was developed.[76,78] Phosphate prodrugs had previously been used to enhance the solubility and, consequently, exposure of small molecules.[2,3] *In vivo*, fosamprenavir was hydrolyzed to APV and inorganic phosphate at the gut epithelium by alkaline phosphatases.[78] In the Caco-2 model, fosamprenavir did not cross the monolayer; however, APV did cross the monolayer >50-fold faster than fosampernavir after Caco-2 exposure to fosamprenavir.[78] Systemic exposure in the rat and dog was shown to be low after oral administration of fosamprenavir, and portal vein-cannulated animals showed minimal levels of fosamprenavir relative to APV, thus supporting rapid hydrolysis in the gut.[78] In a Phase 1 human clinical trial, very low levels of fosamprenavir were detected in plasma ($<0.17\%$ of APV concentration) after oral administration, supporting rapid and complete conversion of fosamprenavir to APV during absorption.[79,80] Clinical studies comparing APV and fosamprenavir showed equivalent steady-state AUCs and comparable efficacy and safety profiles, but with a reduced pill burden for fosamprenavir dosing (four tablets).[81] Fosamprenavir is currently marketed as Lexiva.

In the continuing effort to develop inhibitors of HIV-1 with novel mechanisms of action, a series of HIV-1 attachment inhibitors were developed. These agents function by binding to the gp120 protein on the HIV-1 viral envelope, thus interfering with a critical cellular CD4 receptor interaction. The first molecule to demonstrate proof of concept for this approach was BMS-488043 (**28**, Figure 12.15).[82,83] BMS-488043 was shown to be a potent inhibitor of HIV-1 infection *in vitro* and demonstrated good oral bioavailability in rats ($F=90\%$), dogs ($F=57\%$) and monkeys ($F=60\%$) when administered as a solution dose. BMS-488043 given twice daily at a dose of 1800 mg for 8 days produced a viral load decline of 1.0–1.5$\log_{10}$ in HIV-1 infected patients.[83] However, to achieve adequate exposure, BMS-488043 required concomitant administration of a high-fat meal. In addition, it was shown that administering a 200 mg dose in solution provided a twofold higher exposure than the solid dosage form.[84] Evidence suggested that poor dissolution and/or poor solubility limited the exposure in humans. To address this dissolution-limited absorption problem, the phosphonooxymethyl prodrug BMS-663749 (**29**, Figure 12.15) was prepared where the promoiety was attached to the indole nitrogen on the parent drug.[84] The attachment of the phosphate promoiety resulted in a dramatic increase in aqueous solubility from 0.04 to >100 mg mL^{-1}. Promoiety cleavage was mediated by alkaline phosphatase (ALP) releasing one molecule of formaldehyde and phosphate.[84] Based on a toxicological assessment, the release of formaldehyde was viewed as acceptable.[85] Animal PK studies showed that BMS-663749 was rapidly converted to the parent BMS-488043 and exhibited absolute bioavailabilities of the parent drug of 62, 93 and 67% in the rat, dog and monkey, respectively.[84] The prodrug also showed a twofold higher AUC of the parent drug in rats compared with oral dosing of the parent. Human clinical studies corroborated the animal PK work and showed rapid conversion of the prodrug to the parent, rapid absorption leading to a shorter $T_{\frac{1}{2}}$ and high bioavailability comparable to solution dosing.[84] Unfortunately, even with the improved PK properties provided by the prodrug, other intrinsic