Table 215.1. Selected viruses shown to be susceptible to GCV.

Virus	Mean EC_{50} value (μM)	References
Cytomegalovirus	1.7–5.9	Plotkin *et al.* (1985); Cole and Balfour (1987); Boivin *et al.* (1993)
Herpes simplex virus type 1	0.57	Collins and Oliver (1985)
Herpes simplex virus type 2	1.67	Collins and Oliver (1985)
	10	Faulds and Heel (1990)
Epstein–Barr virus	0.05–1	Cheng *et al.* (1983b); Lin *et al.* (1984)
Varicella–zoster virus	0.6–8	Field *et al.* (1983); Collins and Oliver (1985)
Human herpesvirus type 6	1–4	Agut *et al.* (1989); Russler *et al.* (1989)
	24	Akesson-Johansson *et al.* (1990)
Human herpesvirus type 8	2.7–4	Kedes and Ganem (1997)
	5.1	Medveczky *et al.* (1997)
Adenovirus	47	Trousdale *et al.* (1994)

1 μg/ml is equivalent to approx. 3.6 μM.

HERPES SIMPLEX VIRUS

Although herpes simplex virus (HSV) is inhibited by low concentrations of GCV, there are differences in susceptibility among HSV strains, and variable results have been obtained depending on the cell types and method used (Smith *et al.*, 1982a). *In vitro,* GCV is more potent than aciclovir against HSV type 1 (HSV-1) and HSV type 2 (HSV-2). Collins and Oliver (1985) reported that the mean EC_{50} of GCV was approximately 3-fold higher for HSV-2 than for HSV-1 (1.67 and 0.57 μM, respectively). The reported EC_{50} of GCV for strains of HSV-1 and -2 as measured by plaque reduction assays ranged from 0.2 to 2.4 μM (Smee *et al.*, 1983; Smee *et al.*, 1985b; Pulliam *et al.*, 1986), although the mean EC_{50} for HSV-2 has been as high as 10 μM in some reports (Faulds and Heel, 1990). The EC_{90} for GCV against HSV-1 in a microtiter virus yield reduction assay was 0.7 μM (Prichard *et al.*, 1990). Other investigators have found a marked reduction (up to 300,000-fold) in virus titers and viral DNA levels when HSV-1-infected Vero cells were cultured in the presence of 5–30 μM GCV (Chun and Park, 1987; van der Horst *et al.*, 1987).

Intraperitoneal GCV given to mice with an intraperitoneal HSV-2 infection provided moderate protection against systemic infection (Yang and Datema, 1991). Several groups have shown that GCV prophylaxis prevented the development of herpetic lesions in a HSV-2 murine model at a dose of 5–10 mg/kg (Klein and Friedman-Kien, 1985; Smee *et al.*, 1985b). In addition, GCV prevented encephalitis due to murine HSV-1 in doses of less than 10 mg/kg and herpetic vaginitis at a daily dose of 50 mg/kg (Smee *et al.*, 1983; Smee *et al.*, 1985b). Early studies (Fraser-Smith *et al.*, 1983) showed that treating guinea pigs with GCV commencing within 3 hours of intravaginal inoculation of HSV-2 prevented the development of primary infection in 33% of animals, whereas a 24-hour delay after inoculation resulted in a 100% infection rate. GCV given by intravitreal injection or by eye drops did not completely protect rabbits from retinitis caused by experimental HSV-1 infection (Naito *et al.*, 1991; Flores-Aguilar *et al.*, 1994), although in an earlier report 0.3% GCV ointment given five times daily for 4 days to rabbits infected with HSV was effective in preventing lesions (Shiota *et al.*, 1987).

VARICELLA–ZOSTER VIRUS

GCV inhibited the replication of varicella–zoster virus (VZV), with mean EC_{50} values ranging from 0.6 to 8 μM (Field *et al.*, 1983; Collins and Oliver, 1985). Matthews and Boehme (1988) reported that GCV had similar efficacy to aciclovir in inhibiting the replication of VZV. GCV improved the outcome of simian VZV infection of African green monkeys when administered at a dose of 10 mg/kg twice daily for 10 days (Soike *et al.*, 1987).

EPSTEIN–BARR VIRUS

GCV is more active against Epstein–Barr virus (EBV) than aciclovir. The EC_{50} of GCV for EBV is 0.05–1 μM, most commonly assessed by inhibition of genome replication, with an EC_{90} of 3–5 μM (Cheng *et al.*, 1983b; Lin *et al.*, 1984; Lin *et al.*, 1986; Yao *et al.*, 1993). GCV suppresses replication of EBV in human lymphoblastoid cells during 70 days of continuous exposure in culture without eradicating the infection; upon removal of the drug, genome copy number returns to baseline (van der Horst *et al.*, 1987). Although GCV has a prolonged inhibitory effect on active viral DNA replication, replication of episomal virus is unaffected by GCV because it does not require a virus-encoded DNA polymerase (Lin *et al.*, 1984). GCV therapy inhibited the development of B-cell lymphomas in severe combined immunodeficiency (SCID) mice engrafted with human peripheral blood lymphocytes and subsequently infected with EBV (Boyle *et al.*, 1992).

HUMAN HERPESVIRUS TYPE 6

GCV has been reported to inhibit the *in vitro* replication of human herpesvirus type 6 (HHV-6) with an EC_{50} of 1–4 μM (Agut *et al.*, 1989; Russler *et al.*, 1989; Burns and Sandford, 1990), although other investigators have found higher EC_{50} values around 25 μM (Akesson-Johansson *et al.*, 1990) with only partial inhibition of viral expression (Streicher *et al.*, 1988).

ADENOVIRUSES

Several strains of adenoviruses (subgenus D) have been shown to be susceptible to GCV *in vitro*, although it has only limited activity against other human adenoviruses. GCV has been reported to have some activity against human adenovirus type 5 that is associated with severe ocular disease (Wildner *et al.*, 2003). As assessed by plaque reduction, the ED_{50} was 47 μM. Three weeks of topical GCV (3%) treatment of eyes of cotton rats inoculated with this adenovirus strain resulted in a statistically insignificant trend toward virus suppression when compared with placebo (Trousdale *et al.*, 1994).