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Multipurpose Intravaginal Ring: Tenofovir / Levonorgestrel

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C|O|N|R|A|D
Leaders in Reproductive Health and HIV Prevention

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:

	LNG-only	LNG + estrogen
Systemic		
Oral	**Daily "mini-pill"**	**Daily combined pill**
	Emergency contraception	Emergency contraception
	Pericoital pill	
Implant	Norplant **Jadelle** **Sino-Implant**	
Transdermal	LNG patch	LNG + ethinyl estradiol patch
Genital tract		
Intrauterine	**Mirena IUS – 20 µg/day** **Skyla IUS – 14 µg/day**	
Intravaginal	LNG ring - 20 µg/day	LNG + estradiol ring
	LNG/carraguard Gel	

(Bold = commercially available. Others investigational or discontinued)

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Systemic vs genital delivery of LNG

- Genital delivery → 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

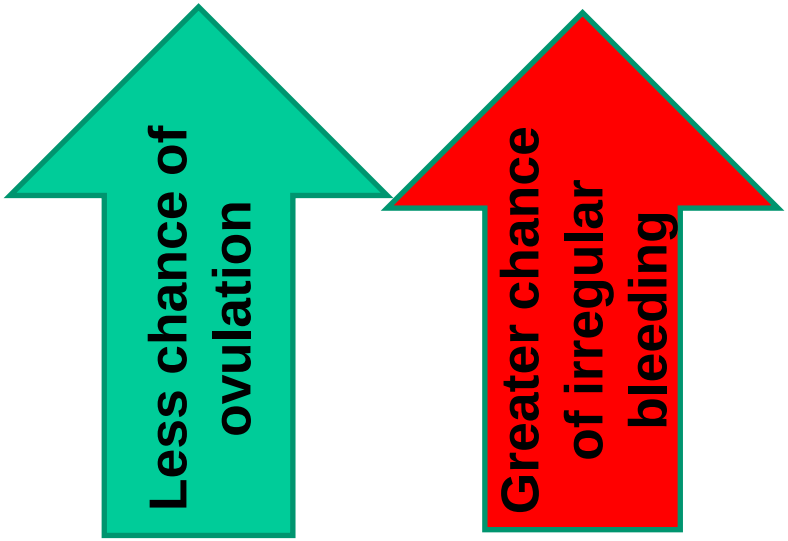
Main mechanisms of action:

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 1st year, and about 75% in the 4th year, but pregnancy rate is 0.7% over 5 years

- Norplant:
  - 20% of cycles are ovulatory in the 1st year, and 50% in the 5th 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]

[1] Dunson 1998 Fertil Steril 69: 258-66 [2]Natavio 2012 Contraception 87(4):426-31 [3]Lewis 2010 Contraception 82(6):491-6 [4]WHO J Steroid Biochem 1979;11(1B): 461-467 [5] Apter 2014 Fert Ster 101(6):1656-62

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 ovulation[1]
- Development discontinued until now

[1]Landgren et al Contraception 1982 26(6): 567-585.

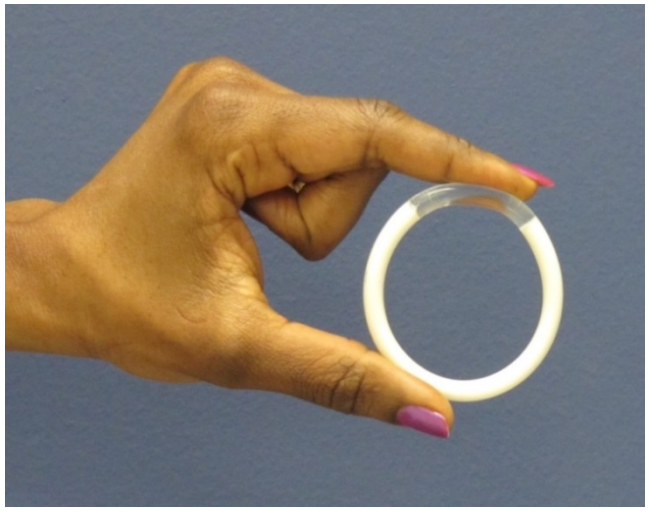
The CONRAD TFV/LNG ring: Design challenges

