



## HIV Drug Resistance: A Major Challenge in Antiviral Therapy of AIDS

**Hiroaki Mitsuya**

Departments of Hematology and Infectious Diseases  
National Kumamoto University, Japan

Combination chemotherapy or highly active antiretroviral therapy (HAART) using reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs) for human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) has been shown to extend the life expectancy of HIV-infected individuals. However, drug resistant HIV variants often emerge, which has been a major factor for treatment failure. The rapid replication rate of HIV *in vivo* coupled with the long duration of viral infection favors the emergence of resistant mutants to virtually any antiviral agent. The very features that contribute to the specificity and efficacy of RTIs and PIs provide the virus with a strategy to mount resistance. Worse, HIV develops high levels of resistance against multiple antiviral drugs by accumulating a variety of amino acid substitutions near (and beyond) the active sites of target viral enzymes. Moreover, HIV already has shown its ability to develop resistance to a few new entry inhibitors.

It is of note that HIV drug resistance poses different challenges than we faced in the design of the first line drugs, as it forces us to think about selection pressure mechanisms in addition to the issues of potency, pharmacology, safety, and mechanism of drug action. Our understanding of functional/structural mechanisms of resistance has been increasingly detailed but is still semi-quantitative and subject to current methodological limitations. Improved approaches to structure-based drug design and the development of quantitative methods of modeling and binding affinity prediction have taken on added significance. It is imperative to search for combinations of drugs with complementary resistance profiles and less side effects and to explore new targets and algorithms in the hopes that at least a stalemate, if not an end game, strategy can be found to more effectively control HIV infection and its related diseases.