Major HIV-1 Drug Resistance Mutations

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Major Nucleoside RT Inhibitor (NRTI)-Resistance Mutations

	Non-TAMs					TAMs						MDR	
	184	65	70	74	115	41	67	70	210	215	219	69	151
Cons	**M**	**K**	**K**	**L**	**Y**	**M**	**D**	**K**	**L**	**T**	**K**	**T**	**Q**
3TC	**VI**	**R**	E									**Ins**	**M**
FTC	**VI**	**R**	E									**Ins**	**M**
ABC	**VI**	**R**	E	**VI**	**F**	L			W	YF		**Ins**	**M**
TDF	***	**R**	E		F	L			W	YF		**Ins**	**M**
ZDV	***	***	*	*		**L**	**N**	**R**	**W**	**YF**	QE	**Ins**	**M**

Bold/underline: High-level reduced susceptibility or virological response. Bold: reduced suceptibility or virological response. Plain text: reduced susceptibility in combination with other NRTI-resistance mutations. Asterisk: increased susceptibility. **Additional NRTIs:** Stavudine (d4T) and didanosine (ddI) are no longer recommended. **TAMs:** Thymidine analog mutations. Selected by AZT and d4T and facilitate primer unblocking. Non-TAMs prevent NRTI incorporation. **MDR:** Multidrug resistance mutations. T69 insertions occur with TAMs. Q151M occurs with non-TAMs and accessory mutations A62V, V75I, F77L, and F116Y. **M184VI:** Although they cause high-level *in vitro* resistance to 3TC/FTC, they are not contraindications to 3TC/FTC because they increase TDF and AZT susceptibility and decrease viral replication fitness. **Additional mutations:** K65N is similar but weaker than K65R. K70GQ is similar to K70E. T69D and V75MT reduce susceptibility to d4T and ddI. T215SCDEIV (T215 revertants) evolve from T215YF in the absence of NRTIs. E40F, E44DA, D67GE, V118I, and K219NR are accessory TAMs. T69 deletions occur in combination with K65R and/or Q151M. With K65R (but not Q151M) they increase AZT susceptibility. **References:** http://hivdb.stanford.edu/DR/NRTIResiNote.html.

Major Non-Nucleoside RT Inhibitor (NNRTI)-Resistance Mutations

	100	101	103	106	138	179	181	188	190	227	230
Cons	**L**	**K**	**K**	**V**	**E**	**V**	**Y**	**Y**	**G**	**F**	**M**
NVP	**I**	**PE**H	**NS**	**AM**		DEF	**CIV**	**LCH**	**ASEQ**	**LC**	**L**
EFV	**I**	**P**EH	**NS**	**AM**		DEF	C	**LCH**	**ASEQ**	L**C**	**L**
ETR	**I**	**P**EH					**CIV**		**EQ**	**C**	**L**
RPV	**I**	**PE**H			**K**AGQ	DEF	**CIV**	**L**	**EQ**	**C**	**L**

Bold/underline: High-level reduced susceptibility or virological response. Bold: reduced suceptibility or virological response. Plain text: reduced susceptibility in combination with other NNRTI-resistance mutations. Asterisk: increased susceptibility. **Abbreviations**: nevirapine (NVP), efavirenz (EFV), etravirine (ETR), rilpivirine (RPV). **Synergistic combinations:** V179D+K103R reduce NVP and EFV susceptibility >10-fold. Y181C+V179F cause high-level ETR and RPV resistance. **ETR genotypic susceptibility score (GSS):** Y181IV (3.0); L100I, K101P, Y181C, M230L (2.5); V90I, E138A, V179F, G190S (1.5); A98G, K101EH, V106I, V179DT, G190A (1.0); <2.5 susceptible; 2.5 to 3.0 intermediate; >3.0 high-level. V90I, A98G, V106I, E138A, V179DT, G190A/S have little effect on ETR susceptibility unless they occur with a bolded mutations. **Additional accessory mutations:** V90I (ETR), A98G (NVP, EFV, ETR, RPV), V108I, V179T (ETR), V179L (RPV), P225H (EFV), K238T (NVP, EFV), L318F (NVP). **References:** http://hivdb.stanford.edu/DR/NNRTIResiNote.html.

