

**Title:** Evaluation of 6% Cellulose Sulfate and 0.5% PRO2000 Gel Microbicide Efficacy in a Single-Dose Intravaginal R5+X4 SHIV Infection Model in Rhesus Macaques Pre-treated with Depo-Provera

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**Background:** Nonhuman primate models play a critical role in preclinical evaluation of topical microbicides. We have shown that 6% cellulose sulfate (CS) gel prevents the development of viremia and seroconversion in rhesus macaques challenged weekly with 100 TCID<sub>50</sub> of R5 and X4 SHIV (3:1 ratio) (R5+X4). The current study was aimed at comparing CS efficacy in Depo-Provera treated animals infected by a single dose of 300 TCID<sub>50</sub> of R5+X4 SHIV.

**Methods:** Animals (n=30) were treated intravaginally with 2 ml of active or placebo gel (using their clinical formulations) and challenged 30 min later with 300 TCID<sub>50</sub> of R5+X4 SHIV. Infection was monitored by measuring plasma viremia, antibody seroconversion and proviral DNA. Results were analyzed with Fisher's exact test.

**Results:** The study was undertaken as two experiments of 12 monkeys each (n=6 per group). The combined outcome showed a statistically significant protection of CS gel compared to placebo (1/12 vs. 7/12 animals were free of systemic infection in the placebo and CS group, respectively; p=0.0272). As in the low-dose repeated challenge model, proviral DNA was occasionally detected in PBMC and lymphoid cells of the aviremic animals. PRO2000 (0.5%) gel, included in the second experiment, protected 4/6 animals in this model (p=0.0217).

**Conclusions:** CS prevented systemic viremia in all animals challenged weekly with 100 TCID<sub>50</sub> R5+X4 SHIV and in about 60% of Depo-treated animals challenged with a single dose of 300 TCID<sub>50</sub>. PRO2000 also protected about 60% of these animals. Given the differences in the models, these results are consistent and demonstrate the preclinical efficacy of these gels. The fact that these results do not predict the outcome of clinical trials may be related to multiple reasons, including definition of protection, cutoff for predictive value and issues related to consistent and proper use of the gels by humans.