Multipurpose Intravaginal Ring: Tenofovir / Levonorgestrel

Christine Mauck, MD, MPH
Why develop a multipurpose ring?

• Providing drug in a **ring** is likely to facilitate use:
  – Long-acting - does not require attention at the time of sex or daily attention, yet woman-controlled unlike implant or IUD
  – Discreet: does not require user to carry or dispose of anything
  – One ring lasts for 90 days - more economical
  – Can deliver other active ingredients
  – Acceptable, expands method mix

• TFV: has shown proof of concept for prevention of HIV & HSV when used topically and systemically
Why develop a multipurpose ring?

- Providing contraception in addition to HIV prevention is likely to facilitate use:
  - Adherence is associated with perception of risk
    - Most women see themselves as at high risk of pregnancy (but not HIV)
  - Use of contraceptive may be more socially acceptable than use of HIV preventive
In this talk, I will describe:

• CONRAD tenofovir/levonorgestrel ring:
  – Choice of LNG
  – Ring design
  – Preclinical testing
  – Clinical study design
Use of Levonorgestrel

- Synthetic progestin used in many contraceptives:

<table>
<thead>
<tr>
<th>Type</th>
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<th>LNG + estrogen</th>
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<tr>
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<tr>
<td>Transdermal</td>
<td>LNG patch</td>
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<td><strong>Genital tract</strong></td>
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(Bold = commercially available. Others investigational or discontinued)
### Use of Levonorgestrel

**Synthetic progestin used in many contraceptives:**

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Systemic vs genital delivery of LNG

- Genital delivery $\rightarrow$ lower plasma levels and higher genital tract levels\(^1\)
- Distribution from the upper vagina into the endometrium may be from uterine vein to uterine artery – “Uterine first pass effect”\(^2\)
- Genital tract effects from genital delivery may differ from those seen after systemic delivery

\(^1\)Devoto 2005 Fertil Steril 84(1):46-51
\(^2\)Lete 2010 Curr Drug Met 11:839-49
Levonorgestrel

Main mechanisms of action:

1) Suppression of ovulation
2) Cervical mucus thickening, impeding sperm migration
Suppression of ovulation

- Complete suppression of ovulation not needed for a contraceptive effect.
- Alterations in endocrine profile can provide contraception while maintaining normal bleeding patterns:
  - No development of the ovarian follicle (and therefore no ovulation)
  - Some follicular development but no ovulation and no increase in progesterone
  - Follicular development with luteinized unruptured follicle and progesterone production
  - Normal ovulation
- If ovulation does occur, changes in cervical mucus prevent pregnancy
Complete suppression of ovulation not needed for contraception

- **Mirena:**
  - Mirena: ~50% of cycles are ovulatory in the 1\textsuperscript{st} year, and about 75% in the 4\textsuperscript{th} year, but pregnancy rate is 0.7% over 5 years

- **Norplant:**
  - 20% of cycles are ovulatory in the 1\textsuperscript{st} year, and 50% in the 5\textsuperscript{th} year, but still contraceptive
LNG’s effect on Cervical Mucus

• Cervical mucus protects uterine cavity from pathogens; controls sperm migration
• Before ovulation: ↑ Estrogen → ↑ secretion and ↑ water → easier sperm migration
• “Quality” assessed via volume, viscosity, spreadability (Spinnbarkeit), crystallization pattern (ferning), and cellularity
  – Score of ≥ 10 out of 15 considered “good”
• Even in ovulatory cycles, LNG → thick mucus with poor sperm penetration
  – Happens quickly:
    • Norplant: 3 days after insertion, sperm penetration becomes poor despite high estradiol levels\(^1\)
    • Mirena users: Cervical mucus becomes poor in 7 out of 10 one day after insertion, in 10 out of 10 by third day\(^2\)
  – Effect is profound:
    • In Mirena 20 µg users, no sperm migration despite ovulation\(^3\)
    • LNG 20 µg ring: Inhibition of sperm migration in 92% of post-coital tests\(^4\)
  – Happens at low dose
    • Seen with lower LNG dose in IUS – Skyla (14 µg)\(^5\)