- 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

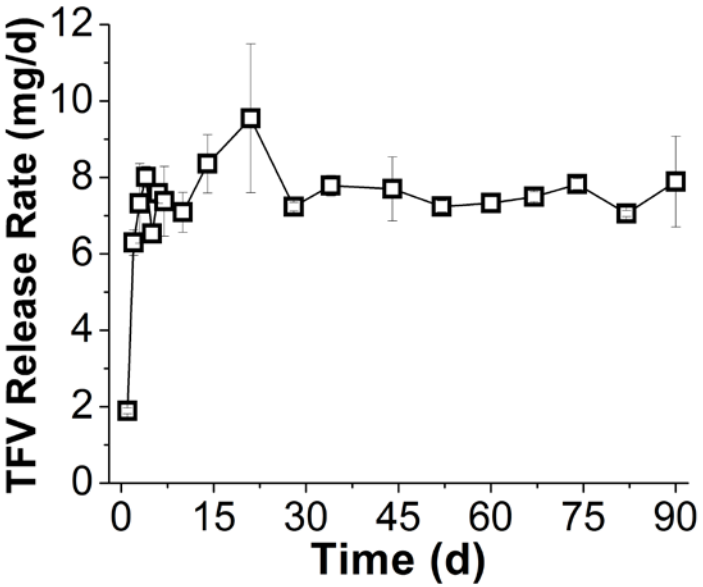
- Developed in collaboration with Patrick Kiser, Northwestern University
- Polyurethane reservoir rings:
  - Using commercially available biomedical grade polyurethanes that range from hydrophilic to hydrophobic

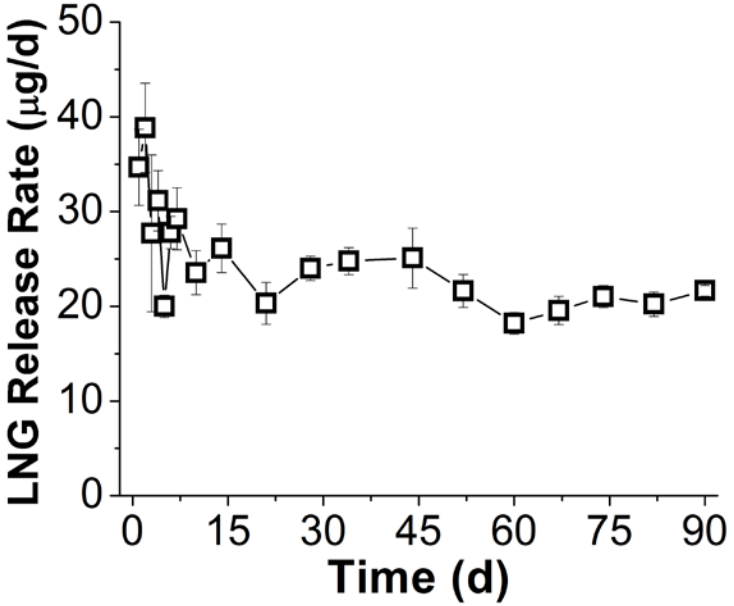


- Suitable for 2 different drugs using 2 different segments, releasing at 2 different rates:
  - TFV segment:
    - Hollow-core reservoir using hydrophilic polyurethane
    - High loading capacity and rate of release
  - LNG segment:
    - Solid-core reservoir using hydrophobic polyurethane
    - Similar to NuvaRing (EVA) design
- Result: tightly controlled steady release for long duration
- Suitable for one or more drugs (similar or diverse)

