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Suppression of Murine Retroviral Disease As a Model for AIDS by 2',3'-Dideoxy-2',3'-didehydrothymidine (D4T). R. W. Sidwell, K. J. Okleberry, R. A. Burger, R. P. Warren, and J. D. Morrey. Institute for Antiviral Research, Utah State University, Logan, UT, USA.

The thymidine analog D4T, a known human immunodeficiency virus inhibitor now undergoing clinical development by Bristol-Myers Squibb Co. as a potential AIDS therapy, was significantly inhibitory to Friend virus complex (FV) infections induced in vitro as determined by a focal immunoenzyme assay, and in F_1 hybrid mice. The hybrid mice used contain the Rfv-$3^{r/s}$ genotype, allowing study of treatment effects on development of specific neutralizing antibodies as well as on viral parameters of splenomegaly, splenic and plasma virus titers, and splenic viral RNA and has proven useful as an animal model for AIDS. The D4T was given by oral gavage 2, 3, or 4 times daily for 14 days beginning 4 hr post-virus inoculation. Dosages ranged from 47 to 750 mg/kg/day. Doses of 94 mg/kg/day and higher were inhibitory to all viral parameters when administered 3 times daily. The 4 times daily treatments were effective at 375 mg/kg/day, the highest used with this regimen. Virus-specific neutralizing antibodies developed in all infected, treated animals. The drug was reasonably well tolerated in toxicity controls, although doses of 375 and 750 mg/kg/day caused host weight loss, variable hematocrit decreases and some depression of natural killer cell activity. This is the first report of the murine retrovirus-inhibitory effects of this compound; the data confirm D4T to be a possible candidate for development as an anti-AIDS therapy. (Supported by Division of AIDS, NIAID, NIH Contract NO1-AI-72662)

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VIROLOGICAL IDENTIFICATION OF THREE SUBGROUPS OF PATIENTS DURING EXTENDED TREATMENT WITH ZIDOVUDINE

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We have performed a detailed virological study from the serial peripheral blood samples of 36 individuals receiving the antiviral drug zidovudine for up to three and a half years We were unable to isolate the human immunodeficiency virus (HIV) from 6 subjects (Group A). Zidovudine sensitive strains of HIV were isolated from 12 subjects (Group B) and 18 individuals yielded zidovudine resistant virus (Group C). Highest levels of CD4+ cells were seen in Group A. A reduced absolute CD4+ count correlated with isolation of zidovudine sensitive virus (Group B) and a further reduction was observed in patients from whom zidovudine resistant virus was isolated (GroupC). The monthly median CD4+ count (cells per cubic millimetre) was plotted against time on AZT for each of the three groups of patients for the first twelve months of treatment. Group A exhibited a marked increase in CD4+ count from 338 at time zero to 486 at three months, during initiation of drug therapy. The CD4+ cell count then stabilised around 400 for the remaining nine monthsof the study. Cell counts in Group B decreased rapidly from 212 at time zero to 112 at two months and then decline steadily to 69 after eleven months of treatment. In Group C, there was no marked increase or decrease in CD4+ counts at any point during therapy. The counts in this group were consistently lower than those of Group B, where CD4+ counts, for most of the time, remained above 125 during the same period. Whether the decline in CD4+ cell count is caused by the emergence of AZT-resitant HIV-1 or whether it is spurious will require further detailed study with a larger group of patients and a more detailed analysis of the HIV-1 itself in conjunction with the clinical state of the patients. Nevertheless, our study indicates the usefulness of detailed virology and the possible application to clinical management of patients.