

Table 215.2. CMV mutations conferring resistance to GCV.

Amino acid mutation	Fold increase EC ₅₀	References	Amino acid mutation	Fold increase EC ₅₀	References
CMV UL97 mutations			N408K	4.2	Lurain and Chou (2010)
L405P	2.5	Chou (2010)	N408S	3.1	Chou (2015)
M460I *	5	Chou <i>et al.</i> (2002)	N410K	2.9	Chou <i>et al.</i> (2003)
M460T	9.3	Chou (2010)	F412C	4.2	Lurain and Chou (2010)
M460V	8.3	Chou <i>et al.</i> (2002)	F412V	4.3	Cihlar <i>et al.</i> (1998)
V466G	3.5	Lurain and Chou (2010)	D413A	6.5	Lurain and Chou (2010)
C518Y	12	Chou (2015)	D413E	4.8	Chou <i>et al.</i> (2003)
H520Q	10	Chou <i>et al.</i> (2002)	D413N	3.8	Chou (2015)
P521L	17	Chou (2015)	L501I	6	Cihlar <i>et al.</i> (1998)
del 591-594	3–10	Chou <i>et al.</i> (2002)	T503I	2.9	Chou <i>et al.</i> (2003)
del 591-607	6.2	Chou <i>et al.</i> (2002)	K513E	5	Cihlar <i>et al.</i> (1998)
C592G	2.9	Chou <i>et al.</i> (2002)	K513N	6	Lurain and Chou (2010)
A594E	3	Chou (2010)	K513R	3.7	Chou (2015)
A594G	13.5	Lurain and Chou (2010)	L516R	2.1	Chou <i>et al.</i> (2003)
A594P	NA	Lurain and Chou (2010)	I521T	3.1	Lurain and Chou (2010)
A594T	2.7	Chou <i>et al.</i> (2002)	P522A	3	Lurain and Chou (2010)
A594V	8.3	Chou <i>et al.</i> (2002)	P522S	3.1	Cihlar <i>et al.</i> (1998)
L595F	15.7	Chou <i>et al.</i> (2002)	del 524	3.5	Chou (2015)
L595S	9.2	Chou <i>et al.</i> (2002)	V526L	5.5	Chou (2015)
L595W	5.1	Chou <i>et al.</i> (2002)	C539G	3.1	Chou (2015)
del 595	13.3	Lurain and Chou (2010)	L545S	3.5	Cihlar <i>et al.</i> (1998)
del 595-603	8.4	Lurain and Chou (2010)	E756K	3.5	Chou <i>et al.</i> (2003)
E596G	2.3	Chou <i>et al.</i> (2002)	I726T	2	Chou (2015)
G598S	NA	Lurain and Chou (2010)	L773V	3	Chou (2015)
K599T	5.3	Lurain and Chou (2010)	L776M	2.5	Lurain and Chou (2010)
del 600	1.9	Chou <i>et al.</i> (2002)	V781I	1–4	Cihlar <i>et al.</i> (1998); Chou (2010)
del 601	NA	Lurain and Chou (2010)	V787L	2.4	Lurain and Chou (2010)
del 601-603	11	Lurain and Chou (2010)	L802M	1.1–3.5	Cihlar <i>et al.</i> (1998)
C603R	3.6–8.3	Chou (2010)	A809V	2.6	Lurain and Chou (2010)
C603S	1.9	Chou (2010)	V812L	2.5	Lurain and Chou (2010)
C603W	8	Chou <i>et al.</i> (2002)	T813S	2.5	Lurain and Chou (2010)
C607F	1.9	Chou <i>et al.</i> (2002)	T821I	4.5	Cihlar <i>et al.</i> (1998)
C607Y	12.5	Chou <i>et al.</i> (2002)	A834P	5.4	Lurain and Chou (2010)
A613V	2.3	Chou (2015)	G841A	3.2	Lurain and Chou (2010)
E655K	1.7	Chou (2015)	G841S	2.2	Chou (2015)
CMV UL54 polymerase mutations			del 981-982	8.3	Lurain and Chou (2010)
D301N	2.6	Chou <i>et al.</i> (2003)	A987G	5.3	Lurain and Chou (2010)
N408D	4.9	Cihlar <i>et al.</i> (1998)			

*Boldface type indicates the most common UL97 mutations.
Abbreviations: NA: data not available.

mary CMV disease after receiving valaciclovir prophylaxis had confirmed UL94 or UL54 resistance mutations (Eid *et al.*, 2008b). One report noted a new viral UL97 mutation that conferred a 15-fold greater GCV resistance in an allogeneic stem cell recipient receiving VGCV (Marfori *et al.*, 2007). Reddy *et al.* (2007) reviewed their experience with GCV-resistant CMV infections in lung transplant recipients. CMV infection occurred in about half of transplanted patients (113 of 210), with GCV resistance developing in 6 of the 113 treated patients. All CMV strains had UL97 mutations, with three also having UL54 (polymerase) mutations.

GCV resistance should be suspected when clinical disease relapses or progresses while a patient is receiving GCV or

VGCV. Genotypic assays for CMV mutations associated with GCV resistance are now available in commercial laboratories. Guidelines for the treatment of GCV-resistant CMV disease are available for transplant patients (Kotton *et al.*, 2013; Tomblyn *et al.*, 2009). For patients with HIV-associated, GCV-resistant CMV disease, continuously updated treatment guidelines are available online (AIDSinfo, nd).

Mutations in the DNA polymerase of HSV that map to a 2.2-kilobase-pair region are responsible for the development of HSV resistance to GCV (Crumpacker *et al.*, 1984; St Clair *et al.*, 1984). High-level GCV resistance emerges with mutations in HSV UL54, which results in changes to the catalytic subunit of the DNA polymerase; these mutations also result