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Prospective use of AZT resistance as a clinical decision-making tool in patients treated with AZT or ddI. B. Conway, D.S. Ko, N. Foss, D.W. Cameron, L.G. Filion, F.J. Diaz-Mitoma. Department of Microbiology & Immunology, University of Ottawa, Ottawa, Canada.

As more antiretroviral agents become available, criteria should be established for the selection of appropriate therapy (Rx) for a given patient. We have followed 26 patients on AZT Rx to determine the stability of the AZT resistance phenotype. For the resistance assays, mononuclear cells isolated from the infected subjects were stimulated with PHA-P and IL-2 (96 hours), then resuspended in fresh viral culture medium in the presence of 0 or 10μM AZT, and incubated for 72 hours. The cells were then harvested for quantitative proviral HIV-1 PCR and proviral load was compared in the two culture conditions. AZT resistant isolates were deemed to be present in cultures showing <25% reduction in proviral load in the presence of 10μM AZT. At entry, 11 patients (median 9mo AZT Rx) had susceptible isolates while 15 (median 12mo AZT Rx) had resistant isolates. In the susceptible group, 5/8 remaining on AZT and 3 changed to ddI retained susceptibility. In the resistant group, 6 remained on AZT and retained resistance. Of the 9 changed to ddI, 6 recovered AZT susceptibility in 1-8 months and retained this phenotype ≥12mo. AZT resistance phenotype (including recovery of susceptibility on ddI) appears to be stable once established. This information could be used, along with other clinical and virologic criteria, in selecting appropriate therapy for HIV-1 infected individuals.

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1,5-Anhydrohexitol Nucleoside Analogues as New Antiviral Entities

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Antiviral activity has been described for several classes of nucleoside analogues with modifications in their sugar part. Well known examples are acyclic nucleoside analogues (e.g. acyclovir), fluorinated pentose nucleosides (e.g. FMAU, FIAC), nucleosides with a four membered ring (e.g. oxetanocin), carbocyclic nucleosides (e.g. carbovir) and phosphorylated analogues (e.g. PMEA). Nucleosides with a six-membered sugar moiety have, to the best of our knowledge, not been reported to exhibit selective antiviral activity (i.e. without cytotoxicity). Here, we report the synthesis and antiviral activities of a new class of nucleoside analogues containing a 1,5-anhydrohexitol moiety. Starting from glucose, the synthesis follows classical carbohydrate manipulations leading to 3-deoxy-1,5-anhydrohexitol derivatives which are then transformed to nucleoside analogues through nucleophilic substitution. Some of the compounds thus obtained proved inhibitory to herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), and thymidine kinase (TK)-deficient mutants of HSV-1 and VZV at concentrations that were not toxic to the host cells. Although the mechanism of action of this new class of antiviral agents needs to be resolved, the mere fact that 1,5-anhydrohexitol nucleoside analogues interfere with the replication of DNA viruses points to their structural resemblance with the natural 2'-deoxynucleosides.