

Anti-Human Immunodeficiency Virus Type 1 Activity and Resistance Profile of 2',3'-Didehydro-3'-Deoxy-4'-Ethynylthymidine In Vitro

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2',3'-Didehydro-3'-deoxy-4'-ethynylthymidine (4'-Ed4T) has been identified as a novel nucleoside analog with potent and selective anti-human immunodeficiency virus type 1 (HIV-1) activity and weak cytotoxicity in cell cultures. 4'-Ed4T proved to be 5- to 10-fold more active than its structurally related compound, stavudine (d4T). However, the drug resistance profile of 4'-Ed4T was different from those of d4T and other existing HIV-1 nucleoside reverse transcriptase inhibitors (NRTIs). Approximately 6- to 11-fold decreases in susceptibility to 4'-Ed4T were observed for HIV-1 carrying NRTI-associated mutations (D67N, K70R, T215F, and K219Q) or the lamivudine (3TC)-resistant mutation M184V. In contrast, the susceptibility of the virus carrying the K65R mutation or the multidrug-resistant mutation with the Q151M complex (A62V, V75I, F77L, F116Y, and Q151M) was not altered. Furthermore, the activity of 4'-Ed4T appeared to be enhanced in the presence of K103N, a major nonnucleoside reverse transcriptase inhibitor-resistant mutation. Although 4'-Ed4T was 4.5- to 17.5-fold less active against multidrug-resistant clinical isolates than against a reference strain isolated from a treatment-naïve patient, it was still inhibitory to these isolates at low concentrations. Analysis of 4'-Ed4T-resistant HIV-1 obtained through in vitro selection revealed that the virus was also resistant to 3TC and had two amino acid mutations (P119S and T165A) in addition to the M184V mutation. Since 4'-Ed4T has increased anti-HIV-1 activity, decreased cytotoxicity, and a different resistance profile, it should be considered for further development as a new member of NRTIs.
