

Sauerbrei A, Bohn-Wippert K, Kaspar M, Krumbholz A, Karrasch M, Zell R. 2015. Database on natural polymorphisms and resistance-related non-synonymous mutations in thymidine kinase and DNA polymerase genes of herpes simplex virus types 1 and 2. J Antimicrob Chemother 71:6-16, doi: 10.1093/jac/dkv285, PMID: 26433780

**Supplementary Table 7:** Resistance-associated aa changes in DNA pol gene of HSV-1 including nt changes, their location, antivirals tested as well as results, methods for phenotypic testing and references.

Amino acid change	Nucleotide change	Domain	Antivirals tested		Drug susceptibility (EC <sub>50</sub> ratio of resistant to sensitive viral isolate or EC <sub>50</sub> value)					Test methods for phenotype	References
			resistant	sensitive	Aciclovir (ACV)	Brtvudin (BVDU)	Penciclovir (PCV)	Foscarnet (FOS)	Cidofovir (CDV)		
L187stop	deletion (C) nt 301	non-conserved region (pre NH <sub>2</sub> -terminal domain)	ACV, BVDU, PCV	CDV, FOS	EC <sub>50</sub> >35.5 µM	EC <sub>50</sub> >35.2 µM	EC <sub>50</sub> >32.0 µM	EC <sub>50</sub> 104.0 µM	EC <sub>50</sub> 4.4 µM	modified dye uptake assay including formazan test	20211650
D368A*	A1103C	conserved region Exo I (3'-5'-exonuclease domain)	ACV, FOS	-	not tested	not tested	not tested	not tested	not tested	DNA pol functional assay	9727026 8910584 14982924
I529M	A1587G	conserved region delta-region C (3'-5'-exonuclease domain)	ACV	BVDU	10.0x	1.3x	not tested	not tested	not tested	plaque reduction assay	20608173
K532T	A1595C	conserved region delta-region C (3'-5'-exonuclease domain)	ACV	FOS	EC <sub>50</sub> 887.5 µM	not tested	not tested	EC <sub>50</sub> <660.0 µM	not tested	plaque reduction assay	14670581
E545D	A1635T/C	conserved region delta-region C (3'-5'-exonuclease domain)	ACV, BVDU	-	10.0x	1.3x	not tested	not tested	not tested	plaque reduction assay	20608173
Y557S*	T1669A/ A1670G	conserved region delta-region C (3'-5'-exonuclease domain)	ACV, phosphonoacetic acid (PAA)	-	not given	not tested	not tested	not given	not tested	plaque reduction assay, DNA pol functional assay, mice <i>in vivo</i> assay	8910584 19691467
Q570R	C1708A/ A1709G	conserved region delta-region C (3'-5'-exonuclease domain)	ACV	FOS	EC <sub>50</sub> 7.1 µM	not tested	not tested	EC <sub>50</sub> 28.2 µM	not tested	yield reduction assay (enzyme linked virus inhibitory reporter assay - ELVIRA)	15456088
V573M*	G1717A	conserved region Exo III (3'-5'-exonuclease domain)	CDV	ACV, FOS	EC <sub>50</sub> 0.1 µM	not tested	not tested	EC <sub>50</sub> 6.9 µM	EC <sub>50</sub> 8.5 µM	plaque reduction assay, mice <i>in vivo</i> assay	10675401 17713155

