Updated March 24, 2010 by Christophe Marchand, Ph.D.
Also discussed in: Métifiot et al., Viruses, 2010

Mutations	3'-P	ST	Dis	Replication (Infectivity)	Resistance (Interaction)	References
E10D/N17S/V72A/L74M/T124A					S	[1]
E10D/N17S/Q148R					35	[1]
D10E/T66I/E92Q/A128T/Q148R					E	[2]
D10E/H114Y/A128T/Q148R					E	[2]
D10E/V321/S39C/V72I/K111R/G123S/A124N/T125A/K127K/Y143R/G193E/N232D/N245K					R	[3]
H12A;N*	+	+	+++	- (-)	(PIC)	[4,5,6,7]
H12C*			+++	(-)		[8,9]
H12N/H16N	-	-	+			[5]
H12C/H16C			+++			[8]
H12Q/H16Y				(-)		[10]
Y15A				(-)		[11]
H16A*				-		[6]
H16C;V*	+++	+++	+++	(-)		[8,9]
N17S/Q148K					R	[1]
N17S/Q148K/G163R					R	[1]
R20K					E	[2]
M22I/T97A/T124A					10	[1]
K34A	++	++		- (-)	(PIC)	[7]
C40A;S*	-	-	+	(-)		[4,12]
C40S/C43S	-	-	++			[4]
D41A/K42A				+		[6]
C43A;S;L*	+	+		(-)		[10,12,13]
K46A				+++		[7]
M50A				+		[12,13]
H51A*				+		[6]
H51Y*		++			E	[14]
H51Y/E92Q/S147G		+			E	[14]
H51Y/E92Q/S147G/E157Q		++			E	[14]
H51R/V72I/L74M/T97A/S119G/T125A/Y143R/V201I					R	[15]
H51D/K111T/S119T/G123S/A124T/R127K/Y143C/N155H/N232D					R	[3]
H51A/D55V				-		[6]
E52Q/N155H					R	[16]
Q53C	+++	+++	++	(-)		[8,9]
Q53K				+++		[17]
D55A				-		[6]
D55A;S				+++		[17]
D55K				-		[17]
C56A*				+++		[18]
C56S*	+++	+++		+++		[19,20]
C56S/C65S				Del		[19]
C56S/C130S				-		[19]
C56S/C65S/C280S	++	++	+++			[19,21]
C56S/C65S/C130S/C280S	++	-	+++			[19]
C56S/C65S/Q148C/C280S	++	-				[19,21]
Q62E	++	++	+++			[22]
Q62K				-		[17]
Q62N	+	-	-			[23]
D64C;R*			-			[23]
D64A;E;N;V*	-	-	-	-		[4,6,8,9,12,24,25]
D64A/D116A				-		[6]
D64R/D116R			-			[23]
D64A/E152A				-		[6]
D64A/D116A/E152A				-		[6]
C65S*	+++	+++		+++		[19,20]
C65A*				+++		[18]
C65S/C130S				-		[19]

T66A*	+	++	++	(++)	R/E	[1,23,26,27]
T66I*	+/++/+++	-/+/++/+++	++	+/++	06/88/S/24/CA/E	[1,2,28,29,30,31,32,33,34,35,36]
T66K					10/35/S/E	[1]
T66I/L74M	+	+		+	06/S/E	[1,30]
T66K/L74M					S/10/35/R/E	[1]
T66I/S153Y				++	06/88/24/CA	[31,32,33]
T66I/E92Q		-			S/10/E/R	[1,2,36]
T66I/T124A					S/E	[1]
T66K/T124A					10/E	[1]
T66K/T125K					10	[1]
T66I/M154I	++	++	++	+	88/CA	[32]
T66I/N155H		-				[36]
T66I/V72A/T124A					S	[1]
T66I/V72A/A128T					E	[1]
T66K/L74M/T125K					10	[1]
T66I/L74M/S230R	+	+		++	06/S	[30]
T66I/E92Q;V/T124A					10	[1]
T66I/E92Q/T124A					E	[1]
T66I/T124A/Q146L					E	[1]
T66I/L74/E92V/T124A					10	[1]
T66K/E92Q/T124A/M154I					10	[1]
T66I/E92Q/A128T/Q148R					E	[2]
H67E*				Del		[17]
H67S*	+++	+++	++			[23]
H67Q/K71E				-		[17]
E69A/K71A				-		[6]
K71E*				+++		[17]
V72I*					10/R	[15,33,37,38]
V72I/N155H					R	[39]
V72I/E92Q/N155H					R	[39]
V72I/F121Y/T125K					S/10/35/R/E	[1]
V72I/T125A/S230N					R	[15]
V72I/M154I/V201I					R	[15]
V72I/S119G/T125A/V201I					R	[15]
V72I/S119R/T125A/V201I					R	[15]
V72I/S119P/T125A/T206S					R	[15]
V72I/F121Y/T125K/V151I					S/10/35/E	[1]
V72I/T125A/G163E/V201I					R	[15]
V72I/T125A/V201I/T206S					R	[15]
V72I/T125A/Y143R/V201I/T206S					R	[15]
V72I/A153G/N155H/N160H/S163G					R	[40]
V72I/L74M/T97A/S119T/E138D/Y143R					R	[15]
V72I/S119G/T125A/G140A/Q148R/V201I					R	[15]
V72I/S119P/T125A/Q146K/N155H/T206S					R	[15]
V72I/S119R/T125A/N155H/V201I/T206S					R	[15]
V72I/T125A/G140S/Q148H/G163K/V201I					R	[15]
V72I/T125AV151I/N155H/G163R/S230N					R	[15]
V72I/V151I/M154I/N155H/G163R/V201I					R	[15]
V72I/E92Q/T97A/S119R/T125A/N155H/V201I					R	[15]
V72I/T97A/S119R/T125A/Y143H/N155H/G163R/V201I					R	[15]
V72I/I113V/G123S/A124N;S/T125A/R127K/Y143R/T206S/I220L/Y227F/N232D					R	[3]
L74M*	+++	+++			06/10/S/E	[2,30,34,35,41]
L74I*					R	[27,37,38]
L74M/E92V					60	[42]
L74M/N155H					S/10/35/R/E	[1]
L74M/E92Q/F121Y					10	[1]
L74M/E92Q/S230N		+			10	[41]
L74M/T97A/ Y143R					R	[39]
L74I/V151I/N155H					R	[16]
L74M/E92Q/T97A/Y143H					R	[43]
L74M/T97A/E138A/Y143R					R	[39]
L74M/T125A/V201I/T206S					R	[15]

