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SYNERGISTIC AND COMPLEMENTARY EFFECTS OF THE ANTI-HIV-1 MICROBICIDES CAP AND UC781 IN COMBINATION

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INTRODUCTION: In order to develop more effective anti-HIV-1 microbicides, it is essential to design combinations of microbicides with different mechanisms of action. Here we determined whether the combination of cellulose acetate 1,2-benzenedicarboxylate (CAP), a polymer that blocks HIV-1 entry by targeting gp120 and gp41, and UC781, a tight-binding HIV-1 reverse transcriptase inhibitor (RTI), has synergistic and complementary effects on HIV-1 infection.

METHODS: The inhibitory activities of the individual and combined microbicides on HIV-1 replication were determined by ELISA for p24 production. The data were analyzed for cooperative effects by using the CalcuSyn program for calculating the combination index (CI).

RESULTS: Combination of CAP and UC781 resulted in effective synergy for inhibition of HIV-1 replication. The EC95 values for the combination were reduced about 15-20-fold as compared with those corresponding to the single compounds. Combinations of CAP with other RTIs, such as efavirenz or AZT, also had significant synergistic effects on inhibition of HIV-1 infection. In addition, CAP and UC781 had complementary effects against HIV-1 infection since: 1) CAP inhibited infection by the UC781-resistant strain HIV-1IIB A17, and 2) Pretreatment of MT-2 cells with UC781, but not CAP, abolished subsequent infection after removal of the compound.

CONCLUSIONS: The combination of CAP and UC781 resulted in significant synergistic and complementary effects against HIV-1 infection. This was translated into meaningful dose reductions for each compound. These findings provide a strong rationale for developing combinations of microbicides with distinct mechanisms of action and

"CAP + UC781" combination represents a promising microbicide combination for prevention of sexual transmission of HIV-1.

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