HIV Drug Resistance Mutations by Drug Class (November 6, 2009)

A regularly updated in-depth referenced summary of HIV drug resistance mutations extracted from the Stanford HIV Drug Resistance Databases. These tables are updated frequently and can be downloaded from http://hivdb.stanford.edu/pages/download/

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Protease Inhibitor (PI) Resistance Mutations

	23	24	30	32	33	46	47	48	50†	53	54	73	76†	82	84	88	90
Cons	L	L	D	V	L	M	I	G	I	F	I	G	L	V	I	N	L
ATV/r		I			F	IL	V	**VM**	**L**	**L**	VTALM	**ST**		ATFS	**VAC**	D**S**	**M**
DRV/r§				**I**	F		**VA**		**V**		**LM**	ST	**V**		VAC		M
FPV/r		I		**I**	F	**IL**	**VA**		**V**		VTA**LM**	ST	**V**	ATFS	**VAC**		**M**
IDV/r		**I**		I		**IL**	V			L	**VTA**LM	ST	V	**AFTS**	**VAC**	S	**M**
LPV/r		I		I	F	IL	V**A**	VM	**V**		**VTALM**		**V**	**AFTS**	**VAC**		M
NFV	**I**	**I**	**N**		F	**IL**	V	**VM**		**L**	**VTALM**	**ST**		**AFTS**	**VAC**	**DS**	**M**
SQV/r		I						**VM**		**L**	**VTA**LM	**ST**		AT	**VAC**	S	**M**
TPV/r¶				I	F	IL	**V**				VAM			AT**F**S**L**	**VAC**		M

LEGEND **Mutations in bold** have been shown to reduce in vitro susceptibility or in vivo virological response. **Mutations in bold underline** are relative contraindications to the use of specific PIs.

ADDITIONAL MUTATIONS Several additional uncommon mutations at the 17 positions in this table are also selected by PIs but have not been evaluated phenotypically including L24F, L33I, M46V, F53Y, I54S, G73CA, V82MC, and N88TG (S Rhee JID 2005). In contrast, V82I and L33V are polymorphisms that are not associated with PI therapy (http://hivdb.stanford.edu/cgi-bin/PRPosMutSummary.cgi).

ACCESSORY MUTATIONS Accessory protease mutations that are not in the table include the polymorphic mutations L10IV, I13V, K20RMI, M36I, D60E, I62V, L63P, A71VT, V77I, and I93L (F Mammano JV 1998, M Nijuis AIDS 1999, J Martinez-Picado JV 1999, N Hoffman Virology 2003) and the nonpolymorphic mutations L10FR, V11I, E34Q, E35G, K43T, K45I, K55R, Q58E, A71IL, T74PAS, V75I, N83D, P79AS, I85V, L89V, T91S, Q92K and C95F (T Wu JV 2003, N Parkin AIDS 2003, V Svicher AAC 2005).

†**HYPERSUSCEPTIBILITY** I50L increases susceptibility to all PIs except ATV/r (R Colonno JID 2004); I50V and I54L increase TPV/r susceptibility (R Elston HIVDRW 2006); N88S increases FPV/r susceptibility (R Ziermann 2006); L76V increases ATV, SQV, and TPV/r susceptibility (S Mueller HIVDRW 2004, H Vermeiren 2007).

§ A GSS for DRV/r derived from the POWER trials identified 11 mutations at 10 positions: V11I, V32I, L33F, I47V, I50V, I54LM, G73S, L76V, I84V, L89V (S De Meyer ARHR 2008). In a subsequent update the substitution of T74P for G73S led to an improved model (S De Meyer Eur HIVDRW 2008).

¶ A GSS for TPV/r derived from the RESIST trials identified 21 mutations at 16 positions: L10V, I13V, K20MRV, L33F, E35G, M36I, K43T, M46L, I47V, I54AMV, Q58E, H69K, T74P, V82LT, N83D, and I84V (J Baxter JV 2006). An updated TPV/r GSS excluded I13V, K20MRV, E35G, and H69K; reclassified I47V, I54AMV, Q58E, T74P, V82LT, and N83D as major mutations; reclassified L10V, M36I, K43T, M46L, and I84V as minor mutations; and included L24I, I50LV, I54L, and L76V as mutations likely to improve TPV/r susceptibility and virological response (J Scherer Eur HIV AIDS Conf 2007). A list of studies of genotypic PI response predictors can be found at http://hivdb.stanford.edu/pages/geno_clinical_review/PI.html.