L74M/T125A/N155H/V201I/T206S					R	15
V75P				(-)		12
V75I*	+++	+				36
V75I/M154I		++				36
V75I/T112S/Q146P					35/E	1
S81R;A	+/-	+/-	+/-	(-)		8,9,12
P90D*	+++	-	-			44
P90D/P145I	-	-	-			44
E92A;Q	+++	+++	+++	+++		22
E92A;N	+	+	++			23
E92K	+	+	+++	-		22
E92G					R	45
E92Q*	+/++/++ +	+/++/++ +		++(+++)	10/S/R/E	1,2,14,27,35,36,41,46,47,48
E92V*					60	42
E92Q/F121Y					10	1
E92Q;I/T124A					10	1
E92V/T124A					E	1
E92Q/G140S					10	1
E92Q/S147G		+			E	14
E92Q/M154I					R	1
E92Q/N155H				+/++	R	48,49
E92Q/S230N		+			10	41
E92Q/E138K/Q148K/M154I					R	1
T93A				(++)		26
T97A*					R	37,38,50
T97A/Y143R					R	39
T97A/Y143C					R	39
T97A/Y143S					R	39
T97A/N155H					S/10/35/E/R	1,39
T97A/E138A/Y143R					R	39
T97A/V151I/N155H					R	16,51
T97A/T125A/V151I/N155H/V201I					R	39
G106A	+++	+++				52
P109A;S*	+/-	+/-	-	+		6,24,53
P109S/T125A	+++	+++	+++	(+/-)		53
T112A	+++	+++				24
T112I						37
112A/G140S/Q148H/G163R					R	39
H114E				++		17
H114Y					E	2
H114Y/A128T/Q148R					E	2
T115A;S	+++	+++	+++	+++		4,12,24,54,55
D116A;E;I;N*	-	-	-	- (-)		4,8,9,12,23,24,54,55,56,57
D116C*			+			23
D116A/E152A**				-		6
D116/A23V**	-	++	-			58
D116/E11D	-	++	-			58
D116/L28R/C65S/ T210N/L213I	-	+	-			58
N117K;Q	++	++	++	Del		4,17,23,55,56
N117S	+	+	+			23
G118A	+++		+++	+++		55,56
G118R					S/10/35	1
G118S					S	1
S119T;G*;A;K	+++	+++				52
N120Q;S*	+++	+++	+++			23
N120I;L;E;G*				(-)		9
N120L;K*				Del		17
N120L/Q148K				-		17
F121A	+/-	-				54
F121Y	+++	+			S/10/35	1,33,35
F121Y/T124A					S/10/E	1
F121Y/T125K					S/10/35/R/E	1
F121Y/G163R					10	1

