early days of the disease, it has become strikingly evident that the most basic part of the equation – getting patients to take their drugs – is a major reason for a lack of efficacy.[2,3] Although patient behavior seems far removed from the discovery laboratory, the field has advanced sufficiently that building the appropriate properties into new antiretroviral drugs to allow for optimal patient convenience is now recognized as equally important to these drugs' virological properties.

HIV virus is relentless and continually evolving under drug pressure to escape control and continue the infection.[4] The transmission of such a resistant virus is of concern and currently a topic of intense debate.[5–7] To complicate matters further, the long-term tolerability and safety of many of the available therapeutic successes are not optimal.[8] This creates more challenges for patient compliance. Of particular interest is finding regimens that allow delay of the use of nucleoside analogs (nuc sparing) until later lines of therapy.[9,10] Ironically, one of the more interesting rationales for continued introduction of antiretroviral agents comes from the curative approaches that are now being explored. It has been argued that intensification of current regimens will be required for complete suppression during transcriptional activation envisaged during attempts to purge latent reservoirs.[11] As such, there continues to be a need for new drugs either from new classes or from further study of existing targets.

The above arguments support a need for new antiretroviral agents, but ones that are optimized for patient needs and that provide clear benefit and differentiation over existing options. On the surface, the field would appear to be well served, with over 30 treatment options. However, on closer inspection, many of these drugs center on the same mechanisms of action and are sufficiently similar that they do not provide unique characteristics orthogonal to other drugs already available. The key challenge for contemporary HIV antiretroviral drug discovery efforts is to choose the right target and match a fully optimized inhibitor while taking into account patient needs.

6.1.1 HIV Integrase

HIV is a retrovirus from the lentivirus family. The virus encodes 15 proteins, of which only three (reverse transcriptase, integrase and protease) have enzymatic activity.[12] Reverse transcriptase (RT) and protease (PR) are responsible for the conversion of single-stranded viral RNA into double-stranded DNA and the proteolysis of the gag polyprotein, respectively. Both RT and PR have proven to be excellent drug targets, with several antiviral drugs having been available for both for many years. Targeting virally encoded proteins or enzymes has traditionally been viewed as desirable due to a higher likelihood for selectivity, since they are not derived from the host. A third virally encoded enzyme is HIV integrase (IN). Integrase is a 32 kDa protein that is responsible for the integration of reverse-transcribed viral double-stranded DNA (dsDNA) into host chromosomal DNA during the retroviral replication cycle. As a result of this unique retroviral step, integrase has become an attractive target for drug discovery. The IN enzyme consists of a 288 amino acid primary sequence