Efficacy of 20 µg LNG ring shown in 2 trials

- Efficacy of silicone ring releasing 20 µg/day studied in 1980s:
  - 90-day ring used for 1 – 2 years
  - WHO study (n = 1005)
    - Pregnancy rate at 1 year: 3.5 per 100 women (95% CI 2.2-5.0)
  - UK study (n = 1591)
    - Pregnancy rate:
      - At 1 year: 5.1 per 100 women (95% CI 3.6-6.6)
      - At 2 years: 6.5 per 100 women (95% CI 4.4-8.6)
  - Within range of other user-controlled hormonal methods

- Suppression of ovulation correlated with irregular bleeding among ring users
  - # days with bleeding and spotting significantly higher in segments with suppressed ovulation vs normal ovulation¹

- Development discontinued until now

The CONRAD TFV/LNG ring: Design challenges

• Goal: meet 2 target release profiles not achieved using any other ring platform:
  – Approximately 10 mg/d TFV for ≥ 90 days
  – 20 µg/d LNG for ≥ 90 days

• Challenges:
  1) Release 2 very different drugs
     • TFV: hydrophilic, poorly released from traditional silicone or EVA rings
     • LNG: hydrophobic
  2) At very different rates
     • TFV: about 10 milligrams/day
       • Requires high drug loading (>1 gram TFV in a 4.5 gram ring)
     • LNG: 20 micrograms/day
  3) At a steady rate over time (zero order) for ≥ 90 days
The CONRAD TFV/LNG Ring: Solutions

- Developed in collaboration with Patrick Kiser, Northwestern University
- Polyurethane reservoir rings:
  - Using commercially available biomedical grade polyurethanes that range from hydrophilic to hydrophobic

- Suitable for 2 different drugs using 2 different segments, releasing at 2 different rates:
  - TFV segment:
    - Hollow-core reservoir using hydrophilic polyurethane
    - High loading capacity and rate of release
  - LNG segment:
    - Solid-core reservoir using hydrophobic polyurethane
    - Similar to NuvaRing (EVA) design

- Result: tightly controlled steady release for long duration
- Suitable for one or more drugs (similar or diverse)

The CONRAD TFV/LNG ring: In vitro target release profiles met

Clark 2014 PLoS ONE 9(3):e88509
The CONRAD TFV/LNG ring: Animal PK studies, TFV

Sheep

Pigtail Macaques

- Median TFV-DP in macaque vaginal tissue: $1.7-7.4 \times 10^4$ fmol/mg
- Time-independent TFV release from ring. Median levels similar to gel.

Johnson et al, AAC 2012 (56): 6272-83; Moss et al, AAC 2012 (56): 5952-5960
Ongoing CONRAD study

• First multipurpose ring in clinical trials:
  – Phase I One-Month Safety, Pharmacokinetic, Pharmacodynamic, and Acceptability Study of Intravaginal Rings Releasing Tenofovir and Levonorgestrel or Tenofovir Alone (Protocol A13-128)

• 100 women consented to complete 50 across 2 sites:
  – Eastern Virginia Medical School, Norfolk, VA: Annie Thurman, PI
  – Profamilia, Santo Domingo, Dominican Republic: Vivian Brache, PI

• 3 treatment groups, randomized 2:2:1
  – TFV-only ring (n=20)
  – TFV/LNG ring (n=20)
  – Placebo ring (n=10)

• About 1 month of 90-day ring use, total 3 months participation
• 8 or 9 visits and 1 follow-up contact
Objectives

- **Primary:**
  - Genital and systemic safety

- **Secondary:**
  - Pharmacokinetics (PK) of LNG and TFV

- **Tertiary:**
  - Pharmacodynamics (PD) of LNG and TFV
  - Acceptability
Selected entry criteria

