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Multipurpose Technologies for Prevention

OPPORTUNITIES AND CHALLENGES

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Women's Sexual & Reproductive Health Risks are Interlinked

Unintended Pregnancy

HIV

Other Sexually Transmitted Infections (STIs)

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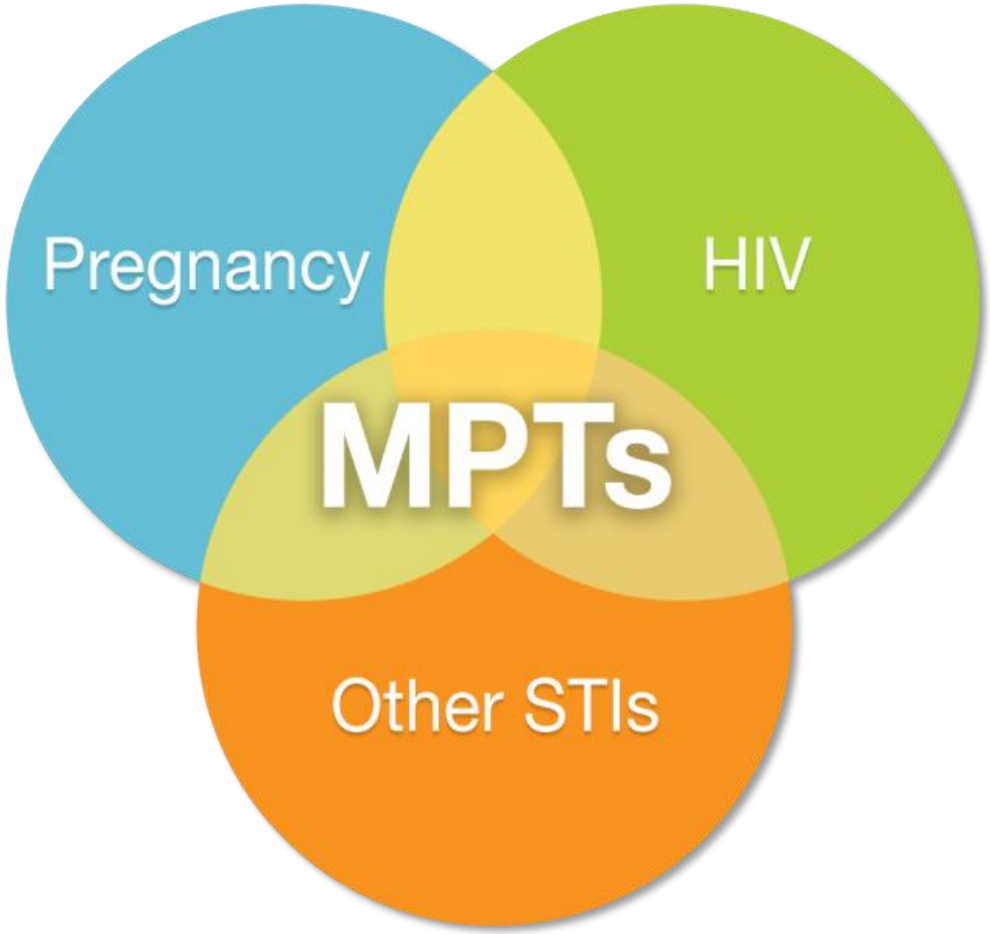
Multipurpose Prevention Technologies

MPTs combine protection against:

- Unintended pregnancy
- HIV and/or Other STIs



Male and female condoms are the only currently available methods for prevention of multiple sexual reproductive health risks

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WHY WE NEED AN MPT

- The end user wants an MPT
- Combined products reduce barriers
- Increased synergy of family planning and HIV services

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HOPE PARTICIPANT QUOTES

"I like the idea of having an MPT because it saves time, and hits two birds with one stone."

"The ring would be better if it was a two-in-one: protect from HIV and from pregnancy…to save women from using two different products."

"My wish is for the ring to also prevent other things, like STI and pregnancies…"

