C_{trough} > 22-fold above the protein adjusted IC_{50} (55 ng/ml). (Huhn *et al.*, 2015). The significance of these data in clinical practice is unclear; and the conflicting data demonstrate the danger of combining untested therapies with cobicistat-boosted drugs.

Cobicistat-boosted elvitegravir (as dosed in Stribild) (see Chapter 250) has not been studied with atazanavir. Pharmacokinetic studies showed that a lower dose of elvitegravir (85 mg) boosted with 150 mg cobicistat and given with 300 mg atazanavir produced similar elvitegravir and cobicistat pharmacokinetics to historical controls, and the small (24%) drop in atazanavir AUC was not clinically relevant in comparison to a ritonavir–atazanavir 300 mg control (Ramanathan *et al.,* 2012b).

Cobicistat-boosted darunavir and atazanavir are not recommended to be used with efavirenz, as the decrease in cobicistat levels may lead to lower protease inhibitor exposure. In addition, for treatment-experienced patients, the use of cobicistat-boosted darunavir with etravirine is not recommended, as there is potential to reduce levels of darunavir. However, in healthy volunteers given cobicistat–darunavir 150/600 mg twice daily with etravirine 200 mg twice daily for 10 days, there was no effect on cobicistat or darunavir exposure (Ramanathan *et al.,* 2012a). The impact of etravirine on once daily darunavir–cobicistat is not clear.

In another pharmacokinetic study, standard dose tipranavir (500 mg), boosted with ritonavir 200 mg, given twice daily, was compared with tipranavir 500 mg plus cobicistat 150 mg twice daily. When boosted with cobicistat, tipranavir concentrations were significantly reduced, the AUC by 53.8% and the C_{max} by 37.8% (Ramanathan *et al.,* 2012a).

These complexities, and the limited studies available make it unwise to combine cobicistat boosted antiretrovirals with any other antiretroviral subject to CYP3A4 metabolism. Extrapolation of data available for ritonavir to cobicistat would be similarly unwise.

Table 248.9 includes information on known interactions with cobicistat.

Reference to frequently updated tables such as those available in the US Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents (aidsinfo.nih.gov) or the websites hivclinic.ca and hiv-druginteractions.org should assist with accurate dosing of combination antiretroviral therapy.

INTERACTIONS WITH NATURAL HEALTH OR COMPLEMENTARY MEDICATIONS

Natural health products, herbal products, and complementary medicines may interact with both cobicistat and ritonavir. As patients taking antiretroviral drugs may also be taking complementary medication—up to 67% in a US survey (Gore-Felton *et al.*, 2003) and 53% in an Australian survey (Braun *et al.,*2015), it is important to consider potential interactions. There is limited knowledge of the effects of co-administration of herbal/complementary medications with antiretroviral drugs. Some of these compounds can induce CYP3A4, such as St. John's wort, or inhibit CYP3A4, such as the flavonoids found in grapefruit juice, which inhibit intestinal 3A4 (Zhou *et al.*, 2003), and silybins, found in milk thistle (Sridar *et al.*, 2004). Cat's claw (*Uncaria tomentosa*) has been shown to inhibit CYP3A4 *in vitro* (Budzinski *et al.*, 2000). Data are lacking about the clinical effects of inhibiting P-glycoprotein with compounds such as silymarin, garlic, green tea, ginseng, and many flavonoids (Lee *et al.*, 2006). Similarly, the effect of inducing glucuronosyltransferases by natural products remains unclear.

Those taking mineral supplements (and vitamin supplements or antacid products containing polyvalent cations) need to be cautioned about the chelation effect of aluminium, iron, calcium, and magnesium on the integrase inhibitors. The administration times need to be significantly separated. Although there is no specific effect on either ritonavir or cobicistat, the cobicistat-boosted elvitegravir product needs to be separated from these compounds by at least 2 hours (Gilead Sciences, 2013).

Documented herbal interactions with ritonavir are few. Garlic has been reported to reduce ritonavir AUC, and there have been two documented cases of severe gastrointestinal side effects, even with rechallenge of low-dose ritonavir (Lee *et al.*, 2006). A case report of virological failure in a patient taking ritonavir-boosted atazanavir and garlic described a significant drop in atazanavir levels, which persisted some 10 days after cessation of garlic (Mills and Duncan, 2013). The mechanism by which garlic affects the protease inhibitors is complex; garlic contains many biologically active compounds, which can affect intestinal absorption as well as metabolism by the cytochrome system (Berginc and Kristl, 2012).

St. John's wort has been shown to significantly reduce the AUC of unboosted indinavir by a mean of 57% in healthy volunteers (Piscitelli *et al.*, 2000a). As it has the potential to decrease other protease inhibitor levels in a similar way, it has been recommended by the product manufacturers that the herb be avoided with protease inhibitors. The same risk applies to cobicistat, which is similarly contraindicated.

A case report of an interaction between cat's claw and the combination of ritonavir-boosted atazanavir and saquinavir described increased serum trough concentrations of all three protease inhibitors (Lopez Galera *et al.*, 2008).

Extracts of *Echinacea angustifolia* have been shown to inhibit CYP3A4 *in vitro* (Budzinski *et al.,* 2000); however, conversely, *Echinacea purpurea* induced metabolism of darunavir, without an effect on overall darunavir or ritonavir pharmacokinetics or clinical outcome (Molto *et al.,* 2011).

Some complementary therapies inhibit or induce CYP enzymes but have little effect on antiviral agents. These include milk thistle (*Silymarin marianum*), goldenseal root (*Hydrastis canadensis*), red yeast rice, aloe, and licorice. Further studies are required (Stolbach *et al.,* 2015).

INTERACTIONS WITH RECREATIONAL DRUGS

Methamphetamine and methylenedioxymethamphetamine (MDMA/ecstasy) are metabolized by CYP2D6 (Lin *et al.*, 1997). Consequently, they can be predicted to interact with ritonavir, which increases their levels through inhibition of the