F121Y/T125K/M154I					10	[1]
S123A	++	++	+++	(+)		[4,12]
G123S/R127K/Y143R/A205S/I208L/K311Q/E212A/N232D					R	[3]
T124A*					S/10/35/R/E	[1]
T124A/Q146L					S	[1]
T124A/Q148K					S	[1]
T124A/Q148R					10	[1]
T124A/N155S					S	[1]
T124A/E138K/Q148K					10	[1]
T124A/G140S/Q148K					10	[1]
T124A/V151I/N155H					R	[1]
T125A*	+++	+++	+++	+ (+++)		[26,53]
T125K*					10	[33]
V125A/V151I/N155H/V201I					R	[39]
K127A				+		[6]
A128T					S/E	[2,34]
A128T/V151L					10	[1]
C130A*	+++	+++		++	OH-C	[18,59]
C130G*				- (-)	OH-C	[18,59]
C130S*				-	OH-C	[19,20,59]
C130A/F185K/C280S	+++	+++			OH-C	[59]
C130S/F185K/C280S	+++	+			OH-C	[59]
W131G/F185K/C280S	++	++				[59]
W132A;G;R//F185K/C280S	+++	-			OH-C	[59]
W132Y/F185K/C280S	+++	++			OH-C	[59]
I135P				(-)		[12]
K136A*	+/-	+/-	+++	-/++		[6,17,22]
K136E;R*	+++	+++	+++	+++		[22]
K136A/E138A	+++	+++	+++	+++		[22]
K136R//F185K/C280S	+++	++				[59]
E138A*				+		[6]
E138K*				++ (++)	S/35	[17,34,60]
E138K/Q148R				++(++)	S/10/35/R/E	[1,39,49,60]
E138K/Q148K				++(+)	S/10/35/R/E	[1,49,60]
E138K/Q148H				+	S/10/R	[1,49]
E138K/Q148K/G163R					R	[1]
E138K/G140S/Y143H/Q148H					R	[39]
G140S*	+/+++	+	+	Del ++(+/++)	CA/88/R/S/35	[27,45,47,48,60,61,62,63]
G140A*	++	+			R	[63]
G140S/Q148H	-/++	-/++/+++		+++	S/10/35/E/R	[1,39,43,45,46,47,48,49,51,63]
G140S/Q148K	++	+		++(++)	S/10/35/E/R	[1,49,60,63]
G140S/Q148R	-	+		++(+)	S/10/35/R/E	[1,39,43,49,63]
G140S/Y143R					R	[39]
G140C/Q148K					R	[1]
G140C/Q148R					S/10/35/R/E	[1]
G140A/Q148H	-	+		+	R	[49,63]
G140A/Q148K	-	-		++	R	[49,63]
G140A/Q148R	+	+		++	R	[49,50,63]
G140S/Q143R/N155H					R	[39]
G140S/Q148H;R/N155H					R	[39,49]
G140S/Q148H/G163R					R	[16,51]
G140C/Q148K/G163R					R	[1]
G140S/Q148R/G163R					R	[39]
G140S/Q148H/S230N				+++	R	[48]
G140A/Y143H;R/Q148R/G163R					R	[50]
G140S/F185K/C280S	+++	+++	+++			[64]
P142F				+++/(+++)		[65]
Y143F				Del		[6,55]
Y143N	+++		+++	Del		[6,55,56]
Y143G				+++/(+++)		[17,26,65]
Y143K					R	[39]
Y143R*	+	++		(+)	R	[3,39,43,45]
Y143C*	+	+		(+)	R	[3]

Y143R/G163R				++	R	48
Y143R/E170A					R	45
Y143R/T206S					R	39
Y143C/G163R					R	50
Y143S/A201I					R	39
N144K				-		17
N144Q				-/(-)		65
P145I*	-	-	-			44
P145A*				+		17
P145F*				-/(-)		65
P145S*					E	1
P145S/T124A					E	1
P145I/F185K/C280S	-	-	-			44
Q146K				+	S	17,34
Q146R					35	1
Q146L/124A					E	1
S147I	-		+++	-		55,56
S147G*		+			E	14
Q148A*	++	-				21
Q148K*	-	-/+		Del + (+)	S/10/35/R/E	1,17,35,49,60,63
Q148L*	+	++	+	Del		17,23
Q148N*	+++	++				21
Q148R	-/+	+		++(+)	S/10/35/R/E	1,2,27,36,49,50,60,63,66
Q148H*	+	-/+		+/++(+)	S/10/R	27,45,47,48,49,63
Q148R/T124A					E	1
Q148R/N155H					R	49,51
Q148H/N155H				+	R	48
Q148K/G163R					R	1
Q148A/F185K/C280S	+	+				59
V150E	+++	+++	+++			44
V151A*				(+)		12
V151I*					10/E	1,33,37,38
V151L					S/10/E	1
V151D/E152Q	-	-	-	-		13
V151T/S153Q	++	-	+++			67
V151L/S153L	+++	-	-			67
V151I/N155H					R	1,16,50,51
V151I/N155H/G163R					R	50,51
V151L/E152V/S153F	++	-	-			67
V151A/E152M/S153A	++	-	-			67
V151Y/E152V/S153P	+++	-	-			67
V151H/E152S/S153T	+++	-	-			67
V151A/E152L/S153T	+++	-	-			67
V151K/E152L/S153T	++	-	-			67
V151S/E152S/S153P	++	-	-			67
V151H/E152G/S153L	+++	-	-			67
V151E/E152S/S153N	++	-	-			67
V151T/E152S/S153M	+++	-	-			67
V151T/E152F/S153C	+++	-	-			67
E152A;C;D;G;H;P;Q;V;K*	-	-	-	- (-)		4,6,8,9,12,17,23,24,44,54,56,57
E152A/K156A				-		6
E152N/S153R	++	-	-			67
S153A;R*	+	+	++	++		4,17
S153A*	+++		+++	+++	S	34,55,56
S153Y*	++	+/++	++	+	06/10/11/12/88/CA	29,32,33,35,68
M154I*	+++	+++	+++	++	06/88/CA	29,32,33,37,38
N155E;K	-	-	-	Del		17,23
N155L	+	+	-	Del		17,23
N155S					S/10/11/12/35/E	1,33,68
N155H*	+/++/+++	-/+/+++		++(+++)	10/11/12/R/E	1,27,35,36,45,46,47,48,49,50,51,66,68
N155T					S/35/E	1

