

Major HIV Drug Resistance Mutations

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Major NRTI-Resistance Mutations

Cons	Discriminatory Mutations				Thymidine Analog Mutations (TAMs)						MDR Mutations	
	184	65	74	115	41	67	70	210	215	219	69	151
	M	K	L	Y	M	D	K	L	T	K	T	Q
3TC	<u>VI</u>	R									Ins	M
FTC	<u>VI</u>	R									Ins	M
ABC	<u>VI</u>	<u>R</u>	<u>V</u>	<u>F</u>	L			W	YF		<u>Ins</u>	<u>M</u>
ddl	<u>VI</u>	<u>R</u>	<u>V</u>		L			W	YF		<u>Ins</u>	<u>M</u>
TDF	***	<u>R</u>	*	F	L		R	W	YF		<u>Ins</u>	M
d4T	***	R			L	N	R	W	<u>YF</u>	QE	<u>Ins</u>	<u>M</u>
ZDV	***	***	*		L	N	R	W	<u>YF</u>	QE	<u>Ins</u>	<u>M</u>

Classification: Bold underline: High level phenotypic and/or clinical resistance. Bold: Moderate phenotypic and/or clinical resistance. Plain: Low-level cross-resistance.

Mechanisms: Discriminatory mutations inhibit NRTI incorporation. TAMs promote excision of chain-terminating NRTIs. T69ins is a 2-amino acid insertion which nearly always occurs with multiple TAMs; Q151M usually occurs with V75I, F77L, and F116Y.

M184VI: Although they cause high-level phenotypic resistance to 3TC and FTC, M184VI are not contraindications to 3TC and FTC because M184VI increase TDF, AZT, and d4T susceptibility (***) and decrease viral replication fitness.

Additional NRTI-selected mutations: K65N and K70E/G (similar but weaker effects than K65R), L74I (ddl/ABC without increased AZT/TDF susceptibility), V75TMAS (ddl, d4T), T69D (ddl), E40F, E44DA, D67GE, T69SAING, K70NQT, V118I, H208Y, D218E, L228HR, N348I. Deletions between codons 67 to 70 similar but weaker effects than T69ins (occurs with TAMs or Q151M). T215SCDEIV evolve from T215YF in the absence of NRTIs.

Major NNRTI-Resistance Mutations

	100	101	103	106	138	181	188	190	230
Cons	L	K	K	V	E	Y	Y	G	M
NVP	I	<u>EP</u>	<u>NS</u>	<u>AM</u>		<u>CIV</u>	<u>LHC</u>	<u>ASE</u>	<u>L</u>
EFV	I	<u>EP</u>	<u>NS</u>	<u>AM</u>		C	<u>LHC</u>	<u>ASE</u>	<u>L</u>
ETR	I	<u>EP</u>			K	<u>CIV</u>	L	ASE	<u>L</u>
RPV	I	<u>EP</u>			<u>K</u>	<u>CIV</u>	<u>L</u>	ASE	<u>L</u>

Classification: Bold underline: High-level phenotypic and clinical resistance. Probable contraindication. Bold: Moderate phenotypic or clinical resistance. Plain: Contributes to resistance.

Additional mutations: Nonpolymorphic, usually accessory: V179F (NVP, ETR), P225H (EFV), F227L (NVP), E138QG (ETR, RPV), K238TN (EFV, NVP), Y318F (NVP), N348I (NVP); Nonpolymorphic, rare: K101HN, K103HT, G190QTCV, F227C; Polymorphic accessory: V90I, A98G, V108I, E138A, V179DE, H221Y. **Genotypic susceptibility scores:** ETR (Tibotec):181IV (3.0); 100I, 101P, 181C, 230L (2.5); 90I, 138A, 179F, 190S (1.5); 98G, 101EH, 179DT, 190A (1.0); <2.5 susceptible; 2.5 to 3.0 intermediate; >3.0 high-level

