suggested that delavirdine slightly inhibited amprenavir metabolism (Justesen *et al*., 2003). The high delavirdine dose combination was considered most suitable for clinical use, but because of the large interindividual variation in steady-state concentrations, the authors suggested that the combination should be supported by therapeutic drug monitoring and restricted to certain patients. Contrary results were seen in another study, which reported that delavirdine-boosted amprenavir trough levels more than 10-fold (Engelhorn *et al*., 2004).

OTHER ANTI-INFECTIVES

Co-administration of delavirdine with either rifabutin or rifampicin, inducers of cytochrome P-450, resulted in 5- and 27-fold increases, respectively, in the clearance of delavirdine; rifampicin co-administration decreased trough plasma concentrations of delavirdine to < 0.05 μM (Borin *et al*., 1997b; Borin *et al*., 1997c). The rifabutin AUC was increased by 100% by co-administration with delavirdine. Co-administration of clarithromycin in a dose of 500 mg twice daily resulted in a 44% increase in the AUC of delavirdine (ViiV Healthcare, product information, 2012). Ketoconazole increased the plasma trough concentration of delavirdine by 80%, whereas co-administration of fluconazole and delavirdine to healthy volunteers showed that there was no effect on the pharmacokinetics of either drug (Borin *et al*., 1997a).

OTHER DRUGS

Fluoxetine increases the trough plasma concentration of delavirdine by about 50% (ViiV Healthcare, product information, 2008). Benzodiazepines, antihistamines such as terfenadine and astemizole, and antimotility agents such as cisapride may all have increased plasma levels if co-administered with delavirdine. Anticonvulsants such as phenytoin and phenobarbital are predicted to decrease delavirdine plasma concentrations (ViiV Healthcare, product information, 2012).

Delavirdine significantly decreased methadone clearance and increased the methadone elimination half-life, resulting in an increase in AUC of 19% and in C_{min} of 29%. The combined effect of delavirdine on the total concentration of levo-alpha acetylmethadol (LAAM) and its active metabolites, norLAAM and dinorLAAM, was to significantly increase AUC by 43%, C_{max} by 30%, and C_{min} by 59% while decreasing time to maximum concentration (t_{max}) (McCance-Katz *et al*., 2006a). Delavirdine increased buprenorphine concentrations, but the effect was not considered clinically significant, and no alterations in buprenorphine effects in the volunteers being studies were seen (McCance-Katz *et al*., 2006a; McCance-Katz *et al*., 2006b).

Castro and Gutierrez (2002) report a case of rhabdomyolysis with renal failure thought to be due to delavirdine raising plasma concentrations of atorvastatin.

6. ADVERSE REACTIONS AND TOXICITY

From phase I/II clinical trials of delavirdine, the most frequent adverse reactions were dermatologic. Mild headache, nausea, and fatigue have been reported but were not consistently related to delavirdine (ViiV Healthcare, product information, 2012).

6a. Dermatologic toxicity

A rash occurs in 30–45% of patients given delavirdine, although in some studies it was reported in < 20% of subjects. It appears to be more commonly seen in patients with CD4 counts < 100 cells/μ than in those with CD4 counts > 300 cells/μl. In a dose-finding monotherapy study of 113 subjects, rash developed in 36% (Para *et al*., 1999). These investigators and others have noted that the rashes are often transient, and treatment can either be continued until the rash fades or be restarted after it fades. In ACTG Study 261, 30% of 407 subjects receiving delavirdine developed a rash, which was severe in only one case (Friedland *et al*., 1999). In another prospective treatment trial, rash occurred in 52% of 89 subjects given delavirdine (Been-Tiktak *et al*., 1999). In an early phase I/II study, the incidence of rash was 44%; it was transient in all cases (Davey *et al*., 1996).

Rashes usually develop between 1 and 2 weeks after starting delavirdine treatment and are unrelated to dose or plasma concentration of drug. The rash is typically diffuse and maculopapular. Usually there are no associated clinical findings although the rash may be pruritic. Dose titration does not significantly reduce the risk of rash. In one study comparing dermatologic complications of nevirapine and delavirdine, the rash due to delavirdine occurred more often but nevirapine rashes were more severe and resulted in hospitalization more frequently (Gangar *et al*., 2000). These same authors found a high frequency of cross-sensitization between these two drugs, suggesting that if a rash was found with one of them, the likelihood of it occurring on challenge with the other was about 70%.

Stevens-Johnson syndrome has been rarely reported (1 case in 1000) (Freimuth, 1996).

6b. Other adverse reactions

Nausea is reported in a slightly higher proportion of patients receiving delavirdine in combination with didanosine or zidovudine than in those receiving either zidovudine or didanosine monotherapy. In the ACTG 261 study, gastrointestinal side effects were experienced by 33% of patients (Friedland *et al*., 1999). Similarly, slightly more patients experience increases in hepatic transaminases when receiving delavirdine in combination with zidovudine (about 2.5%) or didanosine (about 5%) than where receiving either nucleoside as monotherapy (1–3%) (ViiV Healthcare, product information, 2012).

An 8-week study of patients with HIV infection treated with delavirdine combined with nucleoside analog reverse transcriptase inhibitors showed that the combination increased plasma cholesterol and high-density lipoprotein (HDL) concentrations (Roberts *et al*., 2002). The long-term clinical significance of these changes, especially the alteration