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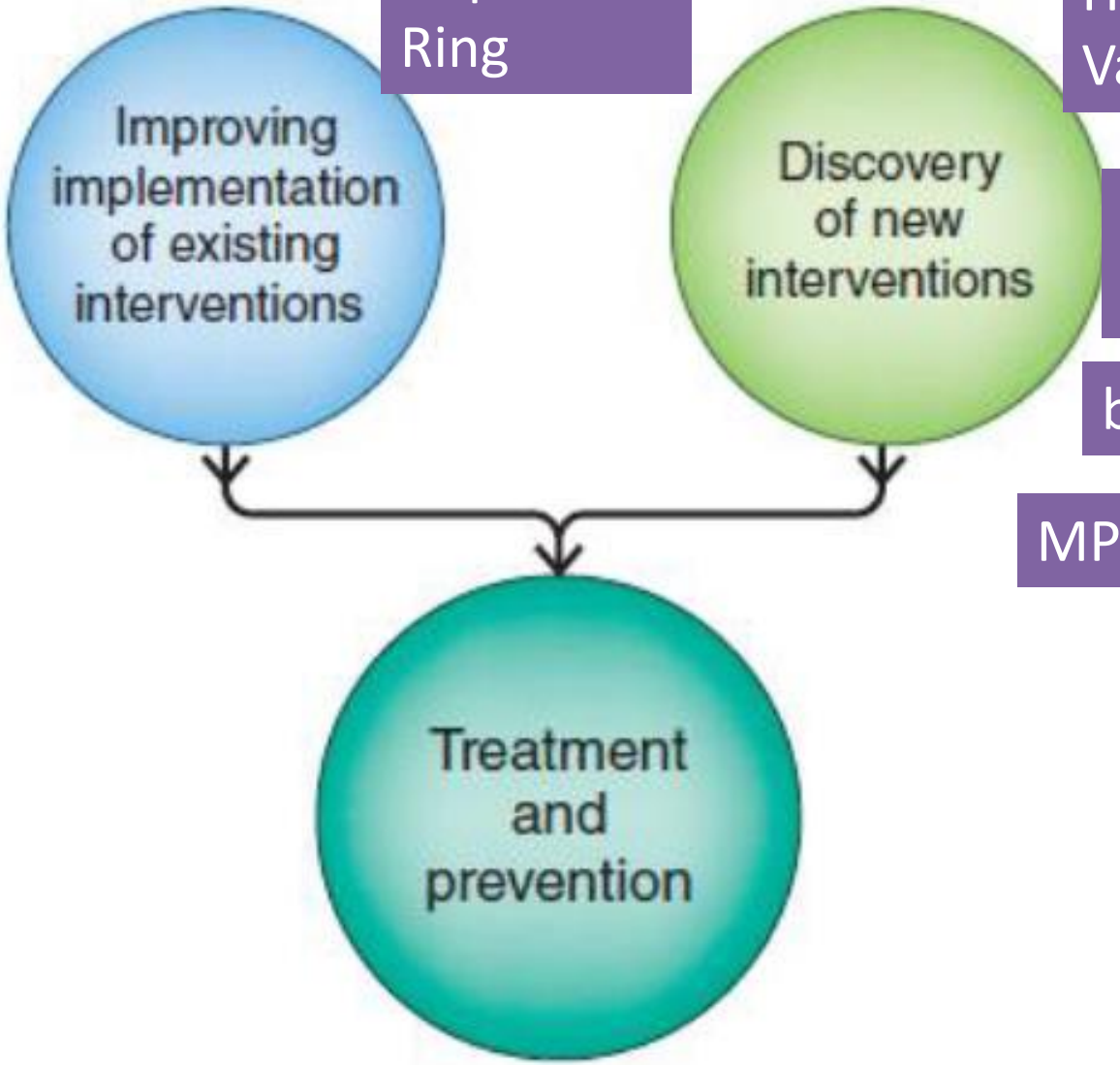
THE NIH INVESTMENT STRATEGY

Truvada as PrEP

Dapivirine Ring

HIV Vaccine



Injectable PrEP

bNABs

MPT?

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A PLACE FOR MPTS IN THE PREVENTION TOOLBOX? THE HYPOTHETICAL ADVANTAGE

- Leveraging market demand for contraception to achieve meaningful uptake and committed use of an HIV prevention intervention in younger populations
  - Increased **demand/uptake** for HIV prevention in MPT vs HIV prevention only products
  - Increased **adherence** with MPT vs HIV only prevention products
- Incremental increases in adherence will result in prevention cost savings
- Efficiencies in delivery and access vs two (or more) separate products

Cost Benefit Model for MPT: HIV and Pregnancy Prevention (BCG/BMGF)

- **Scenario A**: Preventing 10,000 infections in women using HIV PrEP only-
  - Assumptions: 3% Incidence, *50% adherence*, 95% efficacy, PPY cost of PrEP= $150
  - Cost to avert 10,000 infections: **$105M**
- **Scenario B**: Preventing 10,000 infections in women using dual protection HIV/contraceptive
  - Assumptions: 3% incidence, *60% adherence*, 95% efficacy, PPY cost for PrEP + Contraception= $160
  - Cost to avert 10,000 infections: **$94M**

