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viral load from a low once-daily dose. Clinical pharmacology studies showed no evidence of clinically significant drug–drug interactions with lopinavir/ritonavir (r), atazanavir/r, darunavir/r, tenofovir, the proton pump inhibitor omeprazole or multivitamins.[98–101] Additionally, there appears to be a lack of a clinically significant food effect, further improving patient convenience and dosing flexibility.[102] Antacids have been found to impact the clinical PK sufficiently that either dosing 2 h prior to taking antacids or 6 h after is recommended. This may be due to chelate formation in the stomach/GI tract with metal ions in antacids such as Maalox, which decreased absorption. It could also potentially be a result of pH adjustment in the stomach or upper GI compartment as a result of the basic supplement. It has been observed that co-administration with the NNRTI agent etravirine alone leads to significant decrease in exposure of DTG, likely due to induction of the UGT1A1 enzyme, a primary route of metabolic clearance for DTG.[103] If this combination is co-administered with a ritonavir-boosted protease inhibitor, this effect is greatly reduced.

DTG was further examined in the Phase 2b SPRING-1 dose-ranging study in treatment-naive patients. Doses of 10, 25 or 50 mg qd with either Truvada or Epzicom nucleoside backbone agents were compared with the same background therapy with 600 mg of the NNRTI efavirenz (Figure 6.11).[104] Once-daily, unboosted DTG demonstrated durable antiviral activity for all dosing arms, with 88% responding through 96 weeks[105] and a favorable safety profile at the 50 mg qd dose, the dose chosen for further Phase 3 studies outlined below.

A second smaller but important dose-ranging study, termed VIKING, was designed to determine the antiviral effects of DTG in an integrase-resistant, highly treatment-experienced patient population. A first cohort of 27 patients

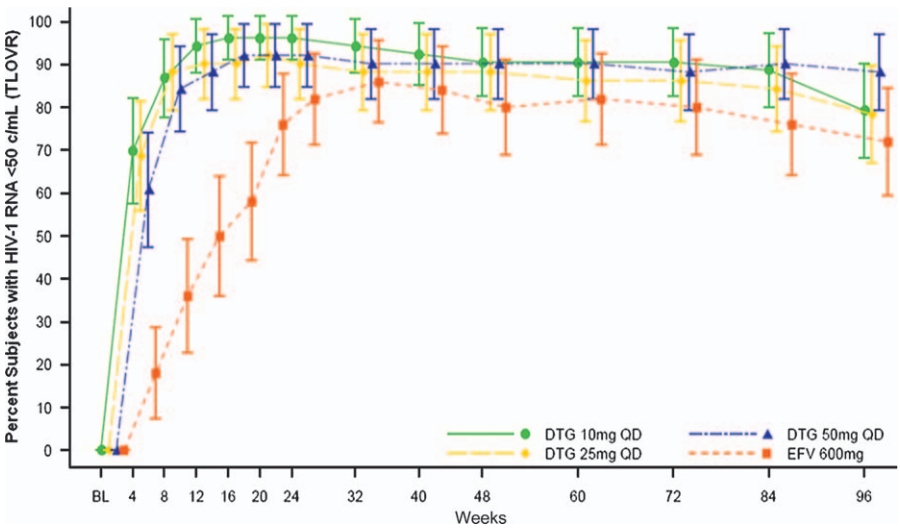

Figure 6.11 SPRING-1 Phase 2b treatment-naive data through 96 weeks.[105]