Sex and gender differences in antiretroviral-based prevention: insights from macaque studies

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Sex and gender differences in antiretroviral-based prevention

- Different drug penetration in rectal and vaginal tissues
  - Same level of adherence may have a different impact on rectal and vaginal efficacy

- Potential alterations of effective drug protection thresholds due to increases in susceptibility to infection
  - Inflammation, CCR5 expression (sexually transmitted infections, hormonal contraceptives)
  - Luteal vs. follicular phase of the menstrual cycle

- Changes in local drug concentrations and systemic drug PK profiles
  - Interactions with hormonal contraceptives
  - Changes in vaginal epithelium due to DMPA use
  - Bidirectional dosing
Different pharmacokinetic profile of FTC and TDF in rectal and vaginal tissues after oral dosing in pigtail macaques

Table 1. Intracellular TFV-DP and FTC-TP concentrations at 24 h and 3 days in vaginal, rectal, and lymphoid tissue after a single oral dose.

<table>
<thead>
<tr>
<th></th>
<th>TFV-DP</th>
<th>FTC-TP</th>
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<tbody>
<tr>
<td></td>
<td>fmols/10⁶ cells</td>
<td>fmols/mg tissue</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>3 days</td>
</tr>
<tr>
<td>Vaginal</td>
<td>24 (22–39)</td>
<td>18 (6–32)</td>
</tr>
<tr>
<td>Rectal</td>
<td>634 (11–783)</td>
<td>110 (51–336)</td>
</tr>
<tr>
<td>Lymphoid (mesenteric, axillary, inguinal)</td>
<td>21.5 (14–39)</td>
<td>25 (16–57)</td>
</tr>
<tr>
<td></td>
<td>24 h</td>
<td>3 days</td>
</tr>
<tr>
<td>Vaginal</td>
<td>122 (91–138)</td>
<td>80 (25–183)</td>
</tr>
<tr>
<td>Rectal</td>
<td>117 (44–125)</td>
<td>56 (19–169)</td>
</tr>
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doi:10.1371/journal.pone.0050632.t001
Can peri-coital Truvada retain prophylactic efficacy against vaginal infection?
Prevention of Vaginal SHIV Transmission in Macaques by a Coitally-Dependent Truvada Regimen

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FTC/TDF (n = 6)*

Placebo (n = 6)

Drug or placebo (-24h)  Drug or placebo (+2h)

*orally by gavage

Figure 2. Complete protection against vaginal SHIV transmission by intermittent PrEP with Truvada. Survival curves represent the cumulative percentage of uninfected macaques as a function of the number of months in the study period (4 challenges per month). Control macaques become infected after a median of 3.5 exposures or about 1 menstrual cycle. Virus challenges in the macaques receiving Truvada were stopped after 18 SHIVs.tg3 exposures or about 4.5 menstrual cycles. Protected animals remained seronegative and RNA/DNA negative during a follow up period of 18 weeks. doi:10.1371/journal.pone.0050632.g002
Different pharmacokinetic profile of maraviroc in rectal and vaginal secretions and tissues after oral dosing
Hormonal contraceptives and efficacy of PrEP

- Women using contraceptives are a target population for PrEP
- Can hormonal contraceptives alter drug protection thresholds by PrEP?
  - Potentially increase susceptibility to infection, particularly injectable formulations
  - Potential interactions with ARVs including drug absorption from vaginal gels
- Depo provera (DMPA)
  - Widely used in areas with high HIV incidence
  - Moderate thinning of the vaginal epithelium in women
  - Macaque dose of 30 mg DMPA optimized to ensure infection and does not recapitulate human effects; causes significant thinning
  - Need to develop relevant animal models to evaluate potential interactions between DMPA and PrEP

Dramatic changes in vaginal epithelium thickness of pigtail macaques after 30 mg DMPA

Normal menstrual cycle

Follicular

Luteal

After 30 mg DMPA

3wk

6wk

9wk

12wk

Progesterone [pg/mL]

30 mg DMPA

Vaginal epithelium thickness

30 mg DMPA
Pharmacokinetic profile of DMPA in pigtail macaques demonstrates dose proportionality