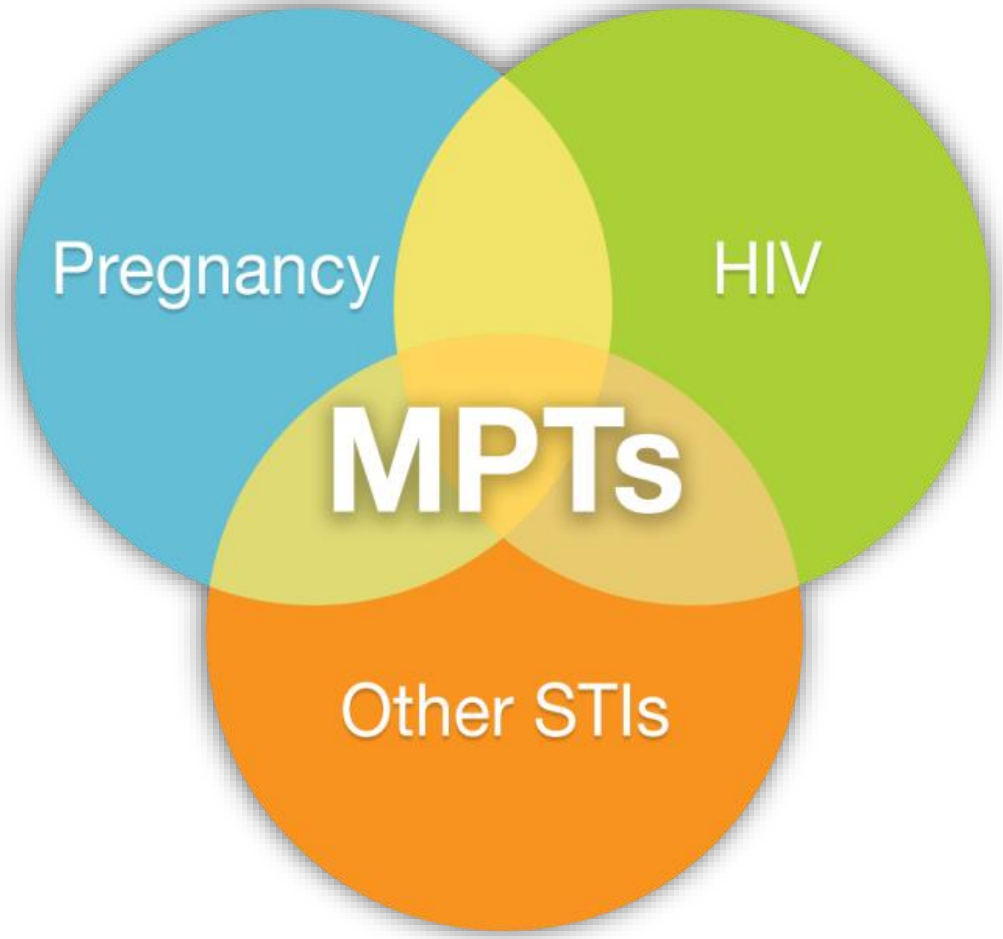
How Reasonable are the Hypothetical Advantages of an MPT for HIV Prevention and Contraception?

- **Pro's**
  - Large number of women at risk for HIV use modern contraception
  - Younger women express greater concern over unintended pregnancy vs HIV infection
  - High percentage of women state a preference for an MPT
- **Con's**
  - HIV indication could stigmatize the contraception component of an MPT
  - Contraceptive efficacy in an MPT should be similar to that of current contraception options
  - Delivery feasibility beyond HIV prevention settings

MULTIPURPOSE PREVENTION TECHNOLOGIES

Questions:

1. *Is there a place for MPTs in the prevention toolbox?*
2. *Which one(s) should move forward?*
3. *What are the key scientific questions?*



Delivery Options for MPTs

Co-formulated:

Multiple API formulated into a single dose

Vaginal ring containing ARV plus LNG

Co-administered:

Two independent products used together

Two implantable rods, one containing ARV, the second containing contraceptive

Co-packaged:

Two different doses packaged together in a single product for simultaneous co-use

Two tablets, one containing ARV, the second containing contraceptive

Non-Barrier co-formulated MPTs in Development with Activity Against HIV

- **Gels n=6**
  - Griffithsin (GRFT) in Carrageenan gel (PC-6500); Griffithsithin gel (Louisville); poly-[1,4-phenylene-(1-carboxy) methylene] (PPCM) SAMMA Gel; SR-2P Gel (acyclovir/tenofovir); VivaGel® (SPL7013)
- **Contraceptive Vaginal Rings n=4**
  - TDF + FTC + Acyclovir + Ethinyl Estradiol + Etonogestrel IVR (Auritec Pharmaceuticals); BioRings TM IVR (tenofovir); Dapivirine + Levonorgestrel IVR(IPM); Tenofovir + Levonorgestrel IVR (CONRAD)
- **STI/HIV Rings n= 4**
  - mAb 2C7 + TDF IVR (GC)
  - Tenofovir / Acyclovir IVR(CONRAD)
  - Griffithsin (GRFT) IVR (PC-7500, Pop Council)
  - Tenofovir IVR (HIV and HSV)
- **Vaginal Films n=1** MB66 plant based antibodies against HIV, HSV and sperm
- **Vaginal/Rectal Inserts n=2**
  - TAF / Elvitegravir Topical Insert (CONRAD);
  - Griffithsin (GRFT) fast dissolve vaginal insert (FDI) [PC-9500]
- **Systemic MPTs n=2**
  - Subcutaneous Contraceptive and HIV Implant Engineered for Long-Acting Delivery (SCHIELD) device
  - Elvitegravir + Copper IUS

