when trough concentrations ($C_{12\,h}$) were maintained above a 33 nM IC_{95}.[57] Interestingly, all doses tested, 100–600 mg bid, showed similar viral load responses during this study, making a dose–response curve difficult to assess fully. Further review of the preclinical PK data showed a similar biphasic elimination curve, with a rapid initial phase followed by a slower terminal phase. Although specific data were not reported for RAL for the early-phase half-life in rat, dog and monkey studies, it was mentioned that RAL showed similar PK to a closely related compound that nicely mimicked the clinical data from the healthy volunteer and monotherapy trials. Overall, RAL showed a 2, 11 and 4 h terminal elimination phase in rat, dog and rhesus i.v. PK studies, respectively. The corresponding clearance values were 39, 6 and 18 mL min^{-1} kg^{-1}; volume of distribution (V_d) measures were 2.0, 0.9 and 1.2 L kg^{-1}.

Elvitegravir (EVG) is derived from a quinolone antibiotic scaffold originally designed for bacterial DNA gyrase activity. The evolution of the quinolone into a potent INI is shown in Figure 6.4a. Shinkai and co-workers designed the quinolone keto acid motif **10** as a bioisostere of the two-metal binding compound L-870,810 (**9**), which was an early-generation INI and the first to show clinical efficacy.[58] Although the keto acid **10** did not have integrase activity, researchers were surprised to see that the structurally simpler acid **11** had low micromolar inhibition of an enzymatic strand transfer assay. Through significant lead optimization, workers at Japan Tobacco were able to build in substantial potency ($IC_{50} = 0.9$ nM, protein-adjusted $IC_{50} = 9.8$ nM) and develop a suitable PK profile to justify clinical development.[59] Preclinical PK showed moderate oral bioavailability in rats and dogs (34.1 and 29.6%) and also modest i.v. clearance rates (0.5 and 1.0 L h^{-} kg^{-1}), respectively. Terminal half-life measures were 2.3 and 5.2 h in rats and dogs, respectively.[60]

EVG is predominantly metabolized via CYP3A. This feature became evident during the early clinical investigations and has manifested itself throughout the EVG development program.[61,62] As a result, EVG requires a PK booster co-dose to achieve a clinically meaningful increase in EVG AUC (area under the curve) measures, which is the key to making EVG a once-daily drug.[63,64] Since the very early monotherapy efficacy investigations, all clinical studies have included a co-dose of ritonavir,[65] which itself is an early-generation HIV protease inhibitor, or of the CYP3A inhibitor cobicistat (COBI), which is based on ritonavir but devoid itself of potent HIV antiviral activity.[66] With the pharmacokinetic booster available along with the two nucleoside analogs tenofovir (TDF) and emtricitabine (FTC), the focal point of the development strategy for elvitegravir has been the four-drug combination pill (QUAD) of EVG–COBI–TDF–FTC.[67,68]

Two key Phase 2 studies looked at EVG in either experienced or treatment-naive patients. In the experienced population, a protease inhibitor was compared with EVG both with study arms including ritonavir and OBT.[69] For naives, the QUAD regimen was compared with the three-drug combination containing Atripla (efavirenz–tenofovir–emtricitabine).[70] In both cases, the primary endpoints were robustly met and EVG progressed into pivotal Phase 3 studies. The first Phase 3 trial to report was a study in experienced patients