Major PI-Resistance Mutations

Cons	30	32	46	47	48	50	54	76	82	84	88	90
	D	V	M	I	G	I	I	L	V	I	N	L
ATVr		I	IL	V	<u>VM</u>	<u>L</u>	<u>VTAM</u>		ATFS	<u>V</u>	<u>S</u>	M
DRVr		I		<u>VA</u>		<u>V</u>	LM	V	F	V		
FPVr		I	IL	<u>VA</u>		<u>V</u>	<u>VTALM</u>	<u>V</u>	ATFS	<u>V</u>		M
IDVr		I	IL	<u>VA</u>			VTA	V	<u>ATFS</u>	<u>V</u>	S	M
LPVr		I	IL	<u>VA</u>	<u>VM</u>	V	<u>VTALM</u>	V	ATFS	V		M
NFV	<u>N</u>		<u>IL</u>	<u>VA</u>	<u>VM</u>		<u>VTALM</u>		ATFS	<u>V</u>	<u>DS</u>	<u>M</u>
SQVr					<u>VM</u>		<u>VTAM</u>		AT	<u>V</u>	S	<u>M</u>
TPVr		I	IL	<u>VA</u>			<u>VTAM</u>		<u>LT</u>	V		

Classification: Bold underline: Significant phenotypic or clinical resistance. Probable contraindication. Bold: Significant contribution to resistance. Plain: Primarily accessory. **Common accessory mutations:** L101VF, V11I, K20TVI, L23I, L24IF, L33F, K43T, F53L, Q58E, A71VTIL, G73STCA, T74PS, N83D, L89V. **Additional nonpolymorphic PI-selected mutations:** Established PI-resistance positions: L10RY, V11L, M46V, G48ASTLQ, F53Y, I54S, V82MC, I84AC, N88TG, V89T. Other positions: A22V, E34Q, E35G, K55RN, I66FVL, C67FL, V75I, P79ASD, I85V, T91S, Q92K, C95F. **Common highly polymorphic compensatory mutations:** K20R, M36I, L63P, V77I, I93L. **Hypersusceptibility mutations:** I50L increases susceptibility to all PIs except ATV. I50V and I54L to TPV. L76V to ATV, SQV, and TPV. N88S to FPV. **Genotypic susceptibility scores:** DRV (Tibotec):11I, 32I, 33F, 47V, 50V, 54LM, 74P, 76V, 84V, 89V; <3 susceptible; 3 to 4 low/intermediate; >4 high/level. TPV (Boehringer): 47V (+4), 74P (+4), 82LT(+4), 83D (4) 58E (3), 84V (3), 36I (2), 43T (2), 54AMV (2), 10V (1), 33F (1), 46L (1), 24I (-2), 76V (-2), 50L/V (-4), 54L (-6); <4 susceptible; 5-10 intermediate; >10 high-level.

Major INI-Resistance Mutations

	66	92	143	147	148	155	Classification: <u>Bold underline</u> : >10-20 fold decreased susceptibility. Probable contraindication. <u>Bold</u> : Significant contribution to phenotypic and/or clinical resistance. <u>Plain text</u> : <5-10 fold decreased susceptibility.
Cons	T	E	Y	S	Q	N	
RAL	A	Q	<u>RCH</u>	G	<u>HRK</u>	<u>H</u>	
EVG	<u>I</u> AK	Q		<u>G</u>	<u>HRK</u>	<u>H</u>	
DTG		Q			HRK		

Phenotypic effects of the most common single and double mutants: Q148RK, N155H, and Y143R decrease RAL susceptibility >10-20-fold. Q148HR+G140SA, N155H+E92Q, and Y143RC+T97A decrease RAL susceptibility >100-fold.

Rare INI-selected resistance mutations: E92V, F121Y, and V151AL decreases RAL and EVG susceptibility. P145S and Q146P decrease EVG susceptibility.

Elvitegravir (EVG) and dolutegravir (DTG) are investigational with probable approval in 2012 and 2013, respectively.

Major Enfuvirtide (ENF)-Resistance Mutations

	36	37	38	40	42	43	Classification: <u>Bold underline</u> >10-fold decrease susceptibility. <u>Bold</u> : 5-10 fold decrease susceptibility. Mutation pairs or single mutations
Cons	G	I	V	Q	N	N	
ENF	<u>DEVS</u>	T	<u>EAMG</u>	<u>H</u>	<u>I</u>	<u>DKS</u>	

with accessory mutations between 36-45 such as L44M and L45M often lead to >100-fold decreased susceptibility and loss of clinical response. Several accessory mutations in HR2 such as N126K, N137K, and S138A improve the fitness of viruses with the above HR1 mutations.

