resistant viruses. Replication under drug selection pressure can then result in the accumulation of further adaptive mutations, conferring a higher degree of resistance and a higher level of fitness. When viruses become resistant to one drug, they are often automatically cross-resistant to the drugs in the same class. The treatment failure of an active treatment regimen is often derived from the emergence of drug-resistant variants and viral rebound, which is more often than not a result of poor compliance with the drug regimens due to their challenging dose schedules and/or poor side-effect profiles.

13.2.2 HIV and HIV-1 Protease Inhibitor Ritonavir

HIV was first isolated in 1983 and was soon identified as the etiological agent of acquired immunodeficiency syndrome (AIDS), responsible for more than 25 million deaths worldwide over the past 30 years. Through the collaborative work of the US Food and Drug Administration (FDA) and scientists from both academia and the pharmaceutical industry, more than 20 drugs covering six mechanistic classes have been approved to date for treating HIV infection/AIDS. Unfortunately, eradication of HIV from humans with antiretroviral therapy has not been achieved. The current goal of antiretroviral therapy is to achieve maximum and durable suppression of plasma viremia, with preservation of CD4+ T cells and minimum development of drug resistance.[1]

Until mid-1995, chemotherapies for the treatment of AIDS and/or HIV infection were limited to only nucleoside reverse transcriptase inhibitors (NRTIs). Although these antiretroviral agents provided long-awaited relief for those suffering from this devastating disease by delaying the progression to AIDS, a death sentence at the time, the clinical benefit was overshadowed by the rapid emergence of resistant strains of HIV.[2]

HIV-1 protease, which is responsible for the processing of the Gag and Gag–Pol polyprotein gene products into mature and functional proteins, plays a critical role in virus replication *in vitro*[3] and has been pursued as a target for inhibiting HIV replication. Part of the family of aspartic proteases, HIV-1 protease is a symmetrically assembled homodimer. The active site is formed at the dimer interface, with the two aspartic acids at positions 25 and 25′ located at the base of the active site. During the proteolytic processing of the substrate, a tetrahedral transition state between the enzyme and substrate bridged by water exists transiently at the active site. HIV-1 protease inhibitors (PIs) bind to the active site of protease in a way that mimics the transition state, preventing the enzyme from cleaving the post-translational polyproteins necessary for the maturation of infectious virions.[4] Treatment with potent PIs produces a rapid fall in plasma HIV RNA, with a concomitant increase in CD4+ T cells.

Three HIV-1 PIs were approved during 1995 and 1996. Ritonavir was the second PI licensed in the USA for the treatment of HIV, with a recommended dosage of 600 mg twice daily (bid). However, the clinical efficacy of PI monotherapy is eventually lost in many patients owing to the development of PI-resistant mutations. It was discovered that the durability of virologic response