Depot-medroxyprogesterone acetate does not increase genital SHIV shedding in macaques

J. Radzio[1], K. Hanley[2], D. Hanson[1], J. Mitchell[1], S. Ellis[1], F. Deyounks[1], L. Jenkins[1], W. Heneine[1], J.G. García-Lerma[1]

[1]Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA, US; [2]Emory University, Department of Pathology, Atlanta, GA, US

I. Background

- Epidemiologic studies in women remain inconclusive on whether the injectable contraceptive depot-medroxyprogesterone acetate (DMPA) increases mucosal HIV shedding.
- Increased mucosal shedding may potentially increase HIV transmission rates.
- We recently identified a low 3 mg DMPA dose that suppresses ovulation in pigtail macaques and recapitulates plasma MPA exposure and changes in vaginal epithelial thickness seen in women *(Radzio, et al. CROI 2013, submitted)*.

The goal of this study is to determine the impact of a physiologic dose of DMPA on acute SHIV viremia and genital virus shedding.

II. Study Design



12 pigtail macaques

6 animals (no DMPA)

6 animals (Monthly injections of 3 mg of DMPA)

Weekly vaginal exposures to low (50 $TCID_{50}$) doses of $SHIV_{162P3}$ until confirmed infection

- Weekly collection of blood, rectal and vaginal secretions
- Secretions collected only after first RNA detection in plasma
- SHIV RNA measured by an RT-PCR assay with a sensitivity of 50 copies/mL
- Virus levels in secretions corrected for blood contamination based on hemoglobin levels, individual macaque hematocrit values, and plasma SHIV RNA levels

III. Animal Characteristics

Untreated Animals

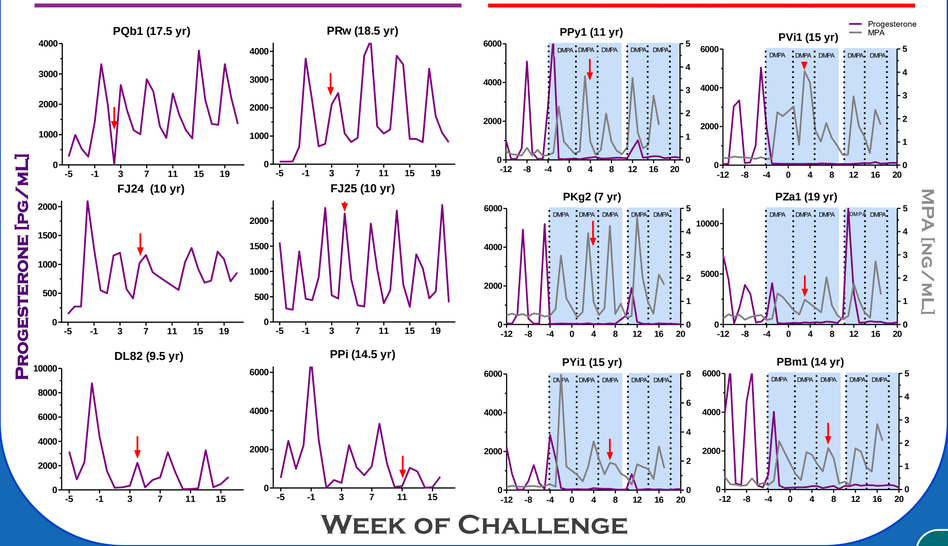
Animal ID	Age	Weight (kg)	Wk RNA (+)
PQb1	17.5	7.83	2
PRw	18.5	7.98	3
FJ24	10	7.26	6
FJ25	10	7.34	5
DL82	9.5	8.4	4
PPi1	14.5	10.74	11
Mean	*13.33*	*8.26*	*5.17*

DMPA-treated Animals

Animal ID	Age	Weight (kg)	Wk RNA (+)
PPy1	11	5.98	4
PVi1	15	9.05	3
PZa1	19	10.54	3
PKg2	7	7.74	4
PYi1	15	10.28	6
PBm1	14	9.38	6
Mean	*13.50*	*8.83*	*4.33*

IV. Progesterone Levels

Figure 2. *Progesterone and MPA levels in macaques prior to and during vaginal challenges.* **Progesterone (purple)** and **MPA levels (gray)** were determined at the University of Wisconsin Primate Research Center. The red arrows indicate first RNA detection. The DMPA dose scheduled for week 9 was not given due to logistic reasons and was delayed to week 10. This 1 week delay resulted in a transient spike in plasma progesterone, in all animals, that was rapidly suppressed. Years of age is also shown.



