has been achieved at 5 μM (Sandstrom *et al.*, 1985). Replication of HIV-1 in H9 T-cell lines was inhibited by 50% by foscarnet in concentrations ranging from 10 to 25 μM (Sandstrom *et al.*, 1985; Koshida *et al.*, 1989). In peripheral blood mononuclear cells, HIV was inhibited by a mean concentration of foscarnet of 29.7 μM (Cox *et al.*, 1994). Foscarnet was active against acute HIV-1 infection of cultured human macrophages, but like zidovudine and other reverse transcriptase inhibitors, was inactive toward chronically infected macrophages (Crowe *et al.*, 1989). Foscarnet reversibly inhibits cell growth by 50% at concentrations of approximately 1000 μM, significantly higher concentrations than those required for inhibition of virus replication (Stenberg and Larsson, 1978).

The *in vitro* data showing that HIV-1 is susceptible to foscarnet have generally been confirmed by *in vivo* studies. For example, 10 HIV-infected patients received 50 mg foscarnet three times daily for 4 weeks, resulting in a 2.1 $\log_{10}$ decrease in the HIV RNA concentration in plasma (HIV viral load), from 4.7 to 2.6 $\log_{10}$ RNA copies/ml. HIV viral load returned to baseline within a week of stopping therapy (Bergdahl *et al.*, 1998). Other clinical trials have confirmed the *in vivo* activity of foscarnet against HIV (Jacobson *et al.*, 1991b; Devianne-Garrigue *et al.*, 1998).

HEPADNAVIRUSES

The human hepatitis B virus (HBV) DNA polymerase (a reverse transcriptase) was inhibited by 10–100 μM foscarnet (Oberg, 1983), and both human and duck HBV were susceptible to foscarnet (Sherker *et al.*, 1986; Fourel *et al.*, 1994; Civitico *et al.*, 1996). *In vivo* studies have confirmed the *in vitro* studies, with foscarnet therapy, resulting in decreases in HBV DNA in plasma as well as reductions in HBeAg and improving liver function tests (Han *et al.*, 2005).

OTHER VIRUSES

Foscarnet, at a concentration of 20 μM, inhibited the RNA polymerase of influenza virus (Helgstrand *et al.*, 1978; Stridh *et al.*, 1979; Oberg, 1983; Strid *et al.*, 1989). Replication of influenza virus was inhibited by 400 μM foscarnet (Oberg, 1983). Rotavirus replication in MA104 cells was inhibited by foscarnet in a dose-dependent manner, with inhibition of both plus- and minus-strand RNA synthesis (Rios *et al.*, 1995). There are no *in vivo* data.

2b. Emerging resistance and cross-resistance

CYTOMEGALOVIRUS

There are numerous reports of foscarnet-resistant strains of CMV, induced by either culturing wild-type isolates in increasing foscarnet concentrations *in vitro* (Sullivan and Coen, 1991; Gilbert *et al.,* 2011) or in clinical isolates from patients treated with foscarnet or ganciclovir (Knox *et al.*, 1991; Leport *et al.*, 1993; Jabs *et al.*, 1998; Cihlar *et al.,* 1998; Chou *et al.,* 1997; Chou *et al.*, 1998; Gilbert *et al.*, 2002; Weinberg *et al.,* 2003; Springer *et al.,* 2005; Ducancelle *et al.,* 2005 & 2007; Lurain and Chou, 2010; Komatsu *et al.,* 2014). In general, the frequency of these resistant CMV strains from foscarnet-treated patients appears to be relatively low, with Weinberg's data indicating the risk of foscarnet resistance increases from 13% after 6 months of treatment to 37% after 1 year of therapy (Tachedjian *et al.*, 1994; Weinberg *et al.,* 2003).

All known mutations mediating phenotypic resistance to foscarnet are located in the DNA polymerase (*UL54*) gene (Smith *et al.,* 1997; Lurain *et al.,* 2001; Komatsu *et al.*, 2014). *UL97* mutations in CMV only mediate resistance to ganciclovir, a drug requiring initial intracellular monophosphorylation by the *UL97* gene for it to be transformed into its active, triphosphate form (Lurain *et al.,* 2001; Smith *et al.,* 1997). These *UL97* mutations never affect susceptibility to foscarnet. In contrast, polymerase (*UL54*) mutations are invariably found in CMV strains resistant to foscarnet, but these mutations may mediate cross-resistant to ganciclovir (a nucleoside analog) or cidofovir (a monophosphorylated nucleoside, called nucleotide) depending on the specific *UL54* mutation, and they are usually seen only in strains highly resistant to foscarnet (Gilbert *et al.,* 2011). On the other hand, the *UL54* mutations that confer ganciclovir resistance usually appear after prolonged treatment with that drug, usually also mediate cidofovir resistance, but only occasionally confer foscarnet resistance.

Multiple mutations in the *UL54* gene have been found in CMV strains resistant to foscarnet (Table 219.2). Both single mutations and multiple mutations are associated with resistance, with a tendency for higher level resistance to be associated with multiple mutations (Gilbert *et al.,* 2011). However, the complexity of the relation between molecular changes and the degree of resistance in the CMV strain under study was emphasized in studies by Weinberg, Smith and their colleagues (Weinberg *et al.,* 2003; Smith *et al.,* 1997) as well as in review articles (Chou and Hakki, 2011; Komatsu *et al.*, 2014). The problem is that even strains of CMV apparently made resistant to foscarnet on the basis of a single polymerase mutation almost always harbor multiple polymorphisms in the polymerase gene, and the influence of these polymorphisms on drug resistance is seldom known (Hakki and Chou, 2011; Komatsu *et al.,* 2014). This problem is emphasized by differences in the degree of resistance (usually assessed as fold increase compared with wild-type virus) among strains with the same main mutation (Komatsu *et al.,* 2014).

Although an increasing number of CMV strains have been sequenced to determine the relationship between *UL54* or *UL97* mutations and antiviral drug resistance, that number is insufficient to reliably associate the relationship between signature resistance mutations (as in Table 219.2) and drug resistance at a phenotypic level, given the background of multiple mutations considered to be possible polymorphisms (Komatsu *et al.,* 2014). Phenotypic resistance of HIV-1 strains to multiple antiretroviral drugs and the efficacy of these drugs for treating specific HIV-1 strains has been, and is continually being, assessed quite rigorously by analysis of genomic mutations, but that high level of certainty is based on analysis