A DMPA (Depot Medroxyprogesterone Acetate) dose modeling human use and its effect on vaginal SHIV acquisition risk

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Introduction Hormonal contraception with DMPA may increase HIV acquisition risk, but observational human studies are inconclusive. Animal models can help evaluate this question. Previous studies in macaques demonstrated increased SIV infection risk associated with high DMPA doses of 30 mg (Veazey et al, Current HIV Research, 2012), equal to 4.3 mg/kg in an average weight (7kg) macaque. Here we test the impact of a lower dose, designed to resemble human contraceptive DMPA use, on vaginal SHIV acquisition risk in pigtail macaques.

Methods Macaques metabolize DMPA faster than do humans, necessitating more frequent administration. We previously identified a low, monthly dose of 1.5 mg/kg can achieve long-lasting suppression of ovulation (Butler et al, in press). The standard human contraceptive dose of 150 mg is given every 3 months, equates to 2 mg/kg in an average weight (75kg) woman. Eight pigtail macaques (Macaca nemestrina) received repeated 1.5 mg/kg DMPA doses monthly, while four served as real-time untreated controls; historical data from 7 additional controls were available. To determine SHIV acquisition risk, we administered 20 weekly vaginal SHIVSF162P3 exposures at 10 TCID-50, designed to cause infection in half of control macaques and allowing detection of increased infection in the DMPA group. DMPA treatments were continued during virus exposures and until at
least 12 weeks after infection. Menstrual cycling was monitored by visual observation and plasma progesterone. Vaginal epithelial thinning was measured in biopsies taken after infection or at conclusion of virus exposures.

**Results** Seven of eight DMPA-treated macaques became infected, compared to six of 11 controls (p=0.18, Fisher’s exact test). It took a median 5.5 challenges to infect DMPA-treated macaques, and 9 challenges for controls (p=0.27; exact conditional logistic regression). The exact odds ratio was 2.2 (CI 0.6 – 8.3). Plasma MPA levels were measureable in all DMPA-treated animals, and menstrual cycling was effectively suppressed. The vaginal epithelium was thinned after DMPA-treatment in all animals (mean 30 and 219 micrometers in DMPA-treated and control macaques, respectively, p<0.0001, unpaired t-test comparing log-10 transformed means).

**Conclusions** SHIV infections in DMPA treated macaques were 2.2 times those of controls, although this was not statistically significant. The result is remarkably similar to observational studies of human DMPA use, which have shown HIV risk increases of a similar magnitude and of variable significance. Taken together with previous studies of higher DMPA doses in macaques, the results suggest a dose-dependent effect of DMPA on SIV or SHIV acquisition.

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