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Retrovirus Infections III

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Identification of Distinct Subgroups of Nonnucleoside Reverse Transcriptase Inhibitors Defined by Cross-Resistance Phenotypes of Drug-Resistant Virus Isolates. R.W. Buckheit, Jr. and V. Fliakas-Boltz, Southern Research Institute-Frederick Research Center, Frederick, MD, USA

Virus isolates resistant to HIV-1 specific, nonnucleoside reverse transcriptase inhibitors have been obtained *in vitro* by serial passage in culture. The agents used in the selection of these isolates include TIBO, thiazolobenzimidazole, diphenyl sulfone, calanolide A, oxathiin carboxanilide and HEPT. With the exception of calanolide A, each of these compounds is inactive against the pyridinone-resistant strain A17. Each of these resistant virus strains exhibits high level resistance (greater than 10-20-fold) to the selecting agent without any change in sensitivity to AZT. Cross-resistance patterns were analyzed to determine if resistance to the selecting agent would necessarily result in the generation of resistance to all members of this structurally diverse class of nonnucleoside inhibitors. The results of these studies suggest that the compounds may be grouped into four distinct classes. The first group (Group I) of nonnucleoside inhibitors includes the compounds thiazolobenzimidazole and oxathiin carboxanilide. The virus isolates resistant to these compounds are cross-resistant to all members of the nonnucleoside class of compounds. Group II includes the natural product calanolide A. Calanolide A-resistant virus is inhibited by all of the compounds except for calanolide A. The nonnucleoside inhibitors diphenyl sulfone, nevirapine and pyridinone comprise Group III. Viruses resistant to these compounds are cross-resistant to all of the HIV-1 specific compounds evaluated except for calanolide A. The diphenyl sulfone-resistant virus is ten-fold more sensitive to calanolide A than to wild type virus. The nevirapine and pyridinone-resistant viruses also exhibit enhanced sensitivity to calanolide A. The final group (Group IV) includes the HIV-1 specific nucleoside HEPT. The HEPT-resistant virus is not cross-resistant to any of the compounds studied and exhibits increased sensitivity to the Group I compounds thiazolobenzimidazole (5-fold) and oxathiin carboxanilide. These results suggest that combination drug therapy using two nonnucleoside inhibitors may be beneficial. Analysis of the mutations responsible for these phenotypes and the *in vitro* selection of multiple drug resistant virus strains are in progress.This work was supported in part by contracts NO1-AI-05087 (NIAID) and NO1-CM-37818 (NCI).