et al., 2004a). The median saquinavir C_{min} values for twice-daily saquinavir–ritonavir and saquinavir–atazanavir regimens were both above the 100 mg/ml target (King *et al.*, 2007). In healthy volunteers it appeared that saquinavir pharmacokinetic targets would be achieved more readily with twice-daily ritonavir boosting, rather than with a once-daily ritonavir-boosted regimen or with atazanavir-boosted regimens (King *et al.,* 2007).

Saquinavir and indinavir

When saquinavir hard gel capsule was combined with indinavir, a five- to eightfold increase in saquinavir AUC was observed (McCrea *et al.*, 1997). An *in vitro* study suggested synergy at low doses and antagonism at high doses between saquinavir and indinavir (Manion *et al.*, 1997). Another study of saquinavir soft gel capsule showed a 620% increase in AUC with no clinically relevant changes to indinavir (Buss, 1998).

Saquinavir and darunavir

Saquinavir C_{min} was reduced by 18% and darunavir AUC was reduced by 26%, and the C_{max} by 17% and C_{min} by 42%, respectively, when darunavir boosted with ritonavir was co-administered with saquinavir at a dose of 400/1000/100 mg twice daily and compared with the levels achieved with boosted saquinavir and boosted darunavir in 32 healthy volunteers. The combination should be avoided due to reduced darunavir effects (Janssen-Cilag, product information, 2014; Sekar *et al.*, 2007).

Saquinavir and tipranavir

When ritonavir-boosted tipranavir was co-administered with ritonavir-boosted saquinavir, significant reductions in saquinavir AUC, C_{max}, and C_{min} (76%, 70%, and 80%, respectively) due to possible induction of CYP3A4 by tipranavir–ritonavir occurred (Walmsley *et al.*, 2008). Saquinavir and tipranavir should not be co-administered (Boehringer Ingelheim, product information, 2013).

ENTRY AND FUSION INHIBITORS

There was no significant change in saquinavir and ritonavir pharmacokinetics nor enfuvirtide AUC and C_{max} when this combination was administered (Ruxrungtham *et al.*, 2004).

The CCR5 inhibitor maraviroc is a substrate for both CYP3A4 and P-glycoprotein. Significant increases in maraviroc exposure by both unboosted and boosted saquinavir have been reported in healthy volunteers. Unboosted saquinavir increased maraviroc AUC and C_{max} by 425% and 332%, respectively. Boosted saquinavir increased the maraviroc AUC and C_{max} by 832% and 423%, respectively. The minimum maraviroc dose of 150 mg twice daily should be used (Abel *et al.*, 2008a). When the CYP3A4 enzyme inducer efavirenz was added to combinations of maraviroc with boosted saquinavir, the magnitude of the increase in maraviroc exposure was reduced (AUC from 977% to 500% and C_{max} from 478% to 226%), but the net effect was still CYP3A4 inhibition (Abel *et al.*, 2008b).

INTEGRASE INHIBITORS

There is unlikely to be a clinically significant drug interaction between raltegravir and saquinavir boosted with ritonavir (Merck, product information, 2015a). The impact of elvitegravir and dolutegravir on saquinavir has not been assessed.

BOOSTED AND UNBOOSTED SAQUINAVIR WITH OTHER ANTIMICROBIAL DRUGS

Data on boosted and unboosted saquinavir with other drugs are summarized in Table 240.4.

Adefovir

There was no significant effect on either saquinavir or adefovir exposure (Kearney *et al.*, 2000).

Bedaquiline

Increased exposure to the antituberculous agent bedaquiline is possible when combined with boosted saquinavir, although the clinical significance is unknown. Patients receiving this combination should be assessed for QTc prolongation and have liver function tests monitored (US DHHS, 2015b).

Clarithromycin

When clarithromycin 500 mg twice a day was given with saquinavir soft gel capsule 1200 mg three times day, the AUC of clarithromycin was increased by 45% and the AUC of saquinavir was increased by 177% in 12 healthy volunteers (Buss, 1998). An increase in the unboosted saquinavir hard gel capsule AUC of 500% has also been reported when combined with clarithromycin (HIV InSite, 2015). No dosage adjustment for either drug is required when given for a limited time at the dosages studied (Malaty and Kuper, 1999). However, the combination of ritonavir-boosted saquinavir with clarithromycin has not been evaluated. Azithromycin, which is not believed to be a substrate or inhibitor of CYP3A4, is a suitable alternative (Walubo, 2007).

Cotrimoxazole (sulfamethoxazole–trimethoprim)

Cotrimoxazole increased the AUC of unboosted saquinavir hard gel capsule by 12%. No dosage adjustment is required for either drug (Maserati *et al.*, 1998).

Dapsone

Increased dapsone exposure may be possible if it is combined with saquinavir. Patients should be monitored for signs of toxicity (Roche, product information).

Erythromycin

Inhibition of CYP3A4 by erythromycin resulted in increased unboosted saquinavir exposure (AUC 99% and C_{max} 106%) when given at a dose of 1200 mg soft gel capsule three times a day in HIV-infected patients. The dose adjustment was not established (Grub *et al.*, 2001). Azithromycin is a suitable alternative (Walubo, 2007).