

POSTER 4**4'C-SUBSTITUTED-2-DEOXYADENOSINE IS A DELAYED CHAIN TERMINATOR OF HIV-1 REVERSE TRANSCRIPTASE**

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Nucleoside reverse transcriptase inhibitors (NRTIs) are important for the treatment of HIV-1 infections. All of the approved NRTIs lack the 3'-OH that is required for extension of viral DNA and act as chain terminators when incorporated by HIV-1 reverse transcriptase (RT). NRTI resistance occurs when RTs have an enhanced ability to discriminate NRTIs from the native nucleosides. We are trying to develop nucleoside analogs that are effective against the known NRTI-resistant viruses by analyzing novel nucleoside analogs that contain a 3'-OH that allows additional normal nucleotides to be incorporated after the analog has been incorporated, protecting the analog from excision. We have found that these delayed and kinetic chain terminators are able to inhibit excision-proficient HIV-1 RT mutants *in vitro* and block the replication of HIV-1-based vectors carrying NRTI-resistant RTs in cultured cells. Our initial studies using 4'C-alkylated thymidine analogs as NRTIs indicated the compounds were not well phosphorylated in cell culture. Additionally the termination mechanism was largely dependent on whether the substituent at the 4'C position was a methyl or ethyl group. Recently we have analyzed the efficacy of 4'C-methyl-2-deoxyadenosine and 4'C-ethyl-2-deoxyadenosine as inhibitors of wild-type and NRTI-resistant HIV-1 vectors. Cell-based screens of these compounds indicate inhibition of viral vectors at sub-micromolar concentrations with favorable selective indices. Both compounds are effective against most common NRTI-resistant mutations, with the exception of the exclusion mutant M184V. Continued exposure of these compounds in replication-competent viruses yields a unique panel of mutations in RT. *In vitro* studies with purified wild-type RT suggest that 4'C-methyl and -ethyl-2-deoxyadenosine triphosphate are incorporated differently than the thymidine analogs and act as delayed chain terminators. These 4'C-modified nucleoside analogs warrant further studies to assess clinical potential.