Non-Barrier MPTs in Development with Activity Against HIV

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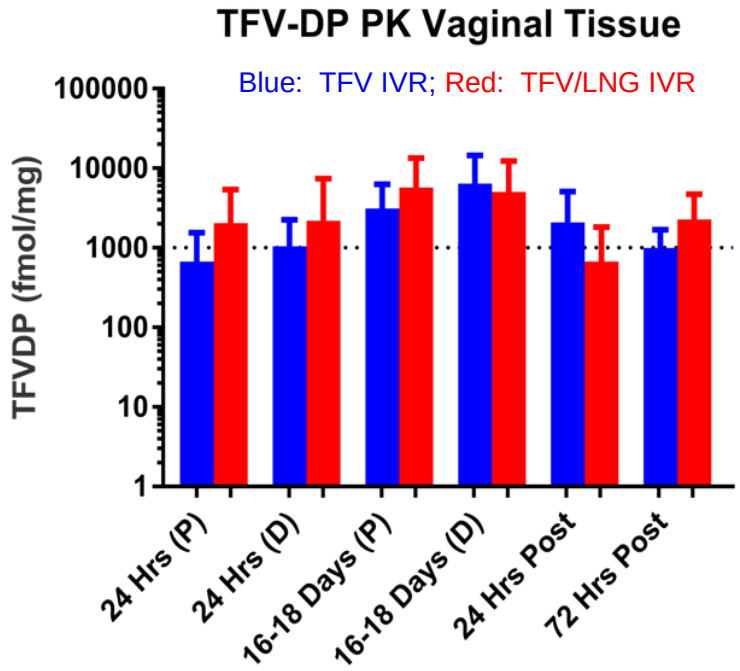
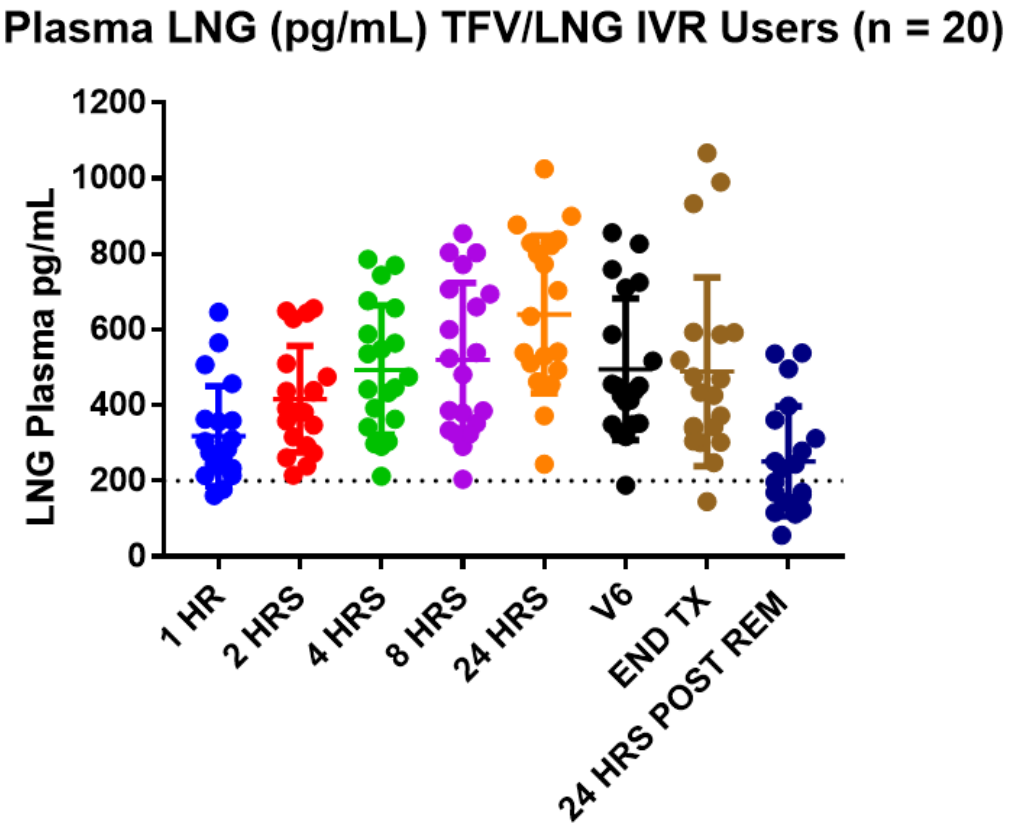
TENOFOVIR LNG RING



