Major HIV-1 Drug Resistance Mutations

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Stanford HIVDB

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**										**Ins**	**M**
FTC	**VI**	**R**										**Ins**	**M**
ABC	VI	**R**	E	**VI**	**F**	L			W	FY		**Ins**	**M**
TFV	***	**R**	E		F	L		R	W	FY		**Ins**	**M**
ZDV	***	***	*	*		**L**	**N**	**R**	**W**	**FY**	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.

TAMs: Thymidine analog mutations. Selected by AZT and d4T; facilitate primer unblocking. Non-TAMs prevent NRTI incorporation.

MDR: Multidrug resistance mutations. T69 insertions occur with TAMs. Q151M occurs with non-TAMs and the 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 TFV and AZT susceptibility and decrease viral replication fitness.

TFV, TDF, & TAF: Tenofovir (TFV) disoproxil fumarate (TDF) and TFV alafenamide (TAF) are TFV triphosphate prodrugs. Although TDF and TAF have similar resistance profiles, TAF attains higher intracellular levels.

Additional mutations: K65N similar but weaker than K65R. K70GQNT similar to K70E. T69D and V75MT reduce susceptibility to d4T and ddI, which are not shown because they are no longer recommended for HIV treatment. T215SCDEIVALN (T215 revertants) emerge from T215YF in the absence of NRTIs. E40F, E44DA, D67GE, V118I, and K219NR are accessory TAMs. D67, T69, K70 deletions have not been well studied. They usually occur in combination with K65R and/or Q151M.

References: hivdb.stanford.edu/s/nrtinotes

Major Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations

	100	101	103	106	181	188	190	227	230
Cons	L	K	K	V	Y	Y	G	F	M
DOR	I	EP		**AM**	CIV	**L**	S**E**	**LC**	**L**
EFV	**I**	E**P**	**NS**	**AM**	CIV	**L**	**ASE**	L**C**	**L**
ETR	**I**	E**P**			**CIV**	L	AS**E**	**C**	**L**
RPV	**I**	**EP**			**CIV**	**L**	AS**E**	**C**	**L**
NVP	**I**	**EP**	**NS**	**AM**	**CIV**	**L**	**ASE**	**LC**	**L**

Bold underline: High-level reduced susceptibility or virological response. **Bold**: Reduced susceptibility or virological response. Plain text: Reduced susceptibility in combination with other NNRTI-resistance mutations.

Abbreviations: Doravirine (DOR), efavirenz (EFV), etravirine (ETR), rilpivirine (RPV), nevirapine (NVP).

Additional Mutations: A98G (DOR, EFV, ETR, NVP, RPV); E138GQKR are nonpolymorphic mutations associated with intermediate/high-level RPV resistance. E138A is a polymorphic mutation associated with low-level RPV resistance. Y188CH are associated with intermediate / high-level resistance to EFV and potential low-level DOR resistance; G190Q is a rare mutation which may have an effect similar to G190E; P225H (DOR, EFV); L234I (DOR), Y318F (DOR, NVP).

Synergistic combinations: V179D+K103R reduce NVP and EFV susceptibility >10-fold. Y181C+V179F cause high-level ETR and RPV resistance.

DOR and ETR often require multiple mutations: DOR - high level with Y188L, V106A, F227L/C, M230L or any combination of V106 and F227 mutations. ETR: L100I, K101P, Y181C/I/V, M230L. But multiple non-DOR mutations at common positions such as Y181 and G190 can reduce susceptibility.

References: hivdb.stanford.edu/s/nnrtinotes

Major Integrase Inhibitor (INSTI) Resistance Mutations

	66	92	118	138	140	143	147	148	155	263
Cons	**T**	**E**	**G**	**E**	**G**	**Y**	**S**	**Q**	**N**	**R**
BIC	K	Q	**R**	KAT	SAC			**HRK**	H	**K**
DTG	K	Q	**R**	KAT	SAC			**HRK**	H	**K**
EVG	**AIK**	**Q**	**R**	**KAT**	**SAC**		**G**	**HRK**	**H**	**K**
RAL	AI**K**	**Q**	**R**	**KAT**	**SAC**	**RC**		**HRK**	**H**	K

Bold underline: High-level reduced susceptibility or virological response. **Bold**: Low-level reduced susceptibility or reduced suceptibility or virological response. Plain text: Rreduced susceptibility in combination with other INSTI-resistance mutations.

