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## 1-( $\beta$ -D-DIOXOLANE) THYMINE IS EFFECTIVE AGAINST HIV-1-CONTAINING TAM AND M184V

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**BACKGROUND:** 1-( $\beta$ -D-dioxolane) thymine (DOT) is a potent inhibitor of HIV-1 with excellent pharmacological properties including good oral bioavailability in rats and monkeys, rapid intracellular phosphorylation to form DOT-TP, and low toxicity. In culture, DOT has shown selective activity against viruses containing thymidine analog mutations (TAM) and M184V. To confirm this and to further characterize its resistance profile, DOT-TP was evaluated against a large panel of purified HIV-1 reverse transcriptases (RT) with multi-nucleoside resistance mutations. Since ATP-dependent excision may also influence the clinical efficacy of FDA-approved nucleoside analogs, enzymatic studies were also designed to explore the mechanism of resistance.

**METHODS:** Site-directed RT mutants were constructed containing M41L, D67N, K70R, L210W, T215Y (TAM-mutant), M41L, T69S-SG, L210W, T215Y (69-mutant), V75I, F77L, F116Y, Q151M (151-mutant), or K65R (65-mutant)—the last 2 representing a non-excision mechanism of resistance, i.e., binding discrimination. The M184V mutation was studied separately and also added to the TAM, 69- and 151-mutant. A non-radioactive HIV-RT assay was used to study the ATP-mediated excision of DOT-MP, zidovudine (AZT)-MP, carbovir-MP, and tenofovir (TFV).

**RESULTS:** DOT-TP had a  $K_i$  value of 0.011  $\mu$ M for wild type RT (HXB2), which was similar to the  $K_i$  for AZT-TP (0.015  $\mu$ M). The 69-mutant RT demonstrated ATP-mediated excision, whereas, the 151- and the 65-mutant showed non-ATP-dependent decreased incorporation rates for all the inhibitors. The TAM-mutant RT demonstrated ATP-mediated resistance for AZT-TP and TFV-DP, whereas the M184V mutation, either by itself or in added form, had no significant effect on DOT-TP resistance. The  $IC_{50}$  of the various RT mutants were determined for the TAM-mutant; 69-mutant; 151-mutant; and 65-mutant RT, respectively, in the presence of 5 mM ATP. The level of resistance as

mutant  $IC_{50}$  /wild type  $IC_{50}$  were: DOT-TP (1.1; 4.1; 18; 3.9), AZT-TP (5.0; 9.6; 20; 2.0), carbovir-TP (ND; 3.4; 7.2; 6.1), and TFV-DP (2.5; 7.3; 3.3; 18), respectively.

**CONCLUSIONS:** Compared with other RT inhibitors, DOT-TP was overall more effective against RT-containing TAM, M184V, and K65R. The 69-mutant demonstrated a lower level of resistance to DOT-TP than AZT-TP and TFV-DP. However, as expected for dioxolane nucleosides, an increased non-ATP-dependent resistance was found with the 151-mutant. These enzymatic studies indicate that DOT resistance mainly involves binding discrimination and only modest ATP-dependent excision.

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