Nucleoside RT Inhibitor (NRTI) Resistance Mutations

	184	Thymidine Analog Mutations (TAMs)						Non Thymidine Analog Regimen Mutations						Multi-NRTI Resistance Mutations				
		41	67	70†	210	215	219	65	70†	74	75†	115	69	151	62	75†	77	116
Cons	M	M	D	K	L	T	K	K	K	L	V	Y	T	Q	A	V	F	F
3TC	**VI**							RN	EG				Ins	M	V			
FTC	**VI**							RN	EG				Ins	M	V			
ABC	VI	L	N		W	FY		**RN**	EG	**VI**	TM	**F**	**Ins**	**M**	V	I	L	Y
DDI	VI	L	N		W	FY		**RN**	EG	**VI**	TM		**Ins**	**M**	V	I	L	Y
TDF		L	N		W	FY		**RN**	EG		M	F	**Ins**	M	V			
D4T		**L**	N	R	W	**FY**	QE	RN			**TM**		**Ins**	**M**	V	I	L	Y
ZDV		**L**	N	R	W	**FY**	QE						**Ins**	**M**	V	I	L	Y

LEGEND **Mutations in bold red** are associated with higher levels of phenotypic resistance or clinical evidence for reduced virological response.

ADDITIONAL MUTATIONS Additional treatment-selected mutations at these positions include D67GE, T69DSAING, K70N, V75AS, and K219NR.

ACCESSORY MUTATIONS Additional accessory mutations include: K43EQN, E44DA, V118I, H208Y, D218E, H221Y, L228HR, and N348I (K Hertogs AAC 2000, MJ Gonzales AIDS 2003, V Svicher JV 2006, SH Yap PLOS Med 2007). The accessory mutations occur with TAMs and are associated with subtle reductions is susceptibility to multiple NRTIs.

HYPERSUSCEPTIBILITY Several mutations are associated with increased susceptibility: M184VI increase susceptibility to ZDV, TDF, and d4T (J Whitcomb JID 2003, K Diallo AC 2003). L74V increases susceptibility to ZDV and TDF (MH St Clair Science 1991, ER Lanier HIV Med 2004, LR Miranada AAC 2005, SY Rhee PNAS 2006); K65R and K70E increase susceptibility to ZDV (C Delaugerre JCV 2005, UM Parikh JV 2006, KL White AVT 2006, RM Kagan AVR 2007, A Antinori AVT 2007).

† K70R occurs in viruses from persons receiving thymidine analogs; K70EG occur with non-thymidine analog containing regimens (C Delaugerre JCV 2005, N Sluis Cremer AAC 2006, D Bradshaw AAC 2007). V75I occurs in combination with Q151M; V75TM occur in a variety of different treatment and mutational contexts.

Non-Nucleoside RT Inhibitor (NNRTI) Resistance Mutations

	98	100	101	103	106	108	179	181	188	190	225	227	230	236	238
Cons	A	L	K	K	V	V	V	Y	Y	G	P	F	M	P	K
NVP	G	**I**	**EP**	**NS**	**AM**	I	DEF	**CIV**	**LHC**	**ASE**		LC	**L**		**T**
DLV	G	**I**	**EP**	**NS**	**AM**	I	DEF	**CIV**	**LHC**	**E**		C	**L**	**L**	**T**
EFV	G	**I**	EP	**NS**	AM	I	DEF	CIV	LHC	**ASE**	H	C	**L**		T
ETR†	G	**I**	EP				DE**F**	**CIV**	LHC	ASE		**C**	**L**		T

LEGEND **Mutations in bold red** are associated with higher levels of phenotypic resistance or clinical evidence for reduced virological response.

ADDITIONAL MUTATIONS Several additional uncommon mutations at these positions are also associated with NNRTI therapy or reduced NNRTI susceptibility including: K101NH, K103TH, G190QCTV (PR Harrigan AIDS 2005, S Rhee JID 2005).

