care. Product monographs, pharmacokinetic data, and frequently updated Web-based drug interaction tables will assist in ensuring the correct doses are co-administered. Regularly updated drug interaction reference tables are available; the US Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents has several tables with drug interaction data (aidsinfo.nih.gov), and the websites hiv-druginteractions.org and hivclinic.ca have a number of excellent referenced tables to assist health professionals.

DRUGS CONTRAINDICATED FOR CO-ADMINISTRATION WITH RITONAVIR

The combination of some drugs with ritonavir is contraindicated (see Table 248.6). The majority are contraindicated because inhibition of their metabolism by ritonavir could produce large increases in plasma concentration, and potentially dangerous side effects may result. However, some drugs are contraindicated because ritonavir induces their metabolism (e.g. voriconazole), rendering them less effective.

DRUGS CONTRAINDICATED FOR CO-ADMINISTRATION WITH COBICISTAT

Table 248.6 lists the drugs contraindicated with cobicistat. Similar to ritonavir, cobicistat can, via inhibition of CYP3A4, increase concentrations of the majority of the contraindicated drugs, resulting in potentially dangerous side effects. Of note, cobicistat is contraindicated with the rifamycins because their effect on cobicistat and the antiviral agent given with it may result in reduced antiviral efficacy.

INTERACTIONS WITH COMMONLY PRESCRIBED DRUGS

Many drugs require dose adjusting or monitoring when used with cobicistat and ritonavir; some examples are in Table 248.7

Commonly prescribed drugs for which an interaction may be significant include the HMG-CoA reductase inhibitors (statins), hormonal contraceptives, glucocorticoids, azole antifungals, rifamycins, anticoagulant and antiplatelet agents, some cardiovascular agents (e.g. calcium channel blockers, amiodarone, digoxin), some anticonvulsants, some psychotropic drugs, and the phosphodiesterase inhibitors (e.g. sildenafil).

It is important to note that ritonavir liquid (a preparation now rarely used) contains alcohol in its formulation; co-administration of disulfiram or drugs that produce disulfiram-like reactions, including metronidazole, should be approached with caution when ritonavir liquid is prescribed.

INTERACTIONS WITH OTHER ANTIRETROVIRAL DRUGS

Using cobicistat or ritonavir as part of combination antiretroviral therapy may involve interactions with other components of the antiretroviral medication regimen (Tables 248.8 and 9). The ritonavir-boosted protease inhibitors can interact with nonnucleoside reverse transcriptase inhibitors and CCR5 inhibitors; some require dose adjustment. Raltegravir plasma concentrations are only weakly affected by ritonavir (Iwamoto *et al.*, 2008). Co-administration of dolutegravir with ritonavir alone has not been studied.

In studies of dolutegravir administered daily with ritonavir-boosted protease inhibitors darunavir and fosamprenavir (given twice daily), the combination lead to a decreased AUC, C_{max}, and C_{trough} of dolutegravir (Song *et al.*, 2011a; Song *et al.*, 2014), not considered to be clinically significant. By contrast, both ritonavir-boosted and unboosted atazanavir increased the AUC, $C_{max,}$ and C_{trough} of dolutegravir (Song *et al.,* 2011b). In the former case, ritonavir may decrease dolutegravir concentrations by induction of its metabolism via UGT1A1 glucuronidation; an action inhibited by atazanavir, meaning higher concentrations in the latter case.

Ritonavir also affects the pharmacokinetics of elvitegravir (see section 5.2.D, Integrase inhibitors) and vicrivaroc and maraviroc (CCR5 antagonists) (Ramanathan *et al.*, 2008; see Chapter 253, Maraviroc). Ritonavir could be used to boost the levels of elvitegravir, through inhibition of CYP3A4, but it has been co-formulated with cobicistat for this purpose. Maraviroc is a substrate of CYP3A4, so dose adjustments are required when given with combination therapy containing cobicistat or ritonavir. Some newer antiretroviral agents currently in trials are also substrates of CYP3A4, including the CCR5 and CCR2 antagonist cenicriviroc (Martin *et al.,* 2011), the nonnucleoside reverse transcriptase inhibitor doravirine, a CYP3A4 and P-glycoprotein substrate (Anderson *et al.*, 2015). Consequently, these drugs could be predicted to interact with both cobicistat and ritonavir. The novel long-acting integrase inhibitor cabotegravir is mostly metabolized by glucuronidation, meaning an interaction with ritonavir is possible. Cytochrome P-450-mediated metabolism is expected to have a minimal role in cabotegravir metabolism (Reese *et al.,* 2014).

Cobicistat and its co-formulated products may similarly interact with other antiretroviral agents, and the limited data describing interactions can be conflicting with respect to clinical outcome. The manufacturers state that cobicistat is not always interchangeable with ritonavir, in particular with protease inhibitors other than atazanavir and darunavir, or to boost darunavir at the 600 mg twice daily dose.

It is further recommended that cobicistat not be given in combinations that include more than one antiretroviral drug requiring pharmacokinetic enhancement, due to the complex nature of any interactions that may occur. An example of this is the interaction between cobicistat-boosted elvitegravir (150 mg) and darunavir 800 mg, all given once daily. The resulting trough concentrations for *both* darunavir and elvitegravir were lower than historical data (Ramanathan *et al.,* 2012a). A small simplification study comparing stable patients taking darunavir 800 mg as part of a multitablet regimen with switching to darunavir 800 mg daily plus tenofovir alafenamide–emtricitabine–elvitegravir–cobicistat daily demonstrated equal efficacy at 24 weeks. The pharmacokinetic substudy showed the elvitegravir C_{trough} > 10-fold above the protein adjusted 95% inhibitory concentration (IC_{95}) (45 ng/ml) and the darunavir