active site (Gilbert *et al.,* 2011). Passaging CMV in increasing concentrations of ganciclovir resulted in 11 CMV strains with polymerase mutations, 10 with single mutations, and 1 with double mutations (L545S + P829S). Of these 11 strains, 5 had high-level (> 2.0) resistance to ganciclovir and 4 were highly resistant to cidofovir, but only 2 (18%) of the 11 strains with *UL54* mutations had high-level foscarnet resistance, which was due to two single *UL54* mutations (V787L and V964L); it is interesting that both of these strains were largely fully susceptible to ganciclovir and cidofovir. In contrast, passage in increasing concentrations of foscarnet (effectively primary foscarnet therapy) resulted in 13 CMV strains with nine single mutations and four double mutations. Of these 13 strains, 6 were highly resistant to ganciclovir and 10 (77%) were resistant to foscarnet. Of the latter 10 strains, 7 had high-level resistance and 3 were resistant to foscarnet and cross-resistant to either ganciclovir or cidofovir (Gilbert *et al.,* 2011).

Gilbert's data clearly show that if CMV disease is treated primarily with foscarnet, and if it results in foscarnet resistance, that resistance is invariably due to *UL54* mutations. In contrast primary ganciclovir therapy is much less likely to drive primary foscarnet resistance because resistance is usually due to the mutations in the *UL97* monophosphorylating gene, which never alters foscarnet efficacy. However, prolonged ganciclovir therapy as sometimes used in patients with significant immunosuppression (e.g. for lung transplantation) may drive both *UL97* and *UL54* mutations, potentially resulting in foscarnet resistance. This situation was documented in a recent paper on treatment of CMV in patients with lung transplants (Minces *et al.,* 2014).

Rapid development of foscarnet-resistant CMV on the basis of a E756K *UL54* mutation without a prior ganciclovir-induced *UL97* mutation was seen in a highly immunosuppressed patient with a hematopoietic stem-cell transplant (Gregg *et al.,* 2014), a situation in which ganciclovir is often contraindicated because of neutropenia.

Three CMV isolates resistant to both ganciclovir and foscarnet each contained a well-known ganciclovir resistance mutation in the viral *UL97* phosphotransferase sequence as well as a mutation (A809V) in conserved region 3 of the polymerase gene (Chou *et al.*, 1998). A recombinant virus containing only the A809V mutation showed 6.3-fold increased foscarnet resistance and 2.6-fold increased ganciclovir resistance. Further experience has shown that this mutation is common in FOS-treated patients and a clinically significant viral genetic marker for decreased susceptibility to both foscarnet and ganciclovir (Chou *et al.*, 1998). Scott and colleagues (2007) studied three CMV isolates from patients failing to respond to foscarnet or ganciclovir. A novel polymerase mutation, A834P, was identified that conferred ganciclovir, cidofovir, and foscarnet resistance; it has also been found frequently in foscarnet-treated patients. A CMV strain recovered from two pediatric hematopoietic stem cell transplant recipients that was resistant to both ganciclovir and foscarnet had novel polymerase mutations (T838A) and D588N) and showed significantly decreased fitness *in vitro* (Springer *et al.*, 2005).

Chou *et al.* (2005) used a new marker transfer technique to insert 10 novel polymerase mutations (9 observed in clinical isolates) into recombinant CMV strains. Mutations E756K, and E756D, which are not located in recognized functional polymerase domains, each conferred foscarnet resistance to the recombinant virus (Chou *et al.*, 2003). Further phenotyping of CMV polymerase region 3 mutations from clinical specimens showed that T813S and G841A each conferred foscarnet resistance and increased ganciclovir resistance by approximately threefold; adding the *UL97* mutation C592G increased ganciclovir resistance to approximately sixfold (Chou *et al.*, 2007). A two-codon deletion in the polymerase (981–982) also mediated combined ganciclovir, cidofovir, and foscarnet resistance (Chou *et al.*, 2000). It is not surprising that foscarnet salvage therapy of multidrug-resistant HIV infection in one patient also resulted in the development of CMV resistance due to a T700A mutation in *UL54* (Boutolleau *et al.,* 2012).

Some understanding of the role of specific mutations in mediating resistance or hypersusceptibility of the CMV polymerase to foscarnet at a molecular level is now available (Tchesnokov *et al.*, 2006) with the caveats mentioned earlier.

There was no cross-resistance of CMV strains between the failed investigational drug maribavir, at least in the small series studied (Drew *et al.*, 2006), nor was there cross-resistance with another investigational drug, letermovir (Goldner *et al.,* 2014), which was expected because resistance to letermovir primarily maps to the terminase gene *UL56* (Chou, 2015).

HERPES SIMPLEX VIRUSES

Foscarnet-resistant HSV strains (see Table 219.3) have been defined by some investigators as having reduced susceptibility (at the EC_{50} level) to concentrations of foscarnet > 100 μg/ml (approximately 330 μM) (Safrin *et al.*, 1994a), whereas others use a cut-off of 400 μM (Drew, 1996). It is generally agreed that these phenotypic drug resistance assays may be difficult to perform, and results are not always predictive of the clinical response of the drug (Wagstaff and Bryson, 1994).

Because aciclovir and famciclovir are the drugs most commonly used to treat HSV infections, most resistance is to those drugs, and that resistance is almost invariably mediated by thymidine kinase mutations. Such strains would be fully susceptible to foscarnet (Stranska *et al.*, 2004; Stranska *et al.*, 2005; Birch *et al.*, 1990; Verdonck *et al.*, 1993). Foscarnet resistance is uncommon in unselected HSV isolates, accounting for 5% in a screen of 320 clinical isolates from 197 patients (Safrin *et al.*, 1994b). Consequently, foscarnet-resistant HSV strains with polymerase mutations (Schmit and Boivin, 1999) are relatively rare and often associated with clinical failure of both drugs related to long-term treatment of resistant HSV infections in immunocompromised patients (Birch *et al.*, 1992; Chen *et al.*, 2000).

Foscarnet-resistant clinical isolates of HSV may retain susceptibility to penciclovir (Safrin and Phan, 1993), cidofovir (Bryant *et al.*, 2001), or to trifluridine (Birch *et al.*, 1992). A foscarnet-resistant HSV-2 strain has been isolated from a patient treated with foscarnet and zidovudine whose strain