Abbreviations: Bictegravir (BIC), dolutegravir (DTG), elvitegravir (EVG), raltegravir (RAL).

Additional mutations: L74MI, T97A, V151I, E157Q, G163KR are common polymorphic accessory DRMs. H51Y, F121Y, S153YF, S230R are additional nonpolymorphic mutations associated with reduced susceptibility to one or more INSTIs. E92GV, Y143HKSGA, P145S, Q146P, Q148N, V151AL, and N155ST are rare nonpolymorphic IN mutations that reduce RAL and/or EVG susceptibility. Mutations outside of IN in the polypurine tract have also rarely been reported to reduce INSTI susceptibility.

Cabotegravir (CAB): CAB has a resistance profile similar to DTG/BIC, however, mutations associated with these INSTIs cause greater reductions in CAB susceptibility. G140R is a novel mutation that emerges under CAB selection pressure and reduces CAB susceptibility.

References: hivdb.stanford.edu/s/instinotes

Major Protease Inhibitor (PI) Resistance Mutations

	32	46	47	48	50	54	76	82	84	88	90
Cons	**V**	**M**	**I**	**G**	**I**	**I**	**L**	**V**	**I**	**N**	**L**
ATV/r	I	IL	V	**VM**	**L**	VTALM		ATFS	**V**	**S**	**M**
DRV/r	**I**		VA		**V**	**LM**	**V**	F	**V**		
LPV/r	**I**	IL	V**A**	VM	**V**	**VTALM**	**V**	**AFTS**	**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), '/r' (ritonavir).

Additional mutations: L10F, V11I, K20TV, L23I, L33F, K43T, F53L, Q58E, A71IL, G73STCA, T74P, N83D, and L89V are common nonpolymorphic accessory resistance mutations. L10F, V11IL, L33F, T74P, and L89V are accessory resistance mutations associated with reduced DRV/r susceptibility. D30N and N88D are nonpolymorphic resistance mutations selected by NFV. L10RY, V11L, L24F, M46V, G48ASTLQ, F53Y, I54S, V82CM, I84AC, N88TG are rare nonpolymorphic variants.

Hypersusceptibility: I50L (each PI except ATV); L76V (ATV).

References: hivdb.stanford.edu/s/pinotes

Mutations for Drug Resistance Surveillance

NRTIs*†		NNRTIs*		PIs*		INSTI‡	
M41	L	**L100**	I	**L23**	I	**T66**	A,I,K
K65	R	**K101**	E,P	**L24**	I	**E92**	G,Q
D67	N,G,E	**K103**	N,S	**D30**	N	**G118**	R
T69	D,Ins	**V106**	M,A	**V32**	I	**F121**	Y
K70	R,E	**V179**	F	**M46**	I,L	**E138**	A,K,T
L74	V,I	**Y181**	C,I,V	**I47**	V,A	**G140**	A,C,S
V75	M,T,A,S	**Y188**	L,H,C	**G48**	V,M	**Y143**	C,H,R,S
F77	L	**G190**	A,S,E	**I50**	V,L	**S147**	G
Y115	F	**P225**	H	**F53**	L,Y	**Q148**	H,R,K
F116	Y	**M230**	L	**I54**	V,L,M,A,T,S	**N155**	H
Q151	M			**G73**	S,T,C,A	**S230**	R
M184	V,I			**L76**	V	**R263**	K
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		

*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.

†K65N, T69del, K70QNSTG, and K70del are nonpolymorphic DRMs that have been reportedly more commonly since TDF/XTC has become the standard NRTI backbone worldwide. These mutations should also be examined in studies of HIVDR surveillance. A62V would be included on this list except for the fact that it is common in subtype A6 sequences due to a founder effect. (Rhee SY, Varghese V, Holmes SP, et al. Mutational Correlates of Virological Failure in Individuals Receiving a WHO-Recommended Tenofovir-Containing First-Line Regimen: An International Collaboration. *EBioMedicine*. 2017 Apr;18:225-235.)

‡Tzou PL, Rhee SY, Descamps D, et al. (in press) Integrase Strand Transfer Inhibitor Resistance Mutations for Surveillance of Transmitted HIV-1 Drug Resistance. *J Antimicrob Chemother*. doi:10.1093/jac/dkz417.

References: hivdb.stanford.edu/s/who