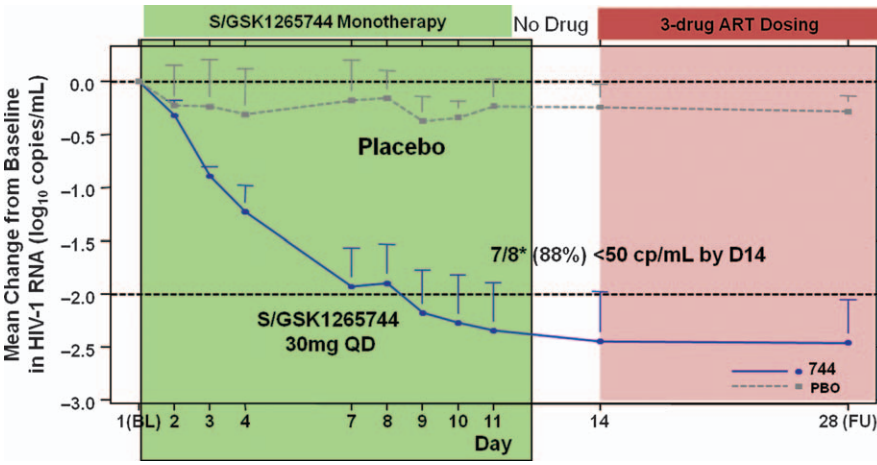

Figure 6.12 S/GSK1265744 Phase 2a monotherapy study.[111]

a 30 mg qd dose provided a 2.6$\log_{10}$ decrease in viral load at day 11, thus verifying the pharmacodynamic response predicted from the antiviral and PK data (Figure 6.12).[111] In addition, a study to examine drug–drug interactions between S/GSK744 and etravirine was completed and it was found that ETR does not affect S/GSK744 pharmacokinetics.[112]

The significant viral load impact observed along with the low dose required to achieve such an effect plus long $t_{\frac{1}{2}}$ led to the proposal for development of S/GSK744 as a long-acting parenteral agent. In this scenario, a suspension of drug is introduced *via* subcutaneous or intramuscular injection and a reservoir of drug is established whereby exposure is achieved through slow absorption from the drug depot. The first evidence of clinical PK, safety and tolerability of S/GSK744 in healthy volunteers has recently been disclosed, showing an apparent $t_{\frac{1}{2}}$ of 21–47 and 45–47 days from intramuscular and subcutaneous injections, respectively.[113] Further studies are currently under way to examine this paradigm-shifting approach whereby daily adherence concerns are removed and new options for antiretroviral therapy are introduced in a situation that now requires relentless daily therapy for the remainder of a patient's life.

6.4 Non-catalytic Site Integrase Inhibitors

Despite the success of integrase strand transfer inhibitors, intensive research is ongoing to seek alternative mechanisms to inhibit this enzyme. The primary concern is the emergence of resistance in clinical use as observed with both raltegravir (RAL) and elvitegravir (EVG). To complicate the situation further, multiple studies have demonstrated cross-resistance between first-generation INIs, as alluded to above.[49,77,79] Although the next-generation integrase inhibitor DTG has a superior resistance profile, the potential for resistance