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The Novel NNRTI SJ-3366 Inhibits HIV-1 Through Multiple Mechanisms of Action: Effects on Reverse Transcriptase and Virus Attachment

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We have identified and characterized a potent new nonnucleoside reverse transcriptase inhibitor of HIV-1 that also is inhibitory against HIV-2. SJ-3366 inhibits HIV-1 replication at concentrations below 1 nM and exhibits a therapeutic index of greater than 4,000,000. Distinct from other members of the pharmacologic class of NNRTIs, SJ-3366 inhibited clinical strains of HIV-2 at a concentration of approximately 150 nM and exhibited a therapeutic index of nearly 20,000. Antiviral evaluations and the selection of drug resistant virus strains has resulted in the definition of amino acid residues Y181, K103, V106, Y181, Y188C and F227 as critical for the activity of SJ-3366. Selection of resistant strains in CEM-SS reproducibly results in the sequential appearance of Y181C, V106I and F227L amino acid changes in the RT. Combination resistance selection assays have suggested that a cocktail of SJ-3366 + 3TC mayt effectively retard the rate of selection of resistant strains compared with the rapid rates of selcetion seen with SJ-3366, nevirapine or 3TC alone or with a combination of SJ-3366 + nevirapine. Biochemically, SJ-3366 exhibited a K_i value of 2.7 nM and 3.8 nM in replicate assays with a mixed mechanism of inhibition (both the K_m and V_{max} were affected by the compound). In these enzymatic assays, SJ-3366 was specific for HIV-1 and did not inhibit HIV-2 reverse transcriptase. SJ-3366 also inhibits the attachment of virus to target cells by a complex mechanism which requires the compound to be added to the mixture of virus and cells, suggesting that SJ-3366 recognizes a complex traget formed when the virus attaches to its target cell. This mechanism of action occurs for both HIV-1 and HIV-2. SJ-3366 is inactive against SIV in both cell based and biochemical assays. Based on its significantly elevated therapeutic index and multiple mechanisms of action against HIV-1, SJ-3366 represents an exciting compound for use in HIV-infected individuals.

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Tenofovir Exhibits a Highly Favorable Profile in the Experimental Cell Culture Models for Renal Tubular Toxicity. T. Cihlar, D. C. Lin, and E. S. Ho. Gilead Sciences, Foster City, CA, USA.

Tenofovir (known also as PMPA), adefovir, and cidofovir are structurally related antiviral therapeutics. While on adefovir or cidofovir therapy, a proportion of the treated patients may develop drug-associated nephrotoxicity detected by changes in laboratory markers of renal tubular functions that are reversible upon drug discontinuation. In contrast, HIV patients enrolled in an ongoing Phase III study with tenofovir disoproxil, an oral prodrug of tenofovir, do not exhibit any significant signs of renal dysfunction even after prolonged (> 48 weeks) treatment. To better understand the differences in renal toxicity observed between these antiviral nucleotide analogs, we studied their *in vitro* cytotoxic effects in several experimental cell culture models. Adefovir and cidofovir inhibited the growth of primary human renal proximal epithelial tubule cells (RPTECs) with CC_{50} of 490 and 295 μM, respectively. In comparison, tenofovir showed only marginal effect on the growth of RPTECs with $CC_{50} \geq 2{,}000$ μM. Similarly, prolonged 25-day treatment of non-dividing RPTECs isolated from two independent donors revealed marked differences in the cytotoxicity of adefovir, cidofovir, and tenofovir (average CC_{50} values of 325, 85, and 2,750 μM, respectively). Recently, human renal organic anion transporter 1 (hOAT1), a membrane transport protein localized specifically in the basolateral membrane of the renal proximal tubule epithelium, has been implicated in the etiology of adefovir- and cidofovir-associated nephrotoxicity. Although tenofovir was transported by hOAT1 with an efficiency similar to that of adefovir and cidofovir, it showed 10- to 15-fold lower cytotoxicity than adefovir or cidofovir in CHO cells stably transfected with hOAT1 cDNA. This suggests that a lack of interference with essential intracellular function(s) rather than a difference in renal transport is responsible for improved nephrotoxicity profile of tenofovir. In conclusion, tenofovir showed a markedly lower cytotoxicity than adefovir or cidofovir in all cell culture models tested. These results correlate with the lack of nephrotoxicity observed in HIV-infected patients on prolonged tenofovir therapy.