V. SHIV RNA levels in plasma and secretions

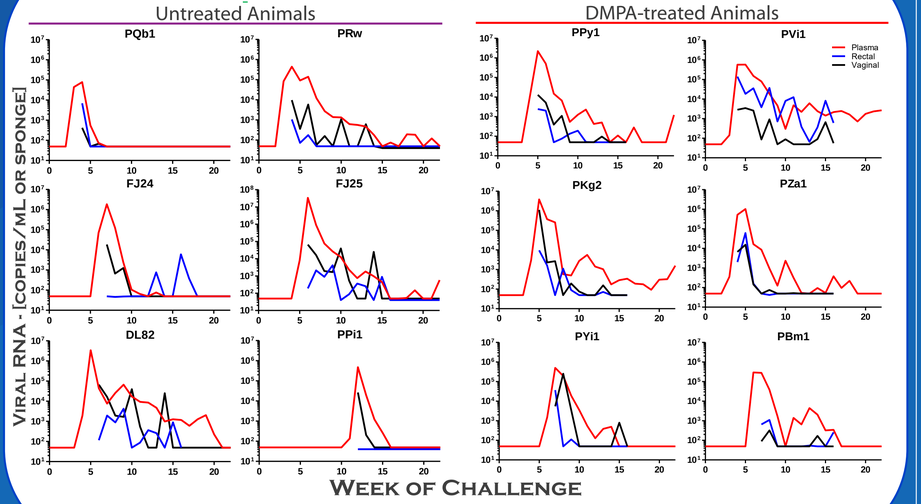


Figure 3. *SHIV RNA in plasma (red), rectal secretions (blue) and vaginal secretions (black).* Vaginal and rectal secretions were collected in Weck-Cel Surgical Spears (Medtronic Ophthalmic) using established protocols (Garcia-Lerma *et. al.*, Sci Trans Med 2010).

VI. Statistical Analysis

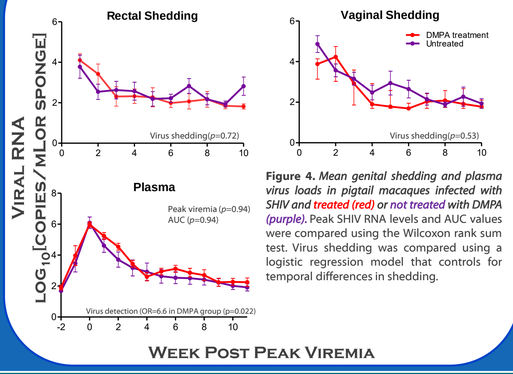


Figure 4. *Mean genital shedding and plasma virus loads in pigtail macaques infected with SHIV and treated (red) or not treated with DMPA (purple).* Peak SHIV RNA levels and AUC values were compared using the Wilcoxon rank sum test. Virus shedding was compared using a logistic regression model that controls for temporal differences in shedding.

VII. Conclusions

- Using this new pigtail model, we show that DMPA has minimal impact on plasma virus loads and no effect on rectal and vaginal SHIV shedding during acute infection.
- This model allows longitudinal and frequent sampling that provides a better representation of the overall levels of shedding, and thus, the observed lack of effect by DMPA documented during periods of high and low viremia is significant.
- Our observations are limited to acute infection, since SHIV infection generally results in low to undetectable virus set points
- These data do not support a role for DMPA in increasing mucosal virus shedding and transmissibility.

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National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Division of HIV/AIDS Prevention – Lab Branch

E-mail: cdcinfo@cdc.gov | Web: www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Contact: Jessica Radzio, vcx8@cdc.gov, 404.639.0234