

POSTER 11**NUCLEOSIDE ANALOGS TARGETED AGAINST NRTI-RESISTANT 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 NNRTIs 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 implies that resistant RTs have an enhanced ability to discriminate between normal dNTPs and the NRTITPs. There are two mechanisms of NRTI resistance. Either the enhanced discrimination takes place at the time the NRTITP is incorporated into DNA (exclusion) or the mutant RT has gained the ability to selectively remove the NRTI after it has been incorporated into DNA (excision). We are trying to develop nucleoside analogs that are effective against the known NRTI-resistant viruses. The excision mechanism used by RT depends on the fact that conventional NRTIs remain at the end of the DNA primer strand. We have been 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 reverse transcriptase mutants *in vitro* and block the replication of HIV-1 based vectors carrying NRTI-resistant RTs in cultured cells. Recently we have analyzed the efficacy of C4'-methyl-2-deoxyadenosine and C4'-ethyl-2-deoxyadenosine as inhibitors of wild-type and NRTI-resistant HIV-1 vectors. Screening of these compounds in cells infected with HIV-1 based vectors indicates that the compounds have low cytotoxicity and inhibit replication at sub-micromolar concentrations. Both compounds are effective against most NRTI-resistant mutants, with the exception of the exclusion mutant M184V. Analysis of viral DNA isolated from infected cells by real-time PCR indicates the compounds are targeting early steps in viral DNA synthesis. *In vitro* studies with purified wild-type RT suggest incorporation of C4'-methyl-2-deoxyadenosine triphosphate is efficiently incorporated into viral DNA, but poorly extended. These C4'-modified nucleoside analogs warrant further studies to assess clinical potential.