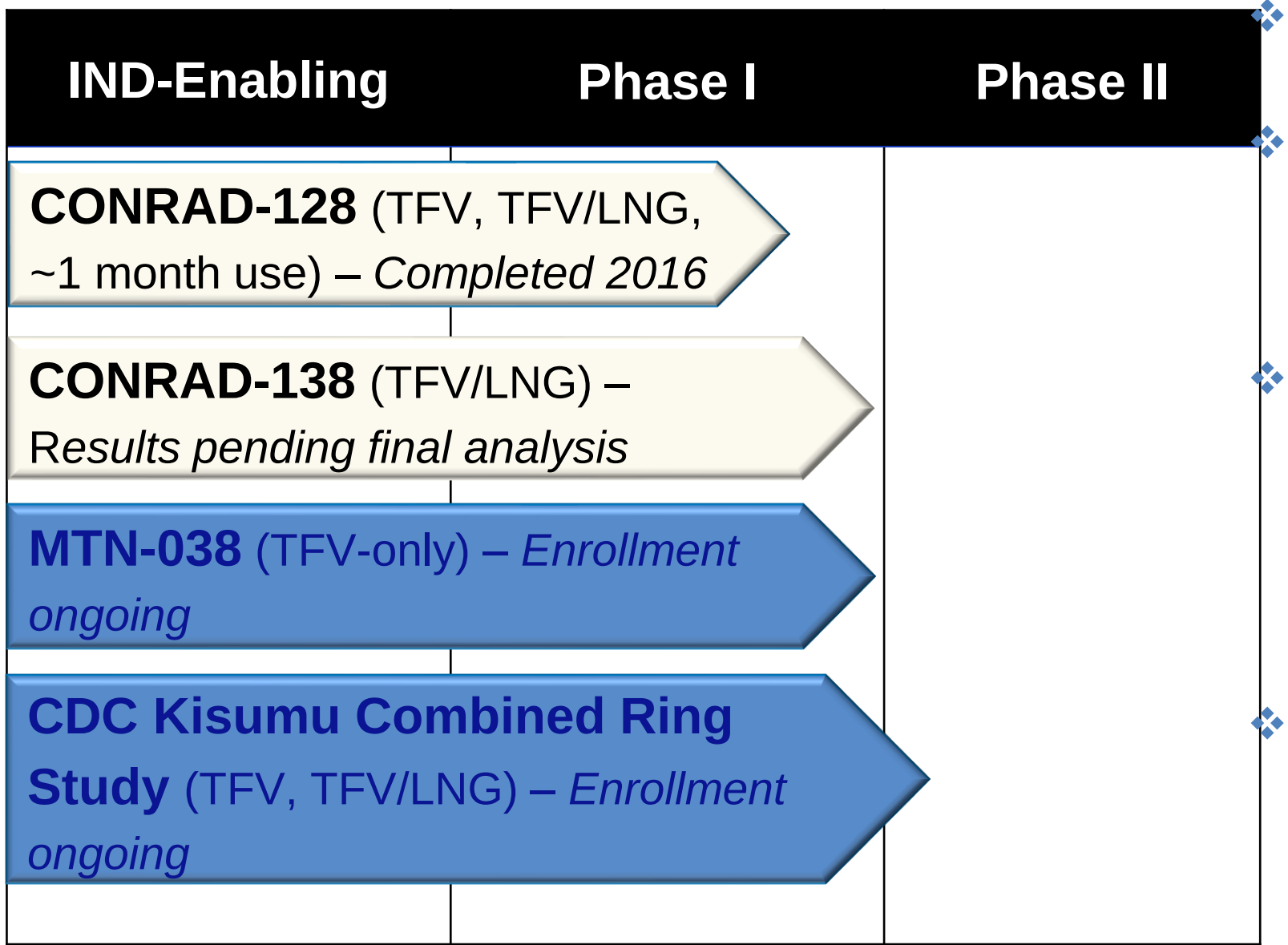
Sustained high TFV-DP levels in CV tissues, compatible with protection in NHP[3]



Plasma levels of LNG similar to highly effective contraceptive implants;

Thurman et al., 2018. PLOS One; *Thurman et al. 2019. PLOS One;* *Dobard et al., 2012. J Virol*

TENOFOVIR LNG 90 DAY RING



- Studies support regulatory path for TFV and TFV/LNG IVRs
- Extended (3-month) ring use data in U.S., Dominican Republic and Kenya expected by late 2019/early 2020
- CONRAD 138 to provide data on pharmacological forgiveness of TFV & LNG, bleeding patterns & acceptability with extended 90-day IVR use (comparing continuous vs. interrupted use)
- No safety signals with or w/o sex

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DAPIVIRINE LNG Ring

- **MTN-030/IPM 041**: 3 month contraceptive dapivirine ring vs 200 mg dapivirine only ring; N=24, 14 days of use; study completed and reported at HIV R4P 2018 (Achilles et al)