Tropism and Maraviroc (MVC) Resistance

At initial infection, >80% of patients have viruses that exclusively use the CCR5 coreceptor (R5 tropic). About 50% of patients eventually develop viruses that use CXCR4 (X4 tropic). The emergence of X4 tropism occurs in later disease stages and, in the absence of ARV therapy, is followed by accelerated CD4 cell decline. When X4-tropic viruses emerge, they usually co-circulate with R5 tropic viruses often as minor variants thus complicating their detection. The genetic determinants of tropism are mainly, but not exclusively, in the V3 loop of gp120. MVC allosterically inhibits gp120 binding to CCR5. HIV-1 may develop MVC resistance by binding to an MVC-bound receptor (which manifests phenotypically as a decrease in maximal inhibition in the drug dose - viral response curve) or, more commonly, by the outgrowth of previously unrecognized X4 variants. Therefore, testing for X4 variants is recommended before using MVC. Tropism can be detected phenotypically or genotypically. The Trofile test (Monogram) assesses the tropism of complete env genes amplified from patient samples using reporter cell lines expressing CCR5 or CXCR4. Given a sufficiently high plasma virus level, its sensitivity for X4 variants can be as low as 1%. Genotypic testing uses algorithms that predict tropism from the V3 loop sequence. These algorithms have a specificity of ~90% and sensitivity of ~75%. Standard sequencing is useful if X4 tropic variants are detected but its sensitivity is suboptimal for detecting minor X4 tropic variants. Deep sequencing approaches are nearly as sensitive as phenotypic testing but are performed primarily in research settings.

HIV-1 RT and Protease Mutations For Drug Resistance Surveillance

NRTI		NNRTI		PI	
Pos	Mut	Pos	Mut	Pos	Mut
M41	L	L100	I	L23	I
K65	R	K101	E, P	L24	I
D67	N, G, E	K103	N, S	D30	N
T69	D, Ins	V106	M, A	V32	I
K70	R, E	V179	F	M46	I, L
L74	V, I	Y181	C, I, V	I47	V, A
V75	M, T, A, S	Y188	L, H, C	G48	V, M
F77	L	G190	A, S, E	I50	V, L
Y115	F	P225	H	F53	L, Y
F116	Y	M230	L	I54	V, L, M, A, T, S
Q151	M			G73	S, T, C, A
M184	V, I			L76	V
L210	W			V82	A, T, F, S, C, M, L
T215	Y, F, I, S, C, D, V, E			N83	D
K219	Q, E, N, R			I84	V, A, C
				I85	V
				N88	D, S
				L90	M

New mutations from the 2007 list are in bold.

Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, Heneine W, Kantor R, Jordan MR, Schapiro JM, Vandamme A, Sandstrom P, Boucher CAB, van de Vijver D, Rhee S, Liu TF, Pillay D, Shafer RW. **Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update**, PLoS One 2009;4:e4724. The following considerations were used to develop this list of drug resistance mutations: (i) the mutations should cause or contribute to drug resistance, (ii) the mutations should not occur in untreated persons (i.e. they should be nonpolymorphic), (iii) the mutation list should be applicable to all group M subtypes, and (iv) the mutation list should be simple, unambiguous, and parsimonious. The prevalence of all protease and RT mutations according to subtype and treatment can be found at <http://hivdb.stanford.edu/cgi-bin/MutPrevBySubtypeRx.cgi>.

Abbreviations

Drug classes: NRTI (Nucleoside RT inhibitors), NNRTI (non-nucleoside RT inhibitors), PI (protease inhibitors), INI (Integrase inhibitors); **NRTIs:** 3TC (lamiduvine), ABC (abacavir), ddI (didanosine), d4T (stavudine), FTC (emtricitabine), TDF (tenofovir), ZDV (zidovudine); **NNRTIs:** DLV (delavirdine), EFV (efavirenz), ETR (etravirine), NVP (nevirapine); RPV (rilpivirine). **PIs:** ATV (atazanavir), DRV (darunavir), FPV (fosamprenavir), IDV (indinavir), LPV (lopinavir), NFV (nefinavir), SQV (saquinavir), TPV (tipranavir); "r" (ritonavir-boosted); **INIs:** RAL (raltegravir), EVG (elvitegravir), DTG (dolutegravir). **Amino acids:** A (alanine), C (cysteine), D (aspartate) E (glutamate), F (phenylalanine), G (glutamine), H (histidine), I (isoleucine), K (lysine), L (leucine), M (methionine), N (asparagine), P (proline), Q (glutamine), R (arginine), S (serine), T (threonine), V (valine), W (tryptophan), Y (tyrosine), Ins (insertion);