N155H/G163R					10/35/R/E	[1,51]
N155H/I204T					R	[1]
K156A*				+/ +++/(+++)		[6,65]
K156E*	-	-	+/-	Del		[17,23,69]
K156R*						[70]
K156I*	-	-	-			[44]
K156N						[37]
K156E/K159E	-	-	-	-		[17,69]
K156A/E157A				+		[6]
E157Q*		++			R/E	[14,37,38,71]
E157A/K159A				+		[6]
L158F	+++	+++	+++			[44]
K159A*				++/(++)		[65]
K159E*	-	-	+++	-/Del		[17,69]
K159N;S*	+	+	+			[23]
K159Q*	+++		+++			[56]
K159R*						[70]
K159A/K160A				+		[6]
K159A;P;Q				(+)		[12,54,55]
K160A*				+++/(+++)		[65]
K160D*					S	[34]
K160E*	+++	+++	+++	-		[69]
G163R					35	[1]
G163K						[37]
V165A	++			- (-)	(PIC)	[7,18]
V165I					S	[34,37,38]
R166A*				-		[6]
R166T*	++	++				[70,72]
R166A/D167A				-		[6]
D167A*				+		[6]
Q168A	+++	+++		(-)	(LEDGF)	[73,74]
Q168L	+++	-		(-)	(LEDGF)	[73]
Q168P	-	-		(-)	(LEDGF)	[73]
E170A/H171A	+++	+++		+/Del		[6,75]
E170A/K173A				+		[6]
H171A/K173A*				+		[6]
L172M*	+++	+++	+++			[44]
L172A/K173A	+++	+++		-		[75]
T174A	+	+		-		[75]
V176A/Q177A	+++	+++		Del		[75]
M178A	-	-		-		[75]
A179P				(-)		[12]
V180A/F181A	-	-		-		[75]
N184D;L				-		[17]
F185A;K;L;H*	+++	+++		(-)		[22]
K186A;Q;E	+++			- (-)		[18,26]
K187A				-		[18]
K188A				-		[18]
G189A	+++	+++				[24]
S195A				(++)		[26]
E198A/R199A				-		[6]
R199A;C*	+++	+++	+++	-/Del (-)		[6,8,9,17,18]
R199E*				-		[17]
R199A/D202A				-		[6]
R199T/D202A				-		[6]
V201I*					S/R	[15,34,37,38]
I203M						[38]
T206S						[38]
K211A*				(++)		[26]
K211A/E212A				+		[6]
Q214L/Q216L	+++			- (-)		[18]
K215A*				+++		[18]
K215A/K219A	++			- (-)		[18]
K219A*				+		[18]
N222A	++	++	++			[76]

F223A	++	++	++		(mAb33)	76,77
R224A	++	++	++		(mAb33)	76,77
Y226					(mAb33)	77
Y227A	++	++	++			76
R228A				- (-)		78
S230R*	+++	+++			S/06/E	2,30
S230N*					10	38,41
R231A	++	+	+	+		76,78
P233A	++	++	++			76
L;V234A	++	++	++	+++		76,78
W235A;E;F	+++	+++	+++	+/- (-)	(PIC)	5,7,8,9,12
K236A*				+++		78
K236E*				- (-)		78
K236A/K240A				-		6
K236/E246A				- (-)		78
L241A	-	-	-	- (-)		76,78
L242A	-	-	+	- (-)		76,78
W243A	++	++	++			76
K244A*				- (-)		78
K244E*	-	-		(-)		79
K244A/E246A				-		6
E246A*	++	++	++	Del (+)		76,78
E246K*				- (-)		78
D253A/D256A				+		6
N254A	++	++	++			76
K258A				- (-)		78
V260E	-	-	-	- (-)		76,78
R262A*				++		78
R262G*	++	++	+			76
R262A/R263A				- (-)		78
R262A/K264A				- (-)		78
R262D/R263V/K264E				- (-)		78
R263A*				Del		78
R263L*	++	++	++			76
K264A*				++		78
K264E*				- (-)		78
K266A;E				- (-)		78
I267					(mAb33)	77
I268					(mAb33)	77
R269A*				Del (+)		78
R269A/D270A				+		6
K273A				+++		78
C280S*	+++	+++				20
S283A				(++)		26
R284G;K	+++	+++				80

