concentration that begins to cause toxicity effects. A drug with a steady-state PK profile that falls between the two concentrations, a C_{max} lower than the 'minimal toxicity concentration' and C_{trough} above the 'minimal effective concentration,' will be desirable for sufficient efficacy and minimal side effects. To reach an adequate C_{trough}, Drug 2 (blue line) needs to be dosed twice daily or once daily at a higher dosage. The C_{max} of a high dosage of Drug 2 is close to the concentration that causes toxicity, which will result in dose-related side effects. Ideally, a drug with a PK profile enabling once-daily dosing (Drug 1, purple line) with a relatively flat PK curve, meaning a lower C_{max}/C_{min} ratio, will perform most effectively. Drug 3 (black line) needs to be dosed three times per day, with a high potential for side effects and for the generation of resistance mutants, since its C_{max} breaks through the 'minimal toxicity concentration,' and its C_{min} falls below the 'minimal effective drug concentration.' More often than not, a potent drug with a good resistance profile has sufficient antiviral properties but suffers from a poor PK profile and fails to attain sufficient C_{trough} for durable viral suppression. A pharmacoenhancer can improve the PK profile of a drug and enable it to achieve adequate exposure at a lower dosage and with less frequent dosing, as exemplified by the PK profile of Drug 2, which can be improved to a level that is similar to that of Drug 1. In clinical practice, ritonavir demonstrated these desired properties and significantly enhanced the PK exposure of a co-dosed PI, enabling HIV PIs to remain a key component for HIV treatment.

13.2.4 Combination Therapy and HAART

High-level viral replication rates in conjunction with the high mutation rate of some viruses, such as HIV, cause any monotherapy treatment to fail.[9] A combination therapy using two or more drugs from different classes against the target virus forces the virus to mutate simultaneously at multiple positions in one viral genome to become resistant and has become the standard therapy for chronic diseases such as HIV-1 infection. Combination therapy results in much greater levels of viral suppression, thus reducing viral turnover, which, in turn, reduces the rate of production of mutants. In addition, the development of resistance is much more complex, as the virus must acquire mutations that induce resistance to a range of drugs, raising the genetic barrier.

The approval of first-generation HIV PIs during 1995 and 1996, followed by the approval of the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine, made combination therapy containing antiretroviral agents from different classes possible and brought a revolution in the treatment of HIV-infected patients. Combination therapy with three or more active agents, or highly active antiretroviral therapy (HAART), resulted in markedly reduced plasma viremia and a concomitant increase in CD4+ T cells in HIV-infected patients. The current standard of care recommended by the US Department of Health and Human Services (DHHS)[1] and the International Antiviral Society-USA (IAS)[10] for the treatment of naive HIV-infected patients is to combine two nucleoside reverse transcriptase inhibitors plus a third agent, whether a