Antifungal agents

An increase in saquinavir levels (AUC of 50% and C_{max} of 56%) has been reported when fluconazole was combined with unboosted saquinavir 1200 mg three times a day, probably due to inhibition of CYP3A4 in the gut wall. Dose adjustments are probably not necessary (Koks *et al*., 2001).

A study comparing the pharmacokinetics of unboosted saquinavir soft gel capsule twice daily with or without itraconazole 100 mg daily as a pharmacoenhancer found that saquinavir levels were adequate and were not significantly different between the regimens (Cardiello *et al*., 2003b). In comparison, when itraconazole 200 mg twice daily was combined with ritonavir-boosted saquinavir, the half-life of itraconazole increased by 414%. Itraconazole and saquinavir effects were increased due to CYP3A4 inhibition by itraconazole, saquinavir, and ritonavir. The authors recommended decreasing the itraconazole dose to 100 mg twice daily (Mackenzie-Wood and Whitfield, 1999).

Ketoconazole 200 or 400 mg once a day has been shown to significantly increase the AUC and C_{max} of saquinavir administered as either hard gel capsule or soft gel capsule (Khaliq *et al*., 2000a; Grub *et al*., 2001). No dosage adjustment for unboosted saquinavir or ketoconazole is required. Fluconazole is a suitable alternative (Walubo, 2007). In comparison, when the effect of ketoconazole 200 mg once daily on the pharmacokinetics of saquinavir boosted with ritonavir 1000/100 mg twice daily and vice versa was assessed, the C_{max} and AUC_{0-12} of saquinavir and ritonavir were not substantially altered. Although ketoconazole exposure increased (C_{max} up by 45% and AUC by 168%) after 14 days due to CYP3A4 inhibition, no unacceptable deterioration in safety or tolerability was experienced. The authors concluded that no dosage adjustment of saquinavir–ritonavir was required, although the dose of ketoconazole should be limited to 200 mg daily (Kaeser *et al*., 2009).

Ketoconazole 400 mg daily was assessed as a pharmacokinetic enhancer and found to be 80% less effective than ritonavir 100 mg when combined with saquinavir 2000 mg once daily. The saquinavir C_{min} was below the target range of 0.1 mg/l when combined with ketoconazole (Autar *et al*., 2007).

The combinations of posaconazole and voriconazole with boosted saquinavir have not been formally assessed. The potential for increased saquinavir and antifungal exposure exists. Posaconazole levels and saquinavir adverse effects should be monitored. The co-administration of voriconazole and boosted saquinavir should be avoided, monitor voriconazole levels if coadministration does occur (Roche, product information; US DHHS 2015b).

Antimalarial agents

Marked increases in (unboosted) saquinavir plasma levels were observed in a case report of a 32-year-old woman with drug-resistant HIV infection when atovaquone–proguanil malarial prophylaxis was commenced. The 274% increase in saquinavir plasma levels is likely to be related to a CYP450 mechanism (Tommasi *et al*., 2011). Mefloquine should be used with caution with ritonavir-boosted saquinavir due to its effects on reducing ritonavir exposure. The effect on ritonavir-boosted protease inhibitors is unknown (US DHHS, 2015b).

Hepatitis C antiviral agents

The combination of boceprevir with boosted saquinavir has not been formally assessed. The combination should be used with caution because reductions in boceprevir and other boosted protease inhibitor levels have been reported when they have been combined (US DHHS, 2015b).

The combination regimen of dasabuvir–paritaprevir–ombitasvir–ritonavir should not be combined with boosted saquinavir, although no formal studies exist (US DHHS, 2015b). Likewise arsunaprevir and simeprevir should not be combined with boosted saquinavir because significant increases in arsunaprevir and simeprevir exposure would be expected (Roche, product information). Daclatasvir should be used with caution with saquinavir. No significant effect with the combination of ledipasvir or sofosbuvir with saquinavir–ritonavir is expected, although if tenofovir were to be added to this combination, increased tenofovir exposure would be expected, and alternative regimens should be considered (US DHHS, 2015b).

Rifabutin, rifampicin, and rifapentine

A pharmacokinetic interaction study assessed the effect of multiple doses of rifabutin 150 mg every third day on the pharmacokinetics of saquinavir–ritonavir 1000/100mg twice daily in 25 healthy subjects. Rifabutin reduced the saquinavir AUC_{0-12}, C_{max}, and C_{min} by 13%, 15%, and 9% respectively. The rifabutin did not affect the ritonavir pharmacokinetics. No dosage of saquinavir–ritonavir adjustment is required. The same study also examined the impact of saquinavir–ritonavir on rifabutin pharmacokinetics for rifabutin doses of 150 mg every 3 days or 150 mg every 4 days. For the 150 mg every 3 days regimen, the AUC_{0-72} of rifabutin and its active moiety 25-*O*-desacetyl-rifabutin increased by 134% and the C_{max} by 130% compared with rifabutin 150 mg daily alone. With the 150 mg every 4 days regimen, the rifabutin AUC_{0-96} increased by 60% and the C_{max} by 111%. The authors suggest monitoring for neutropenia and liver enzyme elevations when rifabutin is combined with saquinavir–ritonavir (Zhang *et al*., 2011).

Daily rifabutin combined with unboosted saquinavir reduced saquinavir AUC by 43% and C_{max} by 30% through CYP3A4 induction. The combination of unboosted saquinavir and rifabutin should be avoided (Roche, product information; Burman *et al*., 1999). In comparison, when ritonavir-boosted saquinavir is given with weekly rifabutin regimens, a reduction in rifabutin dose is recommended to avoid increased rifabutin levels caused by inhibition of CYP3A4 by both saquinavir and ritonavir (Gallicano *et al*., 2001).

Rifampicin is also a potent inducer of CYP3A4 and has been shown to significantly decrease the plasma levels of saquinavir. The combination should be avoided (Burman *et*