+N74S, Q67H+T107N, L56I (204), Q67H+M66I, Q67H+N74D, M66I (>2,700), and reduced replication capacity for most mutant viruses.[124-126]

None of these mutations were found to be polymorphic suggesting there is no need for resistance testing before treatment with lenacapavir.[127] In a phase Ib study, post-monotherapy analyses revealed the emergence of mutation Q67H at the lowest lenacapavir doses.[125,126] 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.[30,128]

In highly treatment-experienced patients experiencing treatment failure in the CAPELLA study, the M66I mutation was most frequently observed.[129] In treatment-naive individuals in the CALIBRATE trial mutations 67H (fold change 7) and 70R were selected.[130,131]

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