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Antiviral Drug Resistance Mutations in HIV-1 Reverse Transcriptase Occur in Specific RNA Structural Regions E. W. Taylor, C. S. Ramanathan, R. M. Lloyd Jr., R. F. Schinazi. Department of Medicinal Chemistry and Computational Center for Molecular Structure and Design, The University of Georgia, GA 30602, USA (E.W.T., C.S.R.), and Department of Pediatrics, Emory University and Veterans Administration Medical Center, 1670 Clairmont Road, Decatur, GA, USA (R.F.S., R.M.L.).

A statistically significant correlation exists between the locations of drug resistance mutations (DRMs) observed for various reverse transcriptase (RT) inhibitors and features of the secondary structure predicted for the RNA coding for HIV-1 RT. The known DRMs map onto bases that are in predominantly non-helical regions (i.e. loops, bulges and bends) of the predicted RNA secondary structure ($p < 0.004$), whereas codons for the key conserved residues of polymerase sequence motifs generally map onto paired bases involved in helical regions ($p < 0.002$). This suggests that the secondary structure of the RNA template (in this case, the RT gene itself) may be a previously unrecognized factor contributing to base misincorporation errors during reverse transcription, and that, rather than being randomly distributed, mutations are more likely to occur in specific regions of the genome. Although it is possible that the RNA structure of the template may play a direct role during transcription, an indirect mechanism may be involved, such as an increased probability of intracellular chemical or enzymatic attack on unpaired vs. paired bases, prior to reverse transcription. The mapping of codons for functionally essential residues of polymerase sequence motifs onto the apparently less mutation-prone helical RNA regions suggests an evolutionary rationale for both the selection of such RNA structures and their function: increased genetic stability and viability by the protection of codons critical for viral replication.