consequently, suboptimal drug concentrations at trough, which is a major cause of treatment failure and the emergence of drug resistance. A pharmacoenhancer, which itself is often not active against the therapeutic target but can inhibit the enzymes that metabolize the active drug, can enhance pharmacokinetic (PK) profiles of the therapeutic drug to achieve adequate trough concentrations at lower dosage and with less frequent dosing. This was especially evident in the treatment of HIV infection. The pharmacoenhancers ritonavir (RTV) and cobicistat (COBI, previously known as GS-9350) have contributed to the success of durable viral suppression *via* simplified treatment regimens with favorable tolerability. This chapter reviews the relationship of drug PK, drug resistance and durable viral suppression using HIV therapy as an example to discuss the role of pharmacoenhancers.

13.2 Antiviral Resistances and HIV Protease Inhibitor Ritonavir

13.2.1 Virus and Drug Resistance Mutations

Pathogenic viruses cause a tremendous burden of disease and death worldwide. Viruses can rapidly adapt to selective pressure and exist with multi-quasi-species (polymorphisms) due to their rapid replication cycles, their error-prone replication process and a large amount of viral progeny from a single infected host cell. However, significant progress has been made in the past half century towards the development of effective and specific antivirals. Although some antiviral agents, such as anti-influenza drugs, have been used in acute infections, many of them are generally used in the treatment of persistent and chronic infections. In recent years, major efforts of antiviral research have been focused on viruses that cause chronic infection affecting millions of individuals worldwide, such as HIV, hepatitis C virus (HCV) and hepatitis B virus (HBV). Many drugs have been approved and many more are in advanced stages of clinical studies. Although the ultimate goal in chronic treatment is to eradicate the viral pathogen from the host, in some cases that goal is unattainable. When eradication is not achievable, the focus is redirected towards achieving durable viral suppression to alleviate or prevent the clinical manifestation and long-term consequences of chronic infection and preventing the transmission of the pathogen itself.

Long-term treatment of chronic viral infections is often fraught with problems regarding adverse effects of drugs, patient compliance and resistance development. Favorable safety profiles, simplified regimens and a low pill burden will favor good compliance, which, in turn, delays the emergence of drug resistance. The emergence of clinically-relevant resistant variants is associated with factors such as selective pressure under the treatment drug, the generic barrier of the drug to resistance and the replication fitness of the resistant variant. The resistant variants will be selected by treatment with drug concentrations insufficient to suppress completely the replication of moderately