- Ovulatory baseline cycle (progesterone ≥3 ng/ml)
- Protected from pregnancy by one of the following non-hormonal methods:
  - Sterilization of either partner
  - Willing to abstain from vaginal intercourse
- BMI <30 kg
- May not use drugs that affect CYP3A4
### Overall study design

<table>
<thead>
<tr>
<th>Screening/Enrollment</th>
<th>Pre-treatment cycle to document ovulation</th>
<th>Ring in place</th>
<th>After ring removal</th>
</tr>
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</table>

Leaders in Reproductive Health and HIV Prevention
Relationship of ring days to cycle days

As determined by ovulation predictor kit.
Expect to see greatest effects of LNG at Visit 6:
  - Less favorable cervical mucus and poorer sperm migration

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Visit 3</th>
<th>Visit 4 (Ring insertion)</th>
<th>Visit 5 (24 hrs after Visit 4)</th>
<th>Visit 6 (At ovulation*)</th>
<th>Visit 7 (Ring removal)</th>
<th>Visit 8 (24 hrs after Visit 7)</th>
<th>Visit 9 (72 hrs after Visit 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ring Day</td>
<td>NA</td>
<td>~ -14</td>
<td>~ -10</td>
<td>1</td>
<td>2</td>
<td>~8</td>
<td>~16-18</td>
<td>~17-19</td>
<td>~19-21</td>
</tr>
<tr>
<td>Cycle Day</td>
<td>Any day</td>
<td>21</td>
<td>24</td>
<td>7</td>
<td>8</td>
<td>~14</td>
<td>~22-24</td>
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# Safety endpoints

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### Soluble immune mediators in CVL
- ✓

### Microflora
- ✓

### Tissue:
- • Histology*
- • Epithelial integrity*
- • Target cell phenotype/activation status
- • Markers of mucosal inflammation (gene expression)
- ✓

### Microbial growth on and in returned rings
- ✓

### Serum chemistries, CBC, lipids
- ✓

### Colposcopy
- ✓ ✓ ✓ ✓ ✓

### AEs
- ✓ ✓ ✓ ✓ ✓ ✓

* = EVMS only
# TFV and LNG PK endpoints

<table>
<thead>
<tr>
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<th>Ring in place</th>
<th>After ring removal</th>
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<td>1</td>
<td>2</td>
<td>~8</td>
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### TFV & LNG in blood
- (1, 2, 4, & 8 hrs)
  - Also TFV-DP in PBMCs
- (1, 2, 4, or 8 hrs)

### TFV in genital fluids (aspirates, swabs)
- (1, 2, 4, or 8 hrs)

### TFV & TFV-DP in tissue
- (1, 2, 4, or 8 hrs)
- 1/2

### LNG in genital fluids (swabs)

### LNG in cervical mucus

### Amount of drug in returned rings
-
# LNG PD endpoints

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Cervical mucus: quality and sperm migration

Blood: estradiol (follicular development)  
Blood: progesterone (ovulation)  
Endometrium: thickness and histology (latter EVMS only)
## TFV PD endpoints

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<tr>
<td><strong>Anti-HIV &amp; anti-HSV in genital fluid</strong></td>
<td>✔️</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-HIV activity in explants (EVMS only)</strong></td>
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Study status

- As of March 13, 2015:
  - Participants enrolled: 45
  - Participants completed (goal 50): 19
- Interim analysis underway:
  - To obtain early indication of ring performance:
    - TFV and LNG PK
    - LNG PD
    - TFV PD (explants)
  - Results expected in mid-May 2015
- Estimated date of last participant visit: January 2016
- Data available Q2 2016
Challenges

• Ring design:
  – Sustained release for 90 days of 2 very different drugs at 2 very different rates, that would meet our preclinical benchmarks

• Study design:
  – Assessing PK and PD of 2 different drugs
    – Example: Visit 7 (ring removal)
      – 10 specimens collected (including 5 cervicovaginal biopsies and 1 endometrial biopsy) and sent to 7 labs
      – Transvaginal ultrasound
      – Colposcopy
      – Multiple procedures on removed ring

• Regulatory approach:
  – 2 indications
  – 2 INDs