POLYMORPHIC MUTATIONS A98S, K101RQ, K103R, V106I, E138A, V179I, and K238R are polymorphic substitutions with little if any effect on drug resistance with one notable exception - K103R, which occurs in 1% to 2% of untreated persons, reduces NVP, DLV, and EFV susceptibility ~15-fold in combination with V179D (N Parkin AAC 2006).

MUTATIONS AT ADDITIONAL POSITIONS E138K has been selected in vitro by ETR and causes low-level reduced susceptibility to each of the NNRTIs (J Vingerhoets JV 2001, G Su AT 2000). L234I has been selected in vitro by ETR and acts synergistically with Y181C to reduce ETR susceptibility (J Vingerhoets JV 2001). L318F is a nonpolymorphic NNRTI-selected mutation that reduces DLV, NVP, and possibly ETR susceptibility (PR Harrigan AIDS 2002, J Vingerhoets JV 2005). Several polymorphic mutations such as K101Q, I135TM, V179I, and L283I and several NRTI-selected mutations such as L74V, H221Y and N348I may cause subtle reductions in NNRTI susceptibility (F Ceccherini-Silberstein JV 2007, SH Yap PLOS Med 2007).

† A univariate analysis of genotype-virological outcome data found that persons with viruses with ≥ 3 of the following mutations responded similarly to placebo and ETR in the DUET trials: V90I, A98G, L100I, K101EP, V106I, V179DF, Y181CIV, and G190AS. (J Vingerhoets HIVDRW 2007). V90I and V106I are polymorphisms that occur at similar frequency in NNRTI-treated and untreated persons (http://hivdb.stanford.edu/cgi-bin/MutPrevBySubtypeRx.cgi or http://hivdb.stanford.edu/cgi-bin/RTPosMutSummary.cgi).

Integrase Inhibitor (INI) Resistance Mutations

	66	92	121	138	140	143	147	148	153	155	263
Cons	T	E	F	E	G	Y	S	Q	S	N	R
Raltegravir†		**Q**	**Y**	AK	**AS**	**RC**H	G	**HRK**		**H**S	
Elvitegravir§	**I**	**Q**	**Y**	AK	**AS**		**G**	**HRK**	Y	**H**S	K

LEGEND INI-resistance mutations selected in persons receiving raltegravir (D Hazuda HIVDRW 2007, I Malet AAC 2008) or elvitegravir (D McColl HIVDRW 2007) are characterized for *in vitro* susceptibility (G Jones CROI 2007, D McColl HIVDRW 2007, C Ren HIVDRW 2007, M Rowley Prog Med Chem 2008). **Mutations in bold red** are associated with >5-10 fold decreased susceptibility.

† Other mutations selected *in vitro* or *in vivo* by raltegravir include the nonpolymorphic mutations H183P, Y226DFH, S230R, and D232N, and the polymorphic mutations L74M, T97A, V151I, G163R, I203M, and S230N (Raltegravir package insert).

§ Other mutations selected *in vitro* or *in vivo* by elvitegravir include the nonpolymorphic mutations H51Y, Q95K, and Q146P (K Shimura JV 2007).

ADDITIONAL MUTATIONS Additional integrase mutations selected by other investigational INIs include the nonpolymorphic mutations T125K, A128T, Q146K, N155S, K160D, and the polymorphic mutations V72I, A154I, V165I, and V201I (M Lataillade AVT 2007).

Fusion Inhibitor Resistance Mutations

	36	37	38	40	42	43	44	45
Cons	G	I	V	Q	N	N	L	L
Enfuvirtide	**DE**VS	V	**EA**MG	**H**	T	**D**KS	M	M

LEGEND **Mutations in bold red** reduce enfuvirtide susceptibility >10-fold in site-directed mutants and most clinical isolates.

ADDITIONAL MUTATIONS N42S is the only common polymorphism between codons 36 to 45. It occurs in ~15% of untreated isolates and does not decrease ENF susceptibility (T Melby ARHR 2006). Most other mutations at these positions are likely to have been selected by ENF, although their effect on ENF susceptibility may not have been reported.

MUTATIONS AT ADDITIONAL POSITIONS Several accessory mutations in the HR2 region corresponding to the peptide sequence of ENF including N126K, N137K, and S138A have been shown to emerge to improve fitness in combination with specific mutations at positions 36 ot 45 (C Su JCV 2006, L Xu AAC 2005, CE Baldwin JV 2004, M Tolstrup AIDS 2007).

