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Effect of drug resistance on combination chemotherapy for HIV

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There is currently much interest in the use of combination chemotherapy for treatment of HIV infection. We followed the effect of three different drug combinations (AZT + FLT, AZT + ddI and FLT + ddI) upon primary isolates of HIV from an HIV-infected patient before, during, and after AZT therapy. Primary isolates of HIV were obtained by co-cultivation from the patient before therapy, after 28 months therapy with AZT, and one year after therapy had been withdrawn. Drug susceptibility was tested in PBMCs using ELISA to quantify virus production and the effect of combinations was analysed using the median effect method. The first and last isolates were susceptible to AZT and other antiviral drugs, whilst the second isolate showed resistance to AZT, with accompanying mutations in the RT. The first isolateshowed synergistic inhibition by AZT + FLT, AZT + ddI, and FLT + ddI. The second isolate, however, showed no synergistic inhibition by combinations containing AZT, showing that in this patient resistance was associated with loss of synergy. The third isolate, which had reverted to AZT sensitivity after withdrawal of the drug, again showed synergistic inhibition by all three combinations. From these results it appears that the benefit of synergistic drug combinations may be lost upon development of resistance, but the synergistic response may be regained if drug sensitivity returns when treatment is withdrawn.

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INHIBITION OF HIV-1 RNASE H BY THE NON-NUCLEOSIDE RT INHIBITORS 9-CL TIBO AND L-697,661

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TIBO, 9-Cl-TIBO and derivatives are potent non-competitive inhibitors of HIV-1 reverse transcriptase (RT). TIBO was reported to have no effect on HIV-1 RNase H activity at up to 300 µM. The pyridinone derivatives L-696,227 and L-697,661, inhibit HIV-1 RT by the same mechanism as TIBO and were reported be weak inhibitors of RNase H activity at 300 µM.

We tested the effect of 9-Cl-TIBO and L-697,661 on HIV-1 RNase activity using purified recombinant heterodimer and ^{35}S-labeled RNA/DNA hybrid as substrate. 9-Cl-TIBO and L-697,661 were found to inhibit HIV-1 RNase H activity with IC_{50} values of approximately 0.3 µM and 0.2 µM respectively.

The effect of TIBO and L-697,661 on RNase H inhibition using different substrates has been investigated. TIBO resistant RT mutants have been studied to determine if the effect of TIBO and L-697,661 on RNase H activity is mediated through the same binding site, and if this site is the same as the polymerase inhibition site.