3'-Fluoro- and 3'-Azido-Substituted Pyrimidine 2',3'-Dideoxynucleoside Derivatives are Potent Anti-Retrovirus Agents. J. Balzarini, M. Baba, R. Pauwels, P. Herdewijn and E. De Clercq. Rega Institute for Medical Research, B-3000 Leuven, Belgium.

A number of 3'-fluoro- and 3'-azido-substituted derivatives of 2',3'-dideoxyuridine (ddUrd), 2',3'-dideoxythymidine (ddThd), 2',3'-dideoxy-5-ethyluridine (ddEtUrd) and 2',3'-dideoxycytidine (ddCyd) have been evaluated for their inhibitory effect on the replication of human immunodeficiency virus (HIV). The most potent inhibitors of HIV-induced cytopathogenicity in human T4 lymphocyte MT4 cells were FddThd (50 %-effective dose 0.001 μM), AzddThd (0.004 μM), FddUrd (0.04 μM), ddCyd (0.30 μM) and AzddUrd (0.36 μM). Their selectivity indexes were 197, 5000, 400, 120 and 677, respectively. None of the 3'-substituted ddEtUrd derivatives had a marked anti-retrovirus effect. Based on their Ki/Km values, the following 3'-substituted 2',3'-dideoxynucleoside derivatives have the highest affinity for 2'-deoxythymidine (dThd) kinase: AzddThd (0.66), FddThd (3.4), AzddEtUrd (28), AzddUrd (71) and FddEtUrd (72). AzddCyd and FddCyd showed a higher affinity for 2'-deoxycytidine (dCyd) kinase (Ki/Km: 58 and 63, respectively) than the parental compound ddCyd (Ki/Km: 404). Thus, although phosphorylation is a prerequisite for the anti-retrovirus activity of the 2',3'-dideoxynucleoside derivatives, no correlation was found between the anti-retrovirus potency of the 3'-substituted 2',3'-dideoxynucleoside analogues and their affinity for either dThd kinase or dCyd kinase.

Potent and Selective Antiviral Activity of a New Nucleoside Analog (NSC-614846) Against Human Immunodeficiency Virus (HIV) *In Vitro*. R. Vince[1], M. Hua[1], J. Brownell[1], W. M. Shannon*[2], G.C. Lavelle[2], K.J. Qualls[2], O. Weislow[3], R. Kiser[3], R. Schultz[4], R.H. Shoemaker[5], J.G. Mayo[5], M.R. Boyd[5], and P.G. Canonico[6]. University of Minnesota, Minneapolis, MN 55455 USA[1], Southern Research Institute, Birmingham, AL 35255 USA[2], Program Resources, Inc., Frederick, MD 21701 USA[3], National Cancer Institute, Bethesda, MD 20892 USA[4], Frederick Cancer Research Facility, NCI, Frederick, MD 21701 USA[5], and U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, MD 21701 USA[6].

The synthesis and *in vitro* antiviral activity of a new nucleoside analog (NSC-614846) and related compounds against human immunodeficiency virus (HIV) will be described for the first time. NSC-614846 was evaluated for its selective inhibitory effects on HIV replication and virus-induced cytopathic effects (cpe) in human T-lymphoblastoid (ATH8 and MT-2) cell lines *in vitro* by means of a cpe-inhibition assay using a microculture tetrazolium XTT procedure to quantitatively assess the ability of the compounds to protect the host cells from the cytotoxic effects of the virus. NSC-614846 exhibited significant activity against HIV in both ATH8 and MT-2 cells with an MIC_{50} in the range of 0.25 to 0.50 μg/ml. Cytotoxicity for the host cells was observed at concentrations of 50 μg/ml for the ATH8 cells and 250 μg/ml for the MT-2 cells. The selectivity ratio was therefore between 100 and 1000, depending on the cell line. Results with NSC-614846 were similar to those obtained with 2',3'-dideoxycytidine (ddC) in parallel assays. (Supported by USAMRIID Contract DAMD17-86-C-6013, NCI Contract NO1-CA-74102, and NIH Grant RO1 CA23263.)