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MUTATION OF LYS-154 IN HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 REVERSE TRANSCRIPTASE MAY INFLUENCE ITS FIDELITY WITH DECREASED SENSITIVITY TO NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

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Since the advent of the first human immunodeficiency virus type one (HIV-1), many antiHIV-1 drugs have been discovered to treat HIV infected and AIDS patients. Most of the antiHIV-1 drugs target HIV-1 reverse transcriptase (HIV-1RT), an enzyme responsible for synthesis of proviral cDNA. Also, the HIV-1 RT exhibits high propensity for misinsertion and mispair extension. While exploring the role of a mutant RT in this context, an analysis of the three-dimensional crystal structure of this enzyme reflects that the interaction of the side chain of K154 in HIV-1RT with the penultimate nucleotide of the template may be crucial in determining fidelity of proviral DNA synthesis as well as sensitivity to antiHIV regimen. This hypothesis was tested by steady-state kinetic studies using wild-type HIV-1 RT and five K154 mutants. These mutants contained replacement of positively charged side chain of Lysine with two amino acids with hydrophobic side chains and two amino acids with negatively charged side chains. In one of the mutants, the positive charge of Lysine was retained but the side chain was enlarged by one carbon atom while replacing it with Arginine. The results indicated that the HIV-1 RT mutants with only negatively charged side chains displayed significant decrease in enzyme activity. Other mutants exhibited almost the wild type activities. Excepting the mutants with negatively charged side chains which displayed higher fidelity than wild type, all other mutants registered enhanced levels of misinsertion and mispair extension; K154R being the most prominent. All of these mutant derivatives of HIV-1 RT when tested for their response to 3TC and other dideoxy nucleotides, displayed significant resistance to these drugs. The mechanism of drug resistance would be explained in the light of 3D crystal structures of apoenzyme, binary and ternary complexes of both the wild type and mutant HIV-1 RTs.

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