

amprenavir 600 mg twice daily and delavirdine 600 mg twice daily was associated with a > 50% reduction in plasma concentrations of delavirdine. Based on these findings, the co-administration of fosamprenavir and delavirdine is contraindicated (Tran *et al.*, 2002; Justesen *et al.*, 2003).

The second-generation nonnucleoside reverse transcriptase inhibitor etravirine (TMC125; see Chapter 238, Etravirine) increases fosamprenavir AUC by 69% and C_{\min} by 77% and therefore should not be co-administered with boosted or unboosted fosamprenavir (Johnson and Saravolatz, 2009).

Protease inhibitors

With the advent of new classes of drugs such as integrase inhibitors or CCR5 inhibitors for salvage situations, there is no clinical indication to combine protease inhibitors.

Pharmacokinetic studies of fosamprenavir plus lopinavir-ritonavir point to a pattern of complex unfavorable drug interactions. In the Adult AIDS Clinical Trials Group (ACTG) study A5143, the patients receiving fosamprenavir plus lopinavir-ritonavir experienced a 64% decrease in the amprenavir AUC and a 50% decrease in the lopinavir AUC compared with patients receiving fosamprenavir-ritonavir alone or lopinavir-ritonavir alone (Kashuba *et al.*, 2005). A5143 was discontinued because of the negative pharmacokinetic findings, but it is interesting that the week 24 analysis of data from 56 of the planned 216 subjects showed similar virologic outcomes among the regimens. Using intent-to-treat analysis at 24 weeks, viral load reached < 50 copies/ml in 54% of the recipients of fosamprenavir plus lopinavir-ritonavir compared with 46% of single-PI subjects. Clinical events and toxicity rates were similar among the groups (Collier *et al.*, 2008).

Another study evaluated fosamprenavir at a dose of 1400 mg plus lopinavir-ritonavir 533/133 mg twice a day versus fosamprenavir-ritonavir 700 mg twice daily plus lopinavir-ritonavir 400/100 mg twice daily plus ritonavir 100 mg twice daily. If the lopinavir plasma concentrations were similar to the values with administration of lopinavir-ritonavir 400/100 mg twice daily, the amprenavir concentrations were low compared with fosamprenavir-ritonavir (Wire *et al.*, 2004); about one-third of the patients discontinued the first regimen because of adverse events (Khanlou *et al.*, 2006). The interactions between fosamprenavir and lopinavir-ritonavir cannot be avoided by separating the doses (Corbett *et al.*, 2006). In summary, there is no established role or generally recommended dosing schedule for fosamprenavir plus lopinavir-ritonavir.

The addition of efavirenz to a regimen containing amprenavir 750 mg and lopinavir 533/133 mg, both twice daily, did not appear to significantly alter amprenavir or lopinavir pharmacokinetics. Substituting fosamprenavir 1400 mg twice daily for amprenavir resulted in an increase in amprenavir C_{\min} , AUC, and C_{\max} without changing lopinavir or ritonavir pharmacokinetics or overall tolerability (Pham *et al.*, 2007). A closer look at the effects of co-administration of lopinavir and amprenavir from the ACTG protocols A5143/A5147s

has shown that there is a significant increase in lopinavir and amprenavir unbound clearance as well as a significant increase in the fraction unbound of amprenavir (Dumond *et al.*, 2015).

A study conducted in rats suggested that saquinavir, nelfinavir, and indinavir have a minimal impact on oral bioavailability of amprenavir (Shibata *et al.*, 2002). There are, however, interactions in humans. For example when saquinavir at a dose of 1000 mg twice daily was co-administered with fosamprenavir 700 mg twice daily along with ritonavir 100 mg twice daily, this combination yielded mild reductions in saquinavir plasma concentrations: -14% for AUC, -9% for C_{\max} , and -24% for C_{\min} . The amprenavir AUC and C_{\min} were decreased by 29% and 40%, respectively. Increasing the dose of ritonavir to 200 mg resulted in a statistically nonsignificant increase in saquinavir exposure compared with baseline (Boffito *et al.*, 2004). There is no established clinical role for double-boosted protease inhibitor combinations that include fosamprenavir. Moreover, the appropriate dosages when combining fosamprenavir with any of these protease inhibitors are uncertain.

Simultaneous administration of fosamprenavir-ritonavir 700/100 mg twice daily plus atazanavir 300 mg daily produced no significant changes in the exposure to amprenavir. The AUC of atazanavir decreased by 22%, whereas C_{\min} of the drug was unchanged (Khanlou *et al.*, 2006). The interactions between atazanavir and fosamprenavir-ritonavir were also investigated in a study of 17 patients who required salvage antiretroviral therapy. The combination of atazanavir 150 mg plus fosamprenavir 700 mg plus ritonavir 100 mg (all twice daily) was given to 9 patients, whereas 5 patients received atazanavir 200 mg plus fosamprenavir 700 mg plus ritonavir 100 mg (all twice daily). A total of 3 patients received atazanavir 400 mg plus fosamprenavir 700 mg twice daily because of ritonavir intolerance. In this small study, amprenavir and atazanavir C_{\min} exceeded the minimum acceptable C_{\min} , defined as 0.28 and 0.27 $\mu\text{g/ml}$ for amprenavir and atazanavir, respectively (Khanlou *et al.*, 2006). The combination was generally well tolerated, and, by week 24, 10/17 (60%) had achieved plasma HIV-RNA suppression to < 50 copies/ml. Nonetheless, there are no large clinical trials of this combination and no clinical indication exists.

Tipranavir 500 mg plus ritonavir 100 mg twice caused an approximately 50% reduction in amprenavir plasma concentrations when it was co-administered with ritonavir 100 mg and amprenavir 600 mg twice daily (Walmsley *et al.*, 2008). Therefore, the combination of tipranavir and fosamprenavir should be avoided.

Integrase inhibitors

Boosted fosamprenavir (700/10 mg) given to healthy subjects has been reported to decrease the AUC and C_{\max} of dolutegravir (50 mg once daily) by 35% and 24%, respectively, in integrase-naïve subjects. This modest, clinically insignificant decrease in dolutegravir exposure does not require dolutegravir dose adjustment (Song *et al.*, 2014).