- **MTN-044/IPM 053/CCN019:** A Randomized, Phase 1, Open-Label Study in Healthy HIV-Negative Women to Evaluate the Pharmacokinetics, Safety and Bleeding Patterns Associated with 90-Day Use of Matrix Vaginal Rings Containing 200 mg Dapivirine and 320 mg Levonorgestrel
  - N=48, fully enrolled as of May 28, 20019, follow-up ongoing

- Plan to evaluate contraceptive efficacy in future CCTN trial

INTERNATIONAL PARTNERSHIP FOR MICROBICIDES

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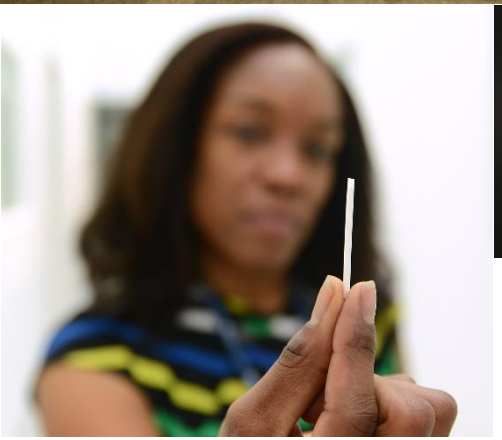
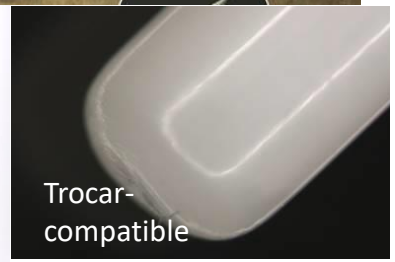
Subcutaneous Contraceptive and HIV Implant Engineered for Long-Acting Delivery (SCHIELD)

A program to develop an MPT Product





MPT IMPLANT FEATURES

- Sustained, long-acting delivery
  - Zero-order release kinetics
  - Dual drugs (ARV + Hormone)
- Discrete & subcutaneously placed
- Target duration >6 months
- User-Independent (supports adherence and reduces patient burden)
- Biodegradable
- Reversible

CURRENT RESULTS

- Demonstrated simultaneous delivery of ARV + Hormone over 340 days (in vitro)
- Ongoing 90-day preclinical PK rabbit study
- Developing processes to align with future manufacturing & scale-up
- End-user and HCP assessments underway in S. Africa and Zimbabwe

***Contact**: Leah Johnson, PhD; leahjohnson@rti.org*

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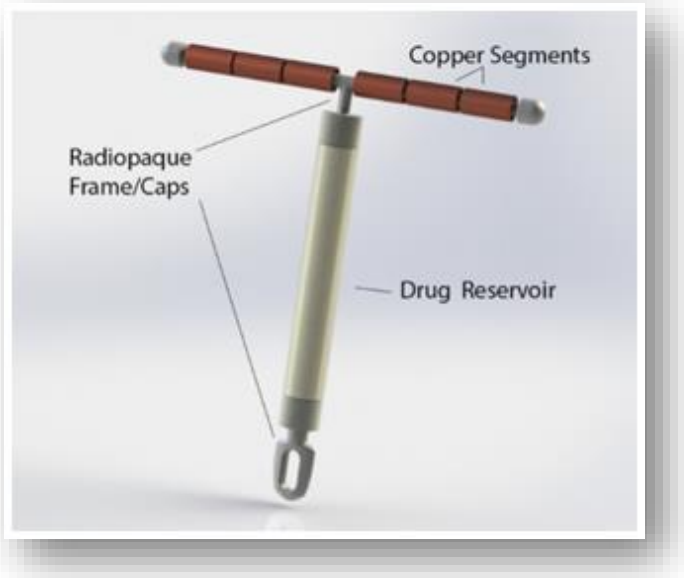
EVG/Copper Intrauterine System
Preclinical Development Update



- Intended for at least 1 year duration
- Used polyurethane reservoir technology inspired by TFV IVRs
- **Preclinical proof-of-concept** demonstrated[1]:
  - No safety issues observed in rabbits or NHPs
  - EVG levels detectable throughout female reproductive tract (in fluid and tissue) in rabbits and NHPs

CONRAD
Leaders in Reproductive Health and HIV Prevention

GILEAD

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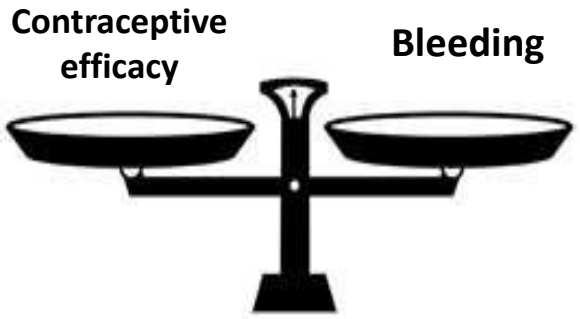
ISSUES WITH CONTRACEPTIVE HORMONES AND MPTS

- Contraceptive efficacy vs bleeding

- Understanding impact of route of administration
  - PK
  - PD



- Understanding Mechanism of Action
  - We lack excellent objective surrogates for contraceptive efficacy
    - Ovulation suppression
    - Cervical mucus—measurement variability
    - Contraceptive hormone levels as predictors of efficacy?

