in association with aciclovir therapy in patients with end-stage renal disease (Johnson *et al*., 1985; Gill and Burgess, 1990; Davenport *et al*., 1992). Tomson *et al*. (1985) described psychiatric side effects, including hallucinations and depression, in adult patients with chronic renal failure after the use of aciclovir in doses higher than those recommended. Neurologic findings associated with intravenous aciclovir treatment include lethargy, agitation, tremor, disorientation, dysarthria, ataxia, myoclonus, hyperesthesia, hyperacusis, transient hemiparesthesia, seizures, and coma (Wade and Meyers, 1983; Johnson *et al*., 1985; Johnson *et al*., 1994; Rajan *et al*., 2000). Improvement or resolution of symptoms occurs within 2 weeks after cessation of aciclovir therapy. An abnormal electroencephalogram is a consistent feature. In a retrospective analysis, Das *et al*. (2006) reported that 15% of 167 renal transplant recipients treated with oral valaciclovir developed neuropsychiatric effects, mainly hallucinations and confusion, within a mean of 4 days after the start of valaciclovir prophylaxis; these were rapidly reversible on cessation of therapy.

## 6c. Gastrointestinal toxicity

Of 23 patients given intravenous aciclovir for zoster, nearly half had two or more of the following symptoms: nausea, vomiting, abdominal pain, and light-headedness. These symptoms appeared to be associated with peak serum aciclovir levels in excess of 25 μg/ml (Bean and Aeppli, 1985). In a more recent study, adverse gastrointestinal symptoms developed in 8% of patients with genital herpes who were treated with a high dose (4 g/day) of oral aciclovir (Wald *et al*., 1994). There is at least one report of aciclovir-associated colitis (Moshkowitz *et al*., 1993). In a phase I study of valaciclovir dosed at either 1 or 2 g four times daily for 30 days, the main reported side effects were gastrointestinal, with nausea, vomiting, diarrhea, and abdominal pain in up to one third of patients; no renal or neurologic side effects were noted, but 4 patients developed grade 3 or 4 neutropenia. None of the side effects observed appeared to be drug related (Jacobson *et al*., 1994).

## 6d. Hemopoietic toxicity

*In vitro* aciclovir has little effect on human bone marrow in concentrations < 50 μg/ml (McGuffin *et al*., 1980; Parker *et al*., 1982). Bean and Fletcher (1985) described neutropenia in three immunocompromised patients who were given high-dose aciclovir therapy and who also had received myelotoxic agents within the previous 30 days. More recently neutropenia has been well described in association with aciclovir therapy (30 mg/kg/day) in an infant (Feder *et al*., 1995). Megaloblastic hemopoiesis without detectable changes in the peripheral blood may occur (Amos and Amess, 1983). A child developed transient leukopenia and erythroblastopenia during intravenous aciclovir therapy that responded promptly to cessation of therapy (Tuncer *et al*., 1989).

## 6e. Thrombotic microangiopathy

In an AIDS Clinical Trials Group (ACTG) study (Trial 204) of patients with advanced HIV infection randomized to receive oral prophylaxis against cytomegalovirus disease (with valaciclovir 2 g four times per day or aciclovir, either high dose, 800 mg, four times daily, or low dose, 400 mg, twice daily), manifestations resembling thrombotic microangiopathy developed significantly more frequently in the valaciclovir-treated subjects compared with those receiving oral aciclovir, and there was a trend toward earlier mortality in those who received high-dose valaciclovir (Bell *et al*., 1997; Feinberg *et al*., 1998). There are no reports of this adverse reaction in immunocompetent patients treated with valaciclovir doses up to 3 g/day; doses of up to 3 g/day have been used in patients with HIV infection and doses of up to 8 g/day have been used in renal and bone marrow transplant patients without any apparent increase in the risk of thrombotic microangiopathy (Lowance *et al*., 1999; Ljungman *et al*., 2002; Winston *et al*., 2003; Reischig *et al*., 2008). Nonetheless, doses of valaciclovir > 3 g/day should be used with caution in immunocompromised patients and should generally not be used in patients with advanced HIV infection.

## 6f. Effects on immune responses

Aciclovir has minimal effects on human lymphocytic cell responses *in vitro* (Wingard *et al*., 1983). Systemic treatment with aciclovir diminishes the humoral antibody response to HSV in patients with initial episodes of genital herpes (Corey *et al*., 1983b; Bernstein *et al*., 1984); it also appears to delay the development and diminish the peak of *in vitro* lymphocyte transformation responses to inactivated HSV antigens in such patients (Lafferty *et al*., 1984). Long-term chemosuppression also suppresses HSV IgG antibody concentrations (Erlich *et al*, 1988). These alterations probably occur because aciclovir treatment, especially long-term chemosuppression, reduces both the frequency and duration of viral shedding and hence antigenic stimulation. Clinical presentation and subsequent immunologic response of the first recurrences of genital herpes are unaltered after aciclovir treatment of the initial episode, but the immunologic response in patients with an existing compromised immune response is unknown (Lafferty *et al*., 1984).

## 6g. Dermatologic toxicity

Allergic contact dermatitis attributed to aciclovir or the propylene glycol in aciclovir cream has been reported infrequently (Valsecchi *et al*., 1990; Goday *et al*., 1991; Kim and Kim, 1994). Rarely cutaneous vesicular eruptions may occur in patients receiving aciclovir (Buck *et al*., 1993). Successful aciclovir desensitization has been reported in a patient with recurrent mucocutaneous HSV infection who developed angioedema with oral aciclovir therapy (Henry *et al*., 1993). Topical aciclovir may cause transient burning when applied