Clark *et al*, PLoS ONE (2014) 9: e88509

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





Clark 2014 PLoS ONE 9(3):e88509

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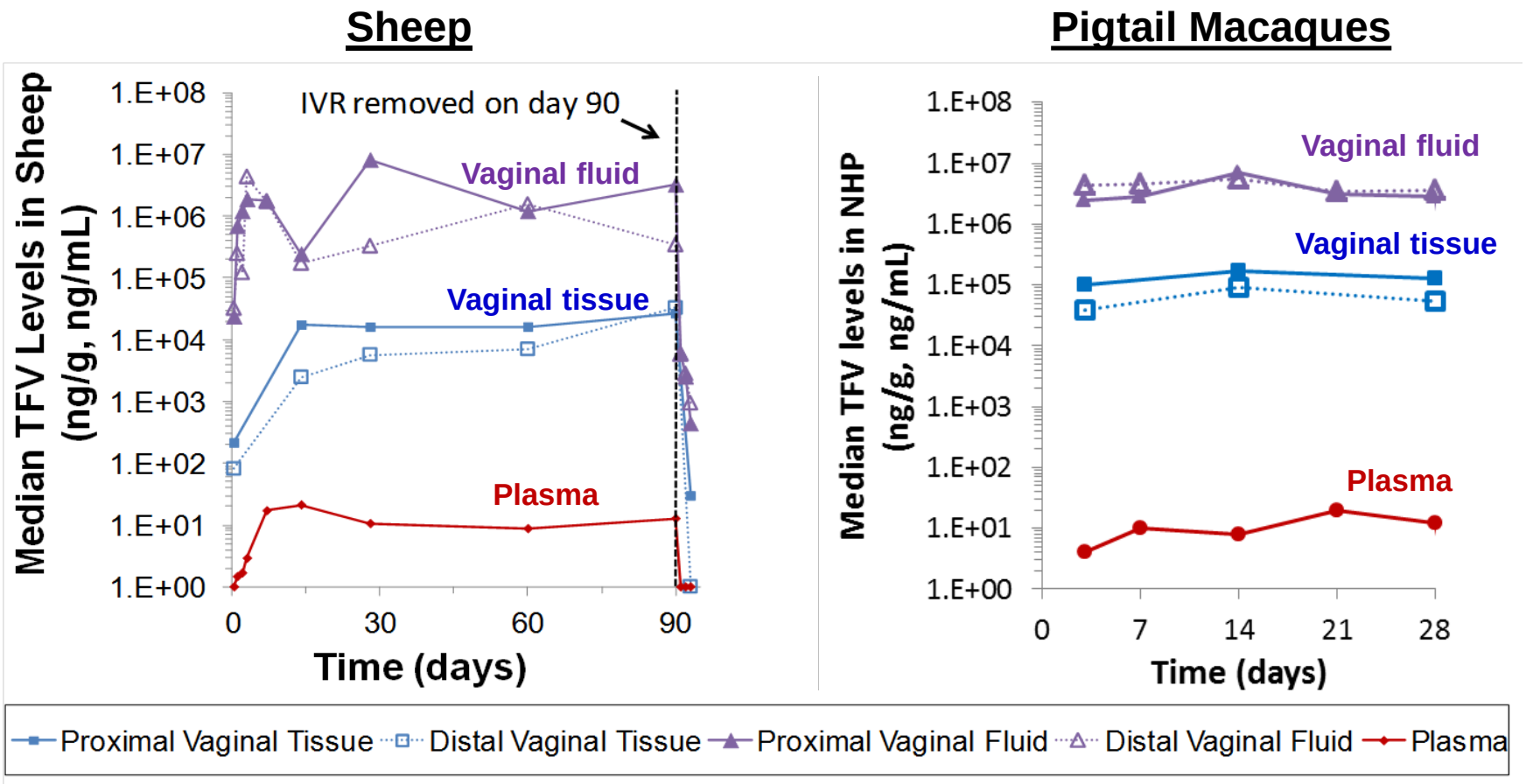
The CONRAD TFV/LNG ring: Animal PK studies, TFV



- **Median TFV-DP in macaque vaginal tissue: 1.7-7.4x10^4 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

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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

Screening/ Enrollment	Pre-treatment cycle to document ovulation	Ring in place	After ring removal

Relationship of ring days to cycle days

	Screening/ Enrollment	Pre-treatment cycle to document ovulation		Ring in place				After ring removal	
Visit #	Visit 1	Visit 2	Visit 3	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation*	Visit 7 Ring removal	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Ring Day	NA	~ -14	~ -10	1	2	~8	~16-18	~17-19	~19-21
Cycle Day	Any day	21	24	7	8	~14	~22-24	~23-25	~25-27

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

Safety endpoints

	Ring in place				After ring removal	
Visit #	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation	Visit 7 Ring removal (8-10 days after Visit 6)	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Cycle Day	7	8	~14	~22-24	~23-25	~25-27
Ring Day	1	2	~8	~16-18	~17-19	~19-21
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

