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Effects of 28 Day Treatment with Azidothymidine (AZT) Initiated 1 to 72 Hours After Infection With Simian Immunodeficiency Virus (SIV). L.N. Martin, M. Murphey-Corb, K.F. Soike and B. Davison-Fairburn. Delta Regional Primate Research Center, Tulane University, Covington, LA, U.S.A.

We have studied the effects of AZT treatment initiated 1, 8, 24 or 72 hr. postinfection (PI) with 10 ID-50 SIV/Delta B670 using 5 monkeys per group. After initiation, the animals were treated every 6 hr. with 25 mg/kg (100 mg/kg/day) for 28 days. AZT treatment resulted in decreased hematocrit compared to untreated infected monkeys (controls) with recovery by 15 days after treatment ceased. Treatment begun as early as 1 hr. PI did not prevent infection. Treatment initiated 1 or 8 hr. PI reduced several indicators of disease progress compared to controls or to monkeys in which treatment was delayed for 24 or 72 hr. including reduced mean antigenemia levels, reduced peak levels of antigenemia attained, reduced duration of antigenemia, reduced titers of infectious SIV in serum, and delayed SIV-induced selective decreases in CD4+ CD29+ helper-inducer cells. One animal in each of the 1 and 8 hr. treatment initiation groups had no detectable antigenemia in contrast to the other groups. Clinical signs were much less frequently observed when treatment was initiated 1 to 8 hr. PI. Delaying treatment for 24 to 72 hr. decreased the effectiveness. The 24 and 72 hr. groups did not display the decreases in antigenemia, the delay in depletion of CD4+CD29+ cells, nor the decreased clinical signs observed in the 1 or 8 hr. treatment initiation groups. However, treatment initiated at 24 or 72 hr. did prevent the development of persistent antigenemia observed in 2 of the 5 controls. (Supported by NIH contract AI62560).

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Initial Pharmacokinetic Studies on the Potent HIV-1 and HIV-2 Inhibitors PVAS and PAVAS

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The sulfated polymer polyvinylalcohol sulfate (PVAS) and its copolymer with acrylic acid (PAVAS) have proved to be potent and selective inhibitors of HIV-1 and HIV-2 *in vitro*. The 50% inhibitory concentration (IC_{50}) of these compounds for HIV-1 ($HTLV\text{-}III_B$) and HIV-2 ($LAV\text{-}2_{ROD}$) replication in MT-4 cells is 0.3-0.5 μg/ml, while no drug toxicity to the host cells is observed at concentrations up to 2.5 mg/ml. We have now conducted initial pharmacokinetic studies with these compounds in rabbits. The compounds were injected intravenously and their serum drug levels were determined based on the inhibition of HIV-2 ($LAV\text{-}2_{ROD}$)-induced cytopathogenicity in MT-4 cells. This bio-assay allowed the detection of serum concentrations of ≥ 0.13 mg/ml for PVAS (MW: 40,000; 84% sulfation), ≥ 0.03 mg/ml for PAVAS # 1 (MW: 20,000; 82% sulfation),and ≥ 0.038 mg/ml for PAVAS # 2 (MW: 5,000; 67% sulfation). The serum concentration of PAVAS and PVAS following intravenous injection at a dose of 0.1 g/kg decayed biphasically with an initial half-life of approximately 90-120 min. At 20 min after injection, serum drug concentrations ranged from 1.4 to 1.5 mg/ml, whereas at 8 h after injection, the following serum concentrations were detected: 0.25 mg/ml for PVAS, 0.32 mg/ml for PAVAS # 1 and 0.12 mg/ml for PAVAS # 2. These serum drug concentrations are far in excess of the concentrations that are required to inhibit HIV-1 or HIV-2 replication *in vitro*.