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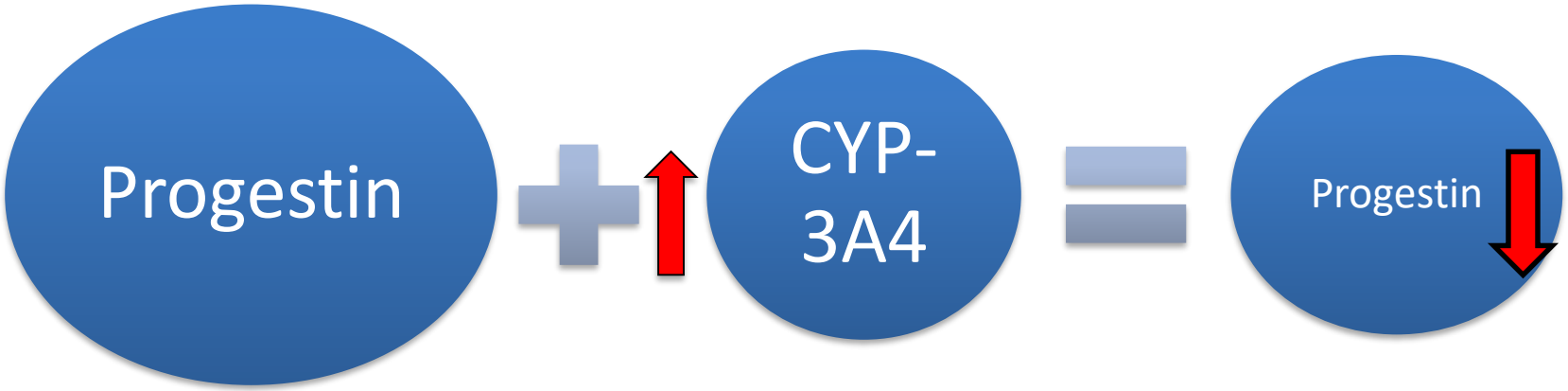
Drug Drug Interactions

- Contraceptive hormones are metabolized by the cytochrome P450 enzyme system – predominately by CYP3A4.
- Some ARVs are CYP3A4 inducers, which could increase progestin metabolism and decreased progestin exposures – leading to contraceptive failures.



Drug-drug interactions
CYP3A4 induction

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IMPACT OF NNRTIS ON IMPLANTABLE LARCS

- Levonorgestrel (Uganda)
  - EFV – 47% decrease in LNG exposure[1],
  - NVP – no significant change in LNG exposure[1]

75 mg levonorgestrel

- Etonogestrel (Brazil and Uganda)
  - EFV – 63.4% (Brazil) [2]to >80%[3](Uganda) decrease in ENG exposure[2]
  - NVP- no significant change in ENG exposure

68 mg etonogestrel

[1]Scarsi KK, et al. *CID.* 2016.· [2]Vieira CS, et al. *JAIDS*. 2014; [3]Chappell, et al. AIDS. 2017

Why Do we Worry About this with MPTs?

- Historically, CYP-mediated drug-drug interactions were thought to be largely avoidable with non-oral drug administration by circumventing first-pass metabolism.
- What happens if hormones are administered topically in a ring?

Combined contraceptive vaginal ring
(NuvaRing®:
ethinyl estradiol/etonogestrel 15/120 mcg/day)