<table>
<thead>
<tr>
<th>Depo provera (mg)</th>
<th>Cmax (ng/ml)</th>
<th>AUC_{0-84} (ng*day/ml)</th>
<th>Tmax (days)</th>
<th>Half-life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.67</td>
<td>22</td>
<td>14</td>
<td>5.6</td>
</tr>
<tr>
<td>3</td>
<td>2.96</td>
<td>68</td>
<td>14</td>
<td>8.4</td>
</tr>
<tr>
<td>15</td>
<td>9.64</td>
<td>206</td>
<td>21</td>
<td>6.7</td>
</tr>
<tr>
<td>30</td>
<td>19.84</td>
<td>391</td>
<td>21</td>
<td>9.9</td>
</tr>
<tr>
<td>Humans (150 mg)*</td>
<td>1-7</td>
<td>100</td>
<td>14-21</td>
<td>30-50</td>
</tr>
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*Bassol et al., Fertility and Sterility 1984; Nanda et al., Fertility and Sterility 2008; Depo-Provera® Prescription insert
The higher the DMPA dose, the more pronounced and prolonged effect on vaginal epithelial thickness.
Plasma MPA levels and vaginal epithelial thickness show a dose response relationship
Plasma progesterone and estradiol in pigtail macaques receiving different DMPA doses

![Graphs showing plasma progesterone and estradiol levels for different DMPA doses (30 mg, 15 mg, 3 mg, 1 mg).]
Monthly cycles of 3 mg IM DMPA efficiently suppress progesterone production in pigtail macaques

Average peak MPA levels in women = 2.5 ng/ml (1.6-3.3 ng/ml); Nanda, Contraception 2008
Average peak progesterone levels in women receiving DMPA = 400 ng/ml (140-110 ng/ml); Clark, Fertility and Sterility 2001

Radzio et al., poster # 992
Integration of pigtail macaque models of HIV risk, transmission, and prevention: model of DMPA and PrEP

MODEL OF HIV TRANSMISSION

MODEL OF HIV RISK

MODEL OF HIV PREVENTION

FTC/TDF (n = 6)*
Placebo (n = 6)

Drug or placebo (-24h)
Drug or placebo (+2h)

*orally by gavage
DMPA does not reduce the prophylactic efficacy of FTC/TDF in pigtail macaques

Efficacy of oral FTC/TDF

<table>
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<tr>
<th>No DMPA</th>
<th>With DMPA</th>
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<tr>
<td>100% (95%CL = 87.5%-100%)</td>
<td>100% (95%CL = 90%-100%)</td>
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Fisher’s exact test; exact unconditional estimation of relative risk
Similar plasma PK profile for FTC and TDF in DMPA-treated and untreated pigtail macaques.
Other potential hormone effects on ARVs: systemic drug absorption and bidirectional dosing following vaginal gel application in macaques

- **Normal menstrual cycle**
  - Substantially higher plasma drug concentrations during the progesterone-dominated luteal phase
  - Higher TFV-DP levels in vaginal lymphocytes during the luteal phase

- **Drug absorption after DMPA use**
  - Extended luteal-like absorption for up to 5 weeks; may provide added protection following DMPA treatment

- **Rectal drug penetration after vaginal gel application (or vice versa)**

Dobard & Heneine, poster W-157
Nuttall et al., AAC 2012
Summary and future directions

- Possibility to integrate macaque models of hormonal contraceptives with models of HIV transmission and prevention
  - Evaluate potential impact on efficacy of PrEP
  - Explore interactions with drug PK and absorption from vaginal gels or rings
  - Understand impact on bidirectional dosing from vaginal gel applications
- Findings in macaques receiving DMPA and FTC/TDF suggest that women using DMPA will fully benefit from PrEP
- Need to integrate other models of HIV risk in women
  - Co-infection models with SHIV, Trichomonas vaginalis, and Chlamydia trachomatis
Acknowledgments

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<th>DHAP, CDC</th>
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Disclaimer: The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

This work was partially supported by Interagency Agreement Y1-Al-0681-02 between CDC and NIH.