- = 0-10%, + = 10-40%, ++ = 40-80%, +++ =80-100%
* = mutant present elsewhere in the table as a combination
/ = separates differential results from independent publications

Abbreviations:
3’-P, 3'-processing;
ST, strand transfer;
Dis, disintegration;
PIC, pre-integration complex;
Del, delayed;
CA, L-chicoric acid;
OH-C, hydroxycoumarin;
R, raltegravir;
E, elvitegravir;
S, S-1360;
06, L-708,906;
10, L-870,810;
11, L-841,411;
12, L-870,812;
24, 118D-24;
35, S/GSK-364735;
60, GS-9160;
88, L-731,988

References

1 Kobayashi, M. *et al.* Selection of diverse and clinically relevant integrase inhibitor-resistant human immunodeficiency virus type 1 mutants. *Antiviral Res.* **80**, 213-222, doi:10.1016/j.antiviral.2008.06.012 (2008).

2 Goethals, O. *et al.* Resistance mutations in HIV-1 integrase selected with Elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors. *J. Virol.*, doi:10.1128/JVI.00470-08 (2008).

3 Delelis, O. *et al.* Impact of Y143 HIV-1 integrase mutations on resistance to Raltegravir in vitro and in vivo. *Antimicrob. Agents Chemother.*, doi:10.1128/AAC.01075-09 (2009).

4 Engelman, A. & Craigie, R. Identification of conserved amino acid residues critical for human immunodeficiency virus type 1 integrase function in vitro. *Journal of virology* **66**, 6361-6369 (1992).

5 Engelman, A., Englund, G., Orenstein, J. M., Martin, M. A. & Craigie, R. Multiple effects of mutations in human immunodeficiency virus type 1 integrase on viral replication. *Journal of virology* **69**, 2729-2736 (1995).

6 Wiskerchen, M. & Muesing, M. A. Human immunodeficiency virus type 1 integrase: effects of mutations on viral ability to integrate, direct viral gene expression from unintegrated viral DNA templates, and sustain viral propagation in primary cells. *Journal of virology* **69**, 376-386 (1995).

7 Lu, R., Vandegraaff, N., Cherepanov, P. & Engelman, A. Lys-34, dispensable for integrase catalysis, is required for preintegration complex function and human immunodeficiency virus type 1 replication. *Journal of virology* **79**, 12584-12591 (2005).

8 Leavitt, A. D., Shiue, L. & Varmus, H. E. Site-directed mutagenesis of HIV-1 integrase demonstrates differential effects on integrase functions in vitro. *The Journal of biological chemistry* **268**, 2113-2119 (1993).

9 Leavitt, A. D., Robles, G., Alesandro, N. & Varmus, H. E. Human immunodeficiency virus type 1 integrase mutants retain in vitro integrase activity yet fail to integrate viral DNA efficiently during infection. *Journal of virology* **70**, 721-728 (1996).

10 Nakamura, T. *et al.* Lack of infectivity of HIV-1 integrase zinc finger-like domain mutant with morphologically normal maturation. *Biochemical and biophysical research communications* **239**, 715-722 (1997).

11 Nomura, Y., Masuda, T. & Kawai, G. Structural analysis of a mutant of the HIV-1 integrase zinc finger domain that forms a single conformation. *Journal of biochemistry* **139**, 753-759 (2006).

12 Cannon, P. M., Wilson, W., Byles, E., Kingsman, S. M. & Kingsman, A. J. Human immunodeficiency virus type 1 integrase: effect on viral replication of mutations at highly conserved residues. *Journal of virology* **68**, 4768-4775 (1994).

13 LaFemina, R. L. *et al.* Requirement of active human immunodeficiency virus type 1 integrase enzyme for productive infection of human T-lymphoid cells. *Journal of virology* **66**, 7414-7419 (1992).

14 Shimura, K. *et al.* Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *Journal of virology* **82**, 764-774, doi:10.1128/JVI.01534-07 (2008).

15 Sichtig, N. *et al.* Evolution of raltegravir resistance during therapy. *J Antimicrob Chemother*, doi:10.1093/jac/dkp153 (2009).

16 Wirden, M. *et al.* Raltegravir has no residual antiviral activity in vivo against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother*, doi:10.1093/jac/dkp310 (2009).

17 Lu, R., Limon, A., Ghory, H. Z. & Engelman, A. Genetic analyses of DNA-binding mutants in the catalytic core domain of human immunodeficiency virus type 1 integrase. *Journal of virology* **79**, 2493-2505 (2005).

18 Lu, R. *et al.* Class II integrase mutants with changes in putative nuclear localization signals are primarily blocked at a postnuclear entry step of human immunodeficiency virus type 1 replication. *Journal of virology* **78**, 12735-12746 (2004).

19 Zhu, K., Dobard, C. & Chow, S. A. Requirement for integrase during reverse transcription of human immunodeficiency virus type 1 and the effect of cysteine mutations of integrase on its interactions with reverse transcriptase. *Journal of virology* **78**, 5045-5055 (2004).

20 Bischerour, J., Leh, H., Deprez, E., Brochon, J. C. & Mouscadet, J. F. Disulfide-linked integrase oligomers involving C280 residues are formed in vitro and in vivo but are not essential for human immunodeficiency virus replication. *Journal of virology* **77**, 135-141 (2003).

21 Johnson, A. A. *et al.* Integration requires a specific interaction of the donor DNA terminal 5'-cytosine with glutamine 148 of the HIV-1 integrase flexible loop. *The Journal of biological chemistry* **281**, 461-467 (2006).

22 Engelman, A., Liu, Y., Chen, H., Farzan, M. & Dyda, F. Structure-based mutagenesis of the catalytic domain of human immunodeficiency virus type 1 integrase. *Journal of virology* **71**, 3507-3514 (1997).

23 Gerton, J. L., Ohgi, S., Olsen, M., DeRisi, J. & Brown, P. O. Effects of mutations in residues near the active site of human immunodeficiency virus type 1 integrase on specific enzyme-substrate interactions. *Journal of virology* **72**, 5046-5055 (1998).

24 Drelich, M., Wilhelm, R. & Mous, J. Identification of amino acid residues critical for endonuclease and integration activities of HIV-1 IN protein in vitro. *Virology* **188**, 459-468 (1992).

25 Cherepanov, P. *et al.* High-level expression of active HIV-1 integrase from a synthetic gene in human cells. *Faseb J* **14**, 1389-1399 (2000).

26 Tsurutani, N. *et al.* Identification of critical amino acid residues in human immunodeficiency virus type 1 IN required for efficient proviral DNA formation at steps prior to integration in dividing and nondividing cells. *Journal of virology* **74**, 4795-4806 (2000).

27 Charpentier, C. *et al.* Drug resistance profiles for the HIV integrase gene in patients failing raltegravir salvage therapy. *HIV Med*, doi:10.1111/j.1468-1293.2008.00628.x (2008).

28 Yoshinaga, T., Sato, A., Fujishita, T. & Fujiwara, T. in *9th Conference on Retrovirures and Opportunistic Infections* (Seattle, WA, 2002).

29 Hazuda, D. J. *et al.* Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. *Science* **287**, 646-650 (2000).

30 Fikkert, V. *et al.* Development of resistance against diketo derivatives of human immunodeficiency virus type 1 by progressive accumulation of integrase mutations. *Journal of virology* **77**, 11459-11470 (2003).

31 Svarovskaia, E. S. *et al.* Azido-containing diketo acid derivatives inhibit human immunodeficiency virus type 1 integrase in vivo and influence the frequency of deletions at two-long-terminal-repeat-circle junctions. *Journal of virology* **78**, 3210-3222 (2004).

32 Lee, D. J. & Robinson, W. E., Jr. Human immunodeficiency virus type 1 (HIV-1) integrase: resistance to diketo acid integrase inhibitors impairs HIV-1 replication and integration and confers cross-resistance to L-chicoric acid. *Journal of virology* **78**, 5835-5847 (2004).

33 Hazuda, D. J. *et al.* A naphthyridine carboxamide provides evidence for discordant resistance between mechanistically identical inhibitors of HIV-1 integrase. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 11233-11238 (2004).

34 Fikkert, V. *et al.* Multiple mutations in human immunodeficiency virus-1 integrase confer resistance to the clinical trial drug S-1360. *AIDS (London, England)* **18**, 2019-2028 (2004).

35 Marinello, J. *et al.* Comparison of Raltegravir and Elvitagravir on HIV-1 Integrase Catalytic Reactions and on a Series of Drug-Resistant Integrase Mutants. *Biochemistry*, doi:10.1021/bi800791q (2008).

36 Dicker, I. B. *et al.* Biochemical Analysis of HIV-1 Integrase Variants Resistant to Strand Transfer Inhibitors. *J. Biol. Chem.* **283**, 23599-23609, doi:10.1074/jbc.M804213200 (2008).

37 Passaes, C. B. *et al.* Lack of primary mutations associated with integrase inhibitors among HIV-1 subtypes B, C, and F circulating in Brazil. *J Acquir Immune Defic Syndr* **51**, 7-12, doi:10.1097/QAI.0b013e31819df3b3 (2009).

38 Low, A. *et al.* Natural Polymorphisms of HIV-1 Integrase and Inherent Susceptibilities to a Panel of Integrase Inhibitors. *Antimicrob. Agents Chemother.*, doi:10.1128/AAC.00397-09 (2009).

39 Canducci, F. *et al.* Genotypic/phenotypic patterns of HIV-1 integrase resistance to raltegravir. *J Antimicrob Chemother* **65**, 425-433, doi:10.1093/jac/dkp477 (2010).

40 Salgado, M. *et al.* Mutation N155H in HIV-2 integrase confers high phenotypic resistance to raltegravir and impairs replication capacity. *J Clin Virol* **46**, 173-175, doi:10.1016/j.jcv.2009.06.020 (2009).

41 Hombrouck, A. *et al.* Mutations in HIV-1 Integrase Confer Resistance to the Naphthyridine L-870,810 and Cross Resistance to the Clinical Trial drug GS-9137. *Antimicrob. Agents Chemother.*, doi:10.1128/AAC.00911-07 (2008).

42 Jones, G. *et al.* Preclinical Evaluation of GS-9160, a Novel Inhibitor of HIV-1 Integrase. *Antimicrob. Agents Chemother.*, doi:10.1128/AAC.00984-08 (2008).

43 Lennox, J. L. *et al.* Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* **374**, 796-806, doi:10.1016/S0140-6736(09)60918-1 (2009).

44 Sayasith, K., Sauve, G. & Yelle, J. Characterization of mutant HIV-1 integrase carrying amino acid changes in the catalytic domain. *Molecules and cells* **10**, 525-532 (2000).

45 Baldanti, F. *et al.* Early emergence of raltegravir resistance mutations in patients receiving HAART salvage regimens. *J Med Virol* **82**, 116-122, doi:10.1002/jmv.21651 (2009).

46 Malet, I. *et al.* Mutations associated with failure of raltegravir treatment affect integrase sensitivity to the inhibitor in vitro. *Antimicrob. Agents Chemother.* **52**, 1351-1358, doi:10.1128/AAC.01228-07 (2008).

47 Delelis, O. *et al.* The G140S mutation in HIV integrases from raltegravir-resistant patients rescues catalytic defect due to the resistance Q148H mutation. *Nucleic Acids Res.*, doi:10.1093/nar/gkn1050 (2009).

48 Buzón, M. *et al.* The HIV-1 integrase genotype strongly predicts raltegravir susceptibility but not viral fitness of primary virus isolates. *AIDS (London, England)*, doi:10.1097/QAD.0b013e328331c81e (2009).

49 Fransen, S. *et al.* Longitudinal analysis of raltegravir susceptibility and integrase replication capacity of HIV-1 during virologic failure. *Antimicrob. Agents Chemother.*, doi:10.1128/AAC.00651-09 (2009).

50 Ferns, R. B. *et al.* The dynamics of appearance and disappearance of HIV-1 integrase mutations during and after withdrawal of raltegravir therapy. *AIDS (London, England)* **23**, 2159-2164, doi:10.1097/QAD.0b013e32832ec4ae (2009).

51 Malet, I. *et al.* Quasispecies variant dynamics during emergence of resistance to raltegravir in HIV-1-infected patients. *J Antimicrob Chemother*, doi:10.1093/jac/dkp014 (2009).

52 Harper, A. L., Skinner, L. M., Sudol, M. & Katzman, M. Use of patient-derived human immunodeficiency virus type 1 integrases to identify a protein residue that affects target site selection. *Journal of virology* **75**, 7756-7762 (2001).

53 Taddeo, B., Carlini, F., Verani, P. & Engelman, A. Reversion of a human immunodeficiency virus type 1 integrase mutant at a second site restores enzyme function and virus infectivity. *Journal of virology* **70**, 8277-8284 (1996).

54 Kulkosky, J., Jones, K. S., Katz, R. A., Mack, J. P. & Skalka, A. M. Residues critical for retroviral integrative recombination in a region that is highly conserved among retroviral/retrotransposon integrases and bacterial insertion sequence transposases. *Molecular and cellular biology* **12**, 2331-2338 (1992).

55 Shin, C. G., Taddeo, B., Haseltine, W. A. & Farnet, C. M. Genetic analysis of the human immunodeficiency virus type 1 integrase protein. *Journal of virology* **68**, 1633-1642 (1994).

56 Oh, J. W., Oh, Y. T., Kim, D. J. & Shin, C. G. Characterization of human immunodeficiency virus type 1 integrase mutants expressed in Escherichia coli. *Molecules and cells* **7**, 688-693 (1997).

57 Engelman, A., Bushman, F. D. & Craigie, R. Identification of discrete functional domains of HIV-1 integrase and their organization within an active multimeric complex. *The EMBO journal* **12**, 3269-3275 (1993).

58 Parissi, V. *et al.* Selection of amino acid substitutions restoring activity of HIV-1 integrase mutated in its catalytic site using the yeast Saccharomyces cerevisiae. *Journal of molecular biology* **295**, 755-765 (2000).

59 Al-Mawsawi, L. Q. *et al.* Discovery of a small-molecule HIV-1 integrase inhibitor-binding site. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 10080-10085 (2006).

60 Nakahara, K. *et al.* Secondary mutations in viruses resistant to HIV-1 integrase inhibitors that restore viral infectivity and replication kinetics. *Antiviral Res.*, doi:10.1016/j.antiviral.2008.10.007 (2008).