Major Protease Inhibitor (PI) Resistance Mutations

	24	32	46	47	48	50	54	76	82	84	88	90
Cons	L	V	M	I	G	I	I	L	V	I	N	L
ATV/r		**I**	IL	V	**VM**	**L**	**VTAM**		**ATSF**	**V**	**S**	M
DRV/r		**I**		**VA**		**V**	**LM**	**V**	**F**	V		
LPV/r	I	**I**	IL	**VA**	VM	**V**	**VTALM**	**V**	**ATSF**	**V**		M

Bold/underline: High-level reduced susceptibility or virological response. Bold: reduced suceptibility or virological response. Plain text: reduced susceptibility in combination with other PI-resistance mutations. **Abbreviations:** atazanavir (ATV), darunavir (DRV), lopinavir (LPV). Administered with ritonavir for pharmacokinetic boosting (/r). **Additional PIs:** Fosamprenavir (FPV), indinavir (IDV), saquinavir (SQV), and tipranavir (TPV) are rarely used. Nelfinavir (NFV) is no longer recommended. FPV/r and IDV/r are never more active than DRV/r and rarely if ever more active than LPV/r vs resistant viruses. TPV/r is occasionally useful for salvage therapy as it can be active vs LPV/r and DRV/r-resistant viruses with mutations that increase TPV susceptibility. Expert consultation +/- phenotypic testing should be obtained prior to using FPV, FPV/r, IDV/r, SQV/r, and TPV/r. **Additional mutations:** D30N and N88D are major NFV-resistance mutations. L10F, V11I, K20TV, L23I, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V are common nonpolymorphic accessory mutations. L10RY, V11L, L24F, M46V, G48ASTLQ, F53Y, I54S, V82CM, I84AC, N88TG are rare nonpolymorphic variants. **Hypersusceptibility:** I50L (each PI except ATV); L10F, L24I, I50V, I54L (TPV); L76V (ATV, SQV, TPV); I47A (SQV); N88S (FPV). **References:** http://hivdb.stanford.edu/DR/PIResiNote.html.

Major Integrase Inhibitor (INI)-Resistance Mutations

	66	92	138	140	143	147	148	155
Cons	T	E	E	G	Y	S	Q	N
RAL	A	**Q**	**KA**	**SAC**	**CRH**		**HRK**	**H**
EVG	**IAK**	**Q**	**KA**	**SAC**		**G**	**HRK**	**H**
DTG		Q	KA	SAC			**HRK**	

Bold/underline: High-level reduced susceptibility or virological response. Bold: reduced suceptibility or virological response. Plain text: reduced susceptibility in combination with other INI-resistance mutations. Asterisk: increased susceptibility. **Abbreviations**: raltegravir (RAL), elvitegravir (EVG), dolutegravir (DTG). **Additional mutations:** H51Y, L74M, T97A, S153YF, G163RK, S230R, and R263K are relatively nonpolymorphic INI-selected accessory resistance mutations. E92GV, E138T, Y143KSGA, Q148N, and N155ST are unusual variants at the positions listed above. P145S and Q146P are rare EVG-resistance mutations. G118R and F121Y are rare nonpolymorphic INI-resistance mutations. **References:** http://hivdb.stanford.edu/DR/INIResiNote.html.

HIV-1 RT and Protease Mutations for Drug-Resistance Surveillance*

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

*Bennett DE, Camacho RJ, Otelea D,et al. Drug Resistance Mutations for Surveillance of Transmitted HIV-1 Drug-Resistance: 2009 Update, PLoS One 2009;4:e4724.Criteria for mutations on this list: (i) Cause/contribute to resistance. (ii) Nonpolymorphic (≤ 0.5% in ARV-naive persons) in 8 most common group M subtypes. http://hivdb.stanford.edu/cgi-bin/MutPrevBySubtypeRx.cgi.