	Ring in place				After ring removal	
Visit #	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation	Visit 7 Ring removal (8-10 days after Visit 6)	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Cycle Day	7	8	~14	~22-24	~23-25	~25-27
Ring Day	1	2	~8	~16-18	~17-19	~19-21
TFV & LNG in blood	✓ (1, 2, 4, & 8 hrs)	✓	✓	✓ Also TFV-DP in PBMCs	✓	
TFV in genital fluids (aspirates, swabs)	✓ (1, 2, 4, or 8 hrs)	✓	✓	✓	✓	
TFV & TFV-DP in tissue		✓		✓	½ ✓	½ ✓
LNG in genital fluids (swabs)			✓			
LNG in cervical mucus			✓		✓	
Amount of drug in returned rings				✓		

LNG PD endpoints

	Ring in place				After ring removal	
Visit #	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation	Visit 7 Ring removal (8-10 days after Visit 6)	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Cycle Day	7	8	~14	~22-24	~23-25	~25-27
Ring Day	1	2	~8	~16-18	~17-19	~19-21
Cervical mucus: quality and sperm migration			✓			
Blood: estradiol (follicular development)			✓	✓		
Blood: progesterone (ovulation)				✓		
Endometrium: thickness and histology (latter EVMS only)				✓		

TFV PD endpoints

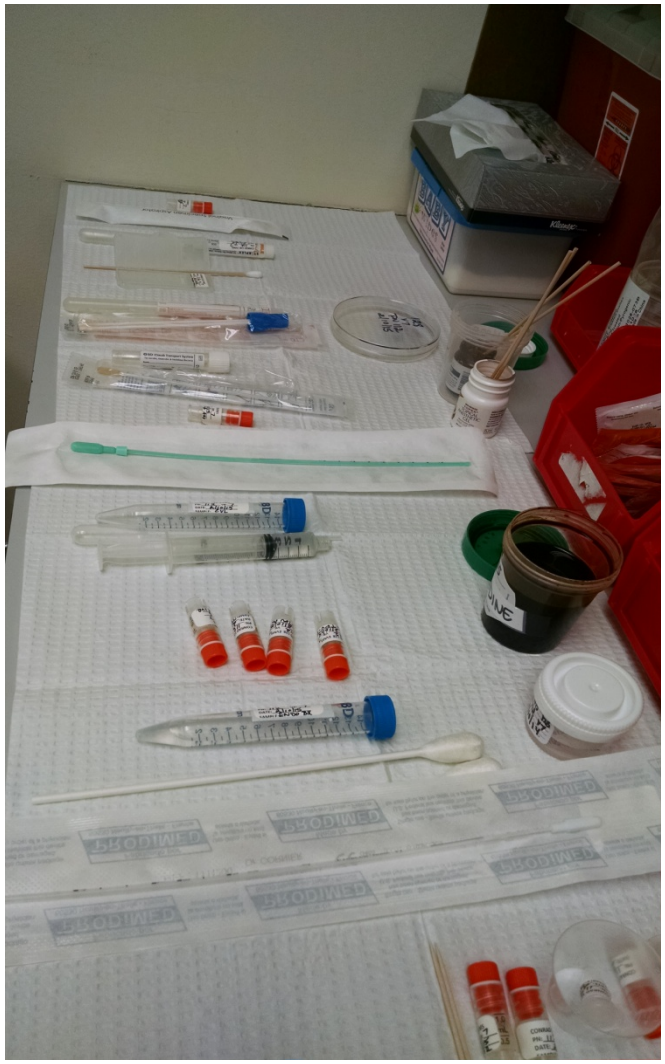
	Ring in place				After ring removal	
Visit #	Visit 4 Ring insertion	Visit 5 (24 hrs after Visit 4)	Visit 6 At ovulation	Visit 7 Ring removal (8-10 days after Visit 6)	Visit 8 (24 hrs after Visit 7)	Visit 9 (72 hrs after Visit 7)
Cycle Day	7	8	~14	~22-24	~23-25	~25-27
Ring Day	1	2	~8	~16-18	~17-19	~19-21
Anti-HIV & anti-HSV in genital fluid				✓		
Anti-HIV activity in explants (EVMS only)				✓		

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



Acknowledgements