low-density lipoprotein (LDL) cholesterol and triglycerides and the total/high-density lipoprotein (HDL) cholesterol ratio, and also a decrease in HDL cholesterol concentration.[25] The increase in triglyceride levels must sometimes be controlled with medication or may even necessitate switching to other drugs. GI side effects, however, are significantly reduced with low-dose ritonavir.

As ritonavir is also a potent HIV-1 PI, the principal liability of a subtherapeutic dose of ritonavir is its potential to select PI-resistant virus in drug regimens that are not fully suppressive and/or do not contain an additional HIV-1 PI. This possibility remains hypothetical, since there are insufficient clinical data to conclude that doses of ritonavir used for boosting can lead to the emergence of PI-resistant viruses.

Despite the expanded understanding of the role of the CYP450 enzyme system in drug interactions, drug interactions remain unpredictable.[26] In addition to inhibiting CYP3A, ritonavir inhibits CYP2D6 and activates xenobiotic-sensing receptors, such as the aryl hydrocarbon receptor (AhR) and the pregnane X receptor (PXR). At boosting doses, the impact of ritonavir on CYP2D6 and AhR appears to be negligible.[27] PXR is a predominant regulator of CYP3A expression. It also controls the expression of CYP2B6 and regulates multidrug-resistant gene 1 (*MDR1*) and other genes.[28] Activating PXR results in the induction of CYP3A and drug transporters.[29] Although the net effect of ritonavir on human CYP3A in the clinic is inhibitory, the inhibitor potency is reduced upon chronic dosing, as the rate of CYP3A re-synthesis is increased *via* induction. Other proteins induced by ritonavir in the clinic include CYP2B6, CYP2C9, CYP2C19, UGT1A4 and MDR1, which further complicate the drug–drug interactions.[30,31] Consequently, the dosage of therapeutic drugs co-dosed with ritonavir needs to be carefully monitored and refined, depending on their metabolism and/or route of clearance.

The poor physicochemical properties of ritonavir generate challenges in its production and formulation. Ritonavir is not bioavailable from the solid state, so it was formulated as either an oral solution or semi-solid capsules, both in an ethanol–water-based solution. The solvent system is believed to be the cause of some of the poor tolerability issues associated with the drug. After 2 years on the market, a new and extremely insoluble crystal form, polymorphism form II, appeared. Unfortunately, studies demonstrated that form II is the thermodynamically more stable form and exhibits an extremely low dissolution rate, resulting in unacceptable bioavailability. Studies of the crystal form of form II showed that it formed strong hydrogen bonds between the two molecules in a transform *via* the hydroxyl group.[32] The two ritonavir molecules depicted in the box in Figure 13.6 is the repeating unit in the crystal packing. To prevent the formation of form II, the semi-solid capsule or oral formulation requires refrigeration prior to use. Therefore, ritonavir is not easily amenable to coformulation with other PIs. Recently, the FDA has approved commercialization of a ritonavir tablet and a combined lopinavir–ritonavir tablet using melt extrusion technology (Meltrex). Overall, the poor physicochemical properties of ritonavir hinder its utility to be combined with other antiretroviral (ARV) agents in the development of a fixed-dose combination (FDC) or a fixed-dose regimen (FDR).