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IMPACT OF ARVS ON HORMONES

Combined contraceptive vaginal ring

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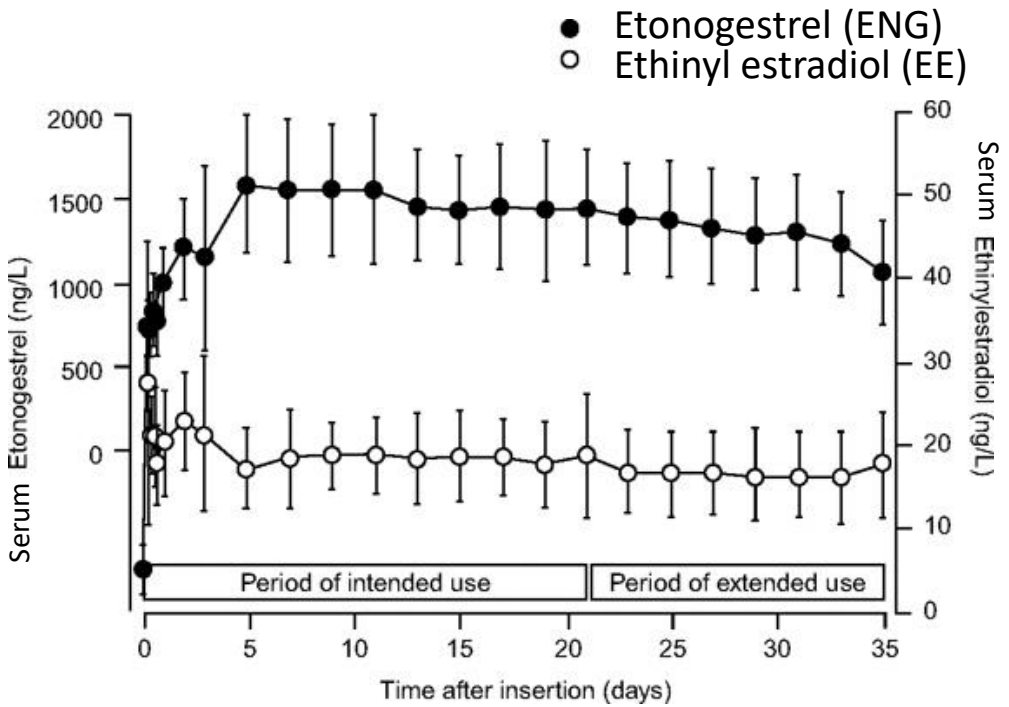


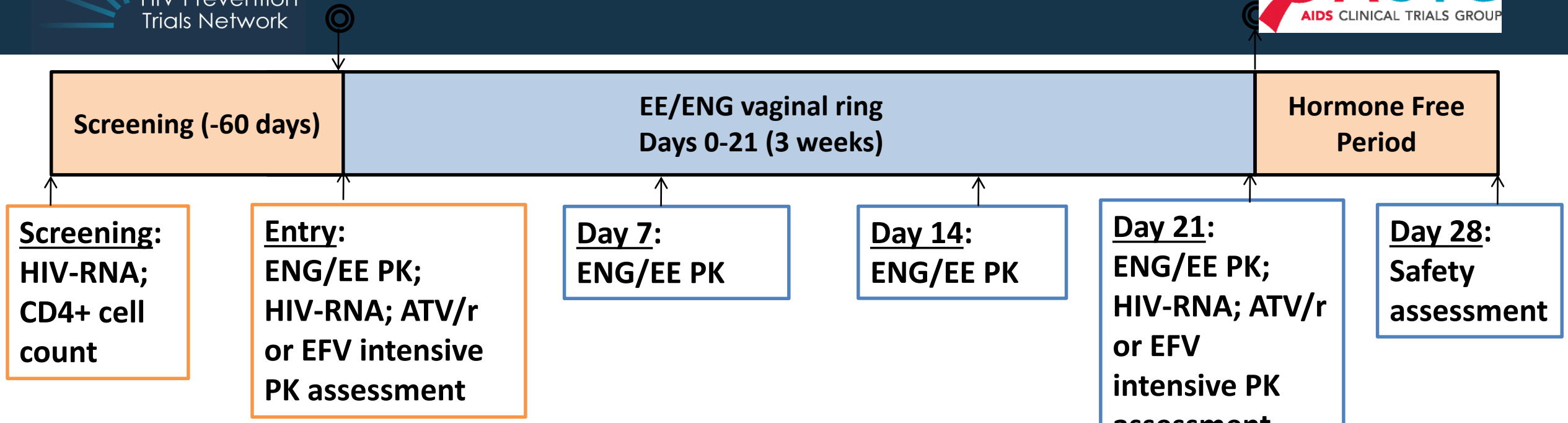
Timmer et al. Clin Pharmacokinet. 2000; 39(3): 233-242.

- **Primary Hypothesis**
  - Plasma concentrations of ethinyl estradiol (EE) and etonogestrel (ENG) when administered via vaginal ring will be altered by co-administration of ATV/r- or EFV-based ART
- **Secondary objectives**
  - Estimate the effect of ENG/EE on the pharmacokinetics of ATV, RTV, and EFV
  - Suppression of ovulation
  - Virologic suppression
  - Safety and Tolerability

CROI 2018, Scarsi

ACTG
AIDS CLINICAL TRIALS GROUP

STUDY DESIGN



- Safety and endogenous progesterone levels were assessed at each visit

EE/ENG pharmacokinetic (PK) and Statistical Analysis:

- ENG/EE were measured from a single plasma sample collected at each visit. EFV and ATV/r were measured 0 (pre-dose), then 1, 3, 4, 5, and 8 hours post-observed dose
- Hormone PK was compared between each ART group and control group by geometric mean ratio (GMR) with 90% confidence intervals and by Wilcoxon-rank sum
- Intraindividual ART PK was compared between Day 21 and Day 0 by GMR (90% CI) and statistically compared with Wilcoxon signed-rank test

HORMONE PK: ETHINYL ESTRADIOL

