

POSTER 13

ACYCLOVIR INHIBITS HIV-1 REVERSE TRANSCRIPTASE AND SELECTS RESISTANT VARIANTS *IN VITRO*

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We found that ACV triphosphate (ACV-TP) is a direct inhibitor of HIV-1 reverse transcriptase (RT). ACV-TP antiretroviral activity can contribute to the reduction of HIV-1 RNA load in HSV-2 coinfecting individuals treated with ACV or its prodrug valacyclovir, that have been documented in several recent clinical trials. ACV-TP binds the nucleoside-binding site of HIV-1 RT and causes HIV-1 DNA chain termination. ACV inhibits the replication of HIV-1 variants resistant to other nucleoside reverse transcriptase inhibitors (NRTIs), in *ex vivo* human lymphoid tissue. ACV drug pressure *in vitro* is linked to emergence of V75I as well as other HIV-1 RT mutations. These mutations emerge in infected cultures of peripheral blood mononuclear cells and MT-4 cell line under the selective pressure of a monophosphorylated prodrug that was designed to bypass the bottleneck in drug activation to the triphosphate form. Sequencing of HIV-1 RT amplified from plasma samples of four antiretroviral naïve patients treated with episodic or chronic herpes suppressive therapy revealed selection of NRTI-related mutations. Further studies of the development of HIV-1 resistance to ACV are necessary for assessing its impact on HIV-1 RT evolution *in vivo* and the potential clinical implications of chronic ACV treatment in HIV-1 infected individuals.