Co-receptor Tropism and CCR5 Inhibitors

At initial HIV-1 infection, >90% of patients have viruses that exclusively use the CCR5 co-receptor (R5 tropic). About 50% of patients with subtype B infections eventually develop viruses that use CXCR4 (X4 tropic). The emergence of X4 tropism usually occurs in later disease stages and, in the absence of ARV therapy, is followed by accelerated CD4 cell depletion. When X4-tropic viruses emerge, they usually co-circulate with R5 tropic viruses often as minor variants thus complicating their detection. The main genetic determinants of tropism are in the V3 loop, although other changes also influence tropism (O Harltey ARHR 2005).

The licensed small molecule inhibitor maraviroc and the investigational inhibitor vicriviroc allosterically inhibit HIV-1 gp120 binding to the CCR5 7-transmembrane G protein-coupled receptor. Whereas HIV-1 gp120 binds to the N terminus and 2nd extracellular loop of CCR5, most inhibitors bind to a pocket or pockets formed by the transmembrane helices. HIV-1 may escape from CCR5 inhibition by binding to a CCR5-inhibitor bound receptor (M Westby JV 2007) or by utilizing CXCR4 (M Westby JV 2006).

The Trofile test (Monogram Biosciences) assesses the tropism of complete env genes amplified from patient samples (J Whitcomb JV 2007) by ligating them into env expression test vectors, which following co-transfection with env-deleted genomic vectors create a population of pseudovirions that are inoculated into reporter cell lines expressing CCR5 or CXCR4. The Trofile is more sensitive than genotypic methods for detecting X4 tropism because it uses complete patient-derived env genes and detects variants below the 20% to 30% detection limit of standard genotypic assays. Novel genotypic approaches will be required to attain sensitivities approaching that of phenotypic assays (T Sing AVT 2007, O Sander PLOS Comput Biol 2007).

HIV-1 Protease and Reverse Transcriptase Mutations For Drug Resistance Surveillance (2009)

NRTI

Pos	Mut
M41	L
K65	R
D67	N, G, **E**
T69	D, Ins
K70	R, **E**
L74	V, **I**
V75	M, T, A, S
F77	L
Y115	F
F116	Y
Q151	M
M184	V, I
L210	W
T215	Y, F, I, S, C, D, V, E
K219	Q, E, **N**, R

NNRTI

Pos	Mut
L100	I
K101	E, **P**
K103	N, S
V106	M, A
V179	**F**
Y181	C, I, **V**
Y188	L, H, C
G190	A, S, E
P225	H
M230	L

PI

Pos	Mut
L23	**I**
L24	I
D30	N
V32	I
M46	I, **L**
I47	V, A
G48	V, **M**
I50	V, L
F53	L, **Y**
I54	V, L, M, A, T, S
G73	S, T, C, A
L76	**V**
V82	A, T, F, S, **C**, M, **L**
N83	**D**
I84	V, A, C
I85	**V**
N88	D, S
L90	M

New mutations 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**, *Publication pending*. The following considerations were used for developing this list of drug resistance mutations for epidemiological studies of transmitted resistance: (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); **PIs**: ATV (atazanavir), DRV (darunavir), FPV (fosamprenavir), IDV (indinavir), LPV (lopinavir), NFV (neflinavir), SQV (saquinavir), TPV (tipranavir); "/r" (ritonavir-boosted); **Amino acids**: A (alanine), C (cysteine), D (aspartate) E (glutmatate), F (phenylalanine), G (glucine), H (histidiine), I (isolleucing), K (lysine), L (leucine), M (methionine), N (asparganine), P (proline), Q (glutamine), R (arginine), S (serine), T (threonine), V (valine), W (tryptophan), Y (tyrosine), Ins (insertion); **Journals**: AAC (Antimicrobial Agents Chemother), ARHR (AIDS Res Hum Retrovirus), AVR (Antviral Res), AVT (Antiviral Ther), JCV (Jnl Clin Virol), JV (Jnl Virol), JVM (J Virol Methods), PLOS (Public Library of Science), PNAS (Proc Natl Acad Sci); **Meetings**: CROI (Conference on Retroviruses and Opportunistic Infections), HIVDRW (HIV Drug Resistance Workshop).