61 King, P. J. *et al.* Human immunodeficiency virus type-1 integrase containing a glycine to serine mutation at position 140 is attenuated for catalysis and resistant to integrase inhibitors. *Virology* **306**, 147-161 (2003).

62 King, P. J. & Robinson, W. E., Jr. Resistance to the anti-human immunodeficiency virus type 1 compound L-chicoric acid results from a single mutation at amino acid 140 of integrase. *Journal of virology* **72**, 8420-8424 (1998).

63 Métifiot, M. *et al.* Biochemical and Pharmacological Analyses of HIV-1 Integrase Flexible Loop Mutants Resistant to Raltegravir. *Biochemistry* **In Press** (2010).

64 Pluymers, W. *et al.* Viral entry as the primary target for the anti-HIV activity of chicoric acid and its tetra-acetyl esters. *Molecular pharmacology* **58**, 641-648 (2000).

65 Ikeda, T. *et al.* Evaluation of the functional involvement of human immunodeficiency virus type 1 integrase in nuclear import of viral cDNA during acute infection. *Journal of virology* **78**, 11563-11573 (2004).

66 Dicker *et al.* Changes to the HIV LTR and to HIV integrase differentially impact HIV integrase assembly, activity and the binding of strand transfer inhibitors. *J. Biol. Chem.*, doi:10.1074/jbc.M704935200 (2007).

67 Calmels, C. *et al.* Biochemical and random mutagenesis analysis of the region carrying the catalytic E152 amino acid of HIV-1 integrase. *Nucleic acids research* **32**, 1527-1538 (2004).

68 Zahm, J. A. *et al.* Mechanisms of human immunodeficiency virus type 1 concerted integration related to strand transfer inhibition and drug resistance. *Antimicrob. Agents Chemother.* **52**, 3358-3368, doi:10.1128/AAC.00271-08 (2008).

69 Jenkins, T. M., Esposito, D., Engelman, A. & Craigie, R. Critical contacts between HIV-1 integrase and viral DNA identified by structure-based analysis and photo-crosslinking. *The EMBO journal* **16**, 6849-6859 (1997).

70 Drake, R. R. *et al.* Identification of a nucleotide binding site in HIV-1 integrase. *Proceedings of the National Academy of Sciences of the United States of America* **95**, 4170-4175 (1998).

71 Ghosn, J. *et al.* Rapid selection and archiving of mutation E157Q in HIV-1 DNA during short-term low-level replication on a raltegravir-containing regimen. *J Antimicrob Chemother* **64**, 433-434, doi:10.1093/jac/dkp182 (2009).

72 Pilon, A. A. *et al.* Mutations in the HIV type 1 integrase of patients receiving long-term dideoxynucleoside therapy do not confer resistance to zidovudine. *AIDS research and human retroviruses* **16**, 1417-1422 (2000).

73 Emiliani, S. *et al.* Integrase mutants defective for interaction with LEDGF/p75 are impaired in chromosome tethering and HIV-1 replication. *The Journal of biological chemistry* **280**, 25517-25523 (2005).

74 Vandekerckhove, L. *et al.* Transient and stable knockdown of the integrase cofactor LEDGF/p75 reveals its role in the replication cycle of human immunodeficiency virus. *Journal of virology* **80**, 1886-1896 (2006).

75 Priet, S., Navarro, J. M., Querat, G. & Sire, J. Reversion of the lethal phenotype of an HIV-1 integrase mutant virus by overexpression of the same integrase mutant protein. *The Journal of biological chemistry* **278**, 20724-20730 (2003).

76 Lutzke, R. A. & Plasterk, R. H. Structure-based mutational analysis of the C-terminal DNA-binding domain of human immunodeficiency virus type 1 integrase: critical residues for protein oligomerization and DNA binding. *Journal of virology* **72**, 4841-4848 (1998).

77 Ramcharan, J., Colleluori, D. M., Merkel, G., Andrake, M. D. & Skalka, A. M. Mode of inhibition of HIV-1 Integrase by a C-terminal domain-specific monoclonal antibody. *Retrovirology [electronic resource]* **3**, 34 (2006).

78 Lu, R., Ghory, H. Z. & Engelman, A. Genetic analyses of conserved residues in the carboxyl-terminal domain of human immunodeficiency virus type 1 integrase. *Journal of virology* **79**, 10356-10368 (2005).

79 Williams, K. L. *et al.* Mass spectrometric analysis of the HIV-1 integrase-pyridoxal 5'-phosphate complex reveals a new binding site for a nucleotide inhibitor. *The Journal of biological chemistry* **280**, 7949-7955 (2005).

80 Hickman, A. B., Dyda, F. & Craigie, R. Heterogeneity in recombinant HIV-1 integrase corrected by site-directed mutagenesis: the identification and elimination of a protease cleavage site. *Protein engineering* **10**, 601-606 (1997).