D581A**	A1742C	conserved region Exo III (3'-5'-exonuclease domain)	phosphono- acetic acid (PAA)	-	not tested	not tested	not tested	EC <sub>50</sub> 330.0 µM	not tested	plaque reduction assay, DNA pol functional assay	12771406 8910584 8847505
L583V	C1747G	conserved region Exo III (3'-5'-exonuclease domain)	ACV	FOS	EC <sub>50</sub> 887.5 µM	not tested	not tested	EC <sub>50</sub> <660.0 µM	not tested	plaque reduction assay, DNA pol functional assay	14670581
E597D*	G1790T	conserved region delta-region C	ACV, PAA	-	10.0x	not tested	not tested	8.0x	not tested	plaque reduction assay	3034575
A605V*	C1814T	conserved region delta-region C	ACV, FOS	PCV, CDV	EC <sub>50</sub> 35.0 µM	not tested	EC <sub>50</sub> 12.4 µM	EC <sub>50</sub> >660.0 µM	EC <sub>50</sub> 2.6 µM	plaque reduction assay	15673740
Y608stop	insertion (G) nt 1788	conserved region delta-region C	ACV	-	EC <sub>50</sub> >25.0 µM	not tested	not tested	not tested	not tested	plaque reduction assay, crystal structure modeling	24055837
Q618H*	G1854T/C	conserved region delta-region C	ACV	BVDU, FOS, CDV	EC <sub>50</sub> 0.6 µM	EC <sub>50</sub> 0.004 µM	not tested	EC <sub>50</sub> 121.4 µM	EC <sub>50</sub> 0.4 µM	plaque reduction assay	17713155
V621S	G1861A/ T1862G	conserved region delta-region C	ACV	-	EC <sub>50</sub> 25.0 µM	not tested	not tested	not tested	not tested	plaque reduction assay, crystal structure modeling	24055837
A657T	G1969A	non-conserved region	ACV, BVDU, PCV	CDV, FOS	EC <sub>50</sub> >35.5 µM	EC <sub>50</sub> 9.7 µM	EC <sub>50</sub> >32.0 µM	EC <sub>50</sub> 61.1 µM	EC <sub>50</sub> 1.5 µM	modified dye uptake assay including formazan test	22155911
R700G*	A2098G	conserved region II	ACV, FOS	PCV	2.0x	not tested	not given	6.0x	not tested	plaque reduction assay, DNA pol functional assay	9497069 9796650
R700M**	G2099T	conserved region II	CDV	ACV, FOS	EC <sub>50</sub> 0.06 µM	0.4x	not tested	EC <sub>50</sub> 27.4 µM	EC <sub>50</sub> 7.8 µM	plaque reduction assay, DNA pol functional assay	12829822 10675401 17713155

L702H	T2105A	conserved region II (palm domain)	ACV, FOS, PCV	CDV	EC <sub>50</sub> 35.5 µM	not tested	EC <sub>50</sub> 194.7 µM	EC <sub>50</sub> 6.0 µM	EC <sub>50</sub> 0.3 µM	plaque reduction assay	12709344
L702P	T2105C	conserved region II (palm domain)	ACV, BVDU	-	128.0x	>257.0x	not tested	not tested	not tested	plaque reduction assay	20608173
V714M*	T2140A	conserved region II (palm domain)	ACV, FOS	BVDU, CDV	EC <sub>50</sub> 0.2 µM	EC <sub>50</sub> 0.01 µM	not tested	EC <sub>50</sub> 214.5 µM	EC <sub>50</sub> 0.5 µM	plaque reduction assay	17713155
V715G	T2144G	conserved region II (palm domain)	ACV, FOS, PCV	CDV	EC <sub>50</sub> >443.8 µM	not tested	EC <sub>50</sub> 176.0 µM	EC <sub>50</sub> >330.0 µM	EC <sub>50</sub> 0.04 µM	plaque reduction assay	12210436
V715M	G2143A	conserved region II (palm domain)	ACV	FOS, CDV	EC <sub>50</sub> 12.7 µM	not tested	not tested	EC <sub>50</sub> 42.7 µM	EC <sub>50</sub> 0.02 µM	plaque reduction assay	12829822
F716L	C2148A/G	conserved region II (palm domain)	ACV, FOS	CDV	1.8x	not tested	not tested	2.9x	2.9x	plaque reduction assay	20608173
A719T	G2155A	conserved region II (palm domain)	ACV, FOS	CDV	5.9x	not tested	not tested	2.2x	1.9x	plaque reduction assay	12829822
A719V	C2156T	conserved region II (palm domain)	ACV, BVDU, PCV	FOS, CDV	EC <sub>50</sub> >35.5 µM	EC <sub>50</sub> >35.2 µM	EC <sub>50</sub> 32.0 µM	EC <sub>50</sub> 120.1 µM	EC <sub>50</sub> 1.9 µM	plaque reduction assay, plaque reduction assay including formazan test, dye uptake assay, DNA reduction assay	22155911 18336925 23026414
S724N	G2171A	conserved region II (palm domain)	PCV, FOS	BVDU	contradictory results	EC <sub>50</sub> 0.4 µM	EC <sub>50</sub> 9.6 µM	EC <sub>50</sub> >422.4 µM	contradictory results	plaque reduction assay including formazan test, yield reduction assay (ELVIRA) DNA reduction assay	15040541 24747042 12829822 23026414
S725G	A2173G	conserved region II (palm domain)	FOS	-	not tested	not tested	not tested	EC <sub>50</sub> >660.0 µM	not tested	plaque reduction assay	12367650

F733C	T2198G	conserved region II (palm domain)	ACV	FOS	EC <sub>50</sub> >10.0 µM	not tested	EC <sub>50</sub> 107.3 µM	not tested	not tested	plaque reduction assay	24075863
E771Q	G2311C	non-conserved region (fingers domain)	ACV	FOS	EC <sub>50</sub> >443.8 µM	not tested	not tested	EC <sub>50</sub> <660.0 µM	not tested	plaque reduction assay	14670581
L774F*	C2320T	conserved region VI (fingers domain)	ACV, FOS	-	3.7x	not tested	not tested	3.2x	not tested	plaque reduction assay, DNA reduction assay, denaturing gradient gel electrophoresis, DNA pol functional assay	14694096 19420083
S775N	G2324A	conserved region VI (fingers domain)	ACV	FOS	EC <sub>50</sub> >10.0 µM	not tested	EC <sub>50</sub> 27.0 µM	not tested	not tested	plaque reduction assay	24075863
L778M	C2332A	conserved region VI (fingers domain)	ACV, FOS, CDV	-	5.5x	not tested	not tested	2.0x	2.0x	plaque reduction assay	8218229
D780N	G2338A	conserved region VI (fingers domain)	ACV, FOS	CDV	6.1x	not tested	not tested	2.2x	1.2x	plaque reduction assay	8218229
W781V*	T2341G G2342T	conserved region VI (fingers domain)	ACV, FOS	-	14.0x	not tested	not tested	3.0x	not tested	plaque reduction assay	25673718
L782I	C2344A	conserved region VI (fingers domain)	ACV, FOS	CDV	6.4x	not tested	not tested	2.3x	1.8x	plaque reduction assay	12829822
P797T*	C2389A	non-conserved region (fingers domain)	ACV, PAA	-	not given	not tested	not tested	not given	not tested	plaque reduction assay	2842788
E798K	G2392A	non-conserved region (fingers domain)	ACV, PCV, FOS	BVDU, CDV	EC <sub>50</sub> 177.2 µM	EC <sub>50</sub> 228.8 µM	EC <sub>50</sub> 132.4 µM	EC <sub>50</sub> 496.0 µM	EC <sub>50</sub> 3.0 µM	plaque reduction assay	23315323

L802F*	C2404T	non-conserved region (fingers domain)	ACV, FOS, CDV	BVDU	EC <sub>50</sub> 0.6 µM	EC <sub>50</sub> 0.02 µM	not tested	EC <sub>50</sub> 166.0 µM	EC <sub>50</sub> 0.6 µM	plaque reduction assay	17713155
V813M*	G2437A	conserved region III (fingers domain)	ACV, PCV, FOS	-	5.0x	not tested	3.0x	4.0x	not tested	plaque reduction assay	9497069
N815S**	A2444G	conserved region III (fingers domain)	ACV, PCV	BVDU, FOS, CDV	EC <sub>50</sub> 16.2 µM	EC <sub>50</sub> <0.2 µM	EC <sub>50</sub> >31.6 µM	EC <sub>50</sub> 24.8 µM	EC <sub>50</sub> 1.9 µM	plaque reduction assay	24747042 3034575
Y818C*	A2453G	conserved region III (fingers domain)	ACV, PCV, FOS, CDV	BVDU	EC <sub>50</sub> 31.1 µM	EC <sub>50</sub> 0.2 µM	EC <sub>50</sub> 6.0 µM	EC <sub>50</sub> >330.0 µM	EC <sub>50</sub> 2.1 µM	plaque reduction assay	24047739
T821M	C2462T	conserved region III (fingers domain)	ACV, CDV	BVDU	6.3x	0.2x	not tested	contradictory results	2.1x	plaque reduction assay, DNA pol functional assay	12829822 17713155
G841C*	G2521T	conserved region III (palm domain)	ACV, PCV, FOS, CDV	-	EC <sub>50</sub> 177.5 µM	not tested	EC <sub>50</sub> 20.0 µM	EC <sub>50</sub> >1320.0 µM	EC <sub>50</sub> 7.4 µM	plaque reduction assay	12709344
G841S	G2521A	conserved region III (fingers domain)	ACV	PAA	29.0x	not tested	not tested	2.6x	not tested	plaque reduction assay	3034575
R842S*	C2524A	conserved region III (fingers domain)	ACV, PCV	-	150x	not tested	4x	not tested	not tested	plaque reduction assay	9497069
M880T	T2639C	conserved region I (palm domain)	ACV	BVDU	10.0x	1.3x	not tested	not tested	not tested	plaque reduction assay	20608173
S889A*	T2665G	conserved region I (palm domain)	ACV, PAA	-	10.0x	not tested	not tested	225.0x	not tested	plaque reduction assay, DNA pol functional assay	8337848

F891C**	T2672G	conserved region I (palm domain)	ACV, PCV, FOS	CDV	10.0x	not tested	2.0x	10.0x	1.7x	plaque reduction assay, DNA pol functional assay	2173770 12829822 9497069
F891Y*	T2672A	conserved region I (palm domain)	ACV, PAA	-	EC <sub>50</sub> 10.0 µM	not tested	not tested	EC <sub>50</sub> >330.0 µM	not tested	plaque reduction assay	2173770
V892M*	G2674A	conserved region I (palm domain)	ACV, PAA	-	EC <sub>50</sub> 10.0 µM	not tested	not tested	EC <sub>50</sub> >330.0 µM	not tested	plaque reduction assay	2173770
G901V	G2702T	conserved region I (palm domain)	ACV	FOS	EC <sub>50</sub> 15.0 µM	not tested	not tested	not given	not tested	modified dye uptake assay including formazan test	26055375
D907V	A2720T	non-conserved region (palm domain)	ACV, FOS	CDV	3.8x	not tested	not tested	2.3x	1.6x	plaque reduction assay, cell growth assay	12829822 16982796
I922N*	T2765A	non-conserved region (palm domain)	FOS	CDV	not tested	not tested	not tested	EC <sub>50</sub> 627.0 µM	EC <sub>50</sub> 0.74 µM	plaque reduction assay	12709344
Y941H	T2821C	conserved region VII (palm domain)	ACV, CDV	-	9.4x	not tested	not tested	contradictory results	0.4x	plaque reduction assay, DNA pol functional assay	14694096 12829822
V958L*	G2872C	conserved region V (thumb domain)	ACV, FOS, PCV	CDV	EC <sub>50</sub> >27.5 µM	not tested	EC <sub>50</sub> 17.2 µM	EC <sub>50</sub> >660.0 µM	EC <sub>50</sub> 4.1 µM	plaque reduction assay	15673740
R959H*	G2876A	conserved region V (thumb domain)	ACV, FOS, CDV	BVDU	EC <sub>50</sub> 0.3 µM	EC <sub>50</sub> 0.21 µM	not tested	EC <sub>50</sub> 230.0 µM	EC <sub>50</sub> 0.5 µM	plaque reduction assay	17713155 15673740
K960R*	A2879G	conserved region V (thumb domain)	CDV	ACV, BVDU, FOS	EC <sub>50</sub> 0.2 µM	EC <sub>50</sub> 0.08 µM	not tested	EC <sub>50</sub> 22.9 µM	EC <sub>50</sub> 2.3 µM	plaque reduction assay	17713155

N961K**	C2883G/A	conserved region V (thumb domain)	ACV	PCV, FOS, CDV	5.3x	not tested	not given	0.8x	1.4x	plaque reduction assay, DNA pol functional assay	12829822 9497069 2842788
W998L*	G2993T	non-conserved region (thumb domain)	ACV, CDV	BVDU, FOS	EC <sub>50</sub> 0.1 µM	EC <sub>50</sub> 0.01 µM	not tested	EC <sub>50</sub> 35.0 µM	EC <sub>50</sub> 1.6 µM	plaque reduction assay	17713155
I1028T	T3083C	non-conserved region (thumb domain)	CDV	BVDU	contradictory results	EC <sub>50</sub> 0.03 µM	not tested	contradictory results	EC <sub>50</sub> 1.9 µM	plaque reduction assay, DNA pol functional assay	12829822 17713155
D1070N*	G3208A	non-conserved region (thumb domain)	ACV, FOS	BVDU, CDV	61.0x	0.1x	not tested	2.7x	contradictory results	plaque reduction assay, <i>mice in vivo assay</i>	17713155 19691467
H1228D	C3682G	non-conserved region (thumb domain)	ACV	-	EC <sub>50</sub> >25.0 µM	not tested	not tested	not tested	not tested	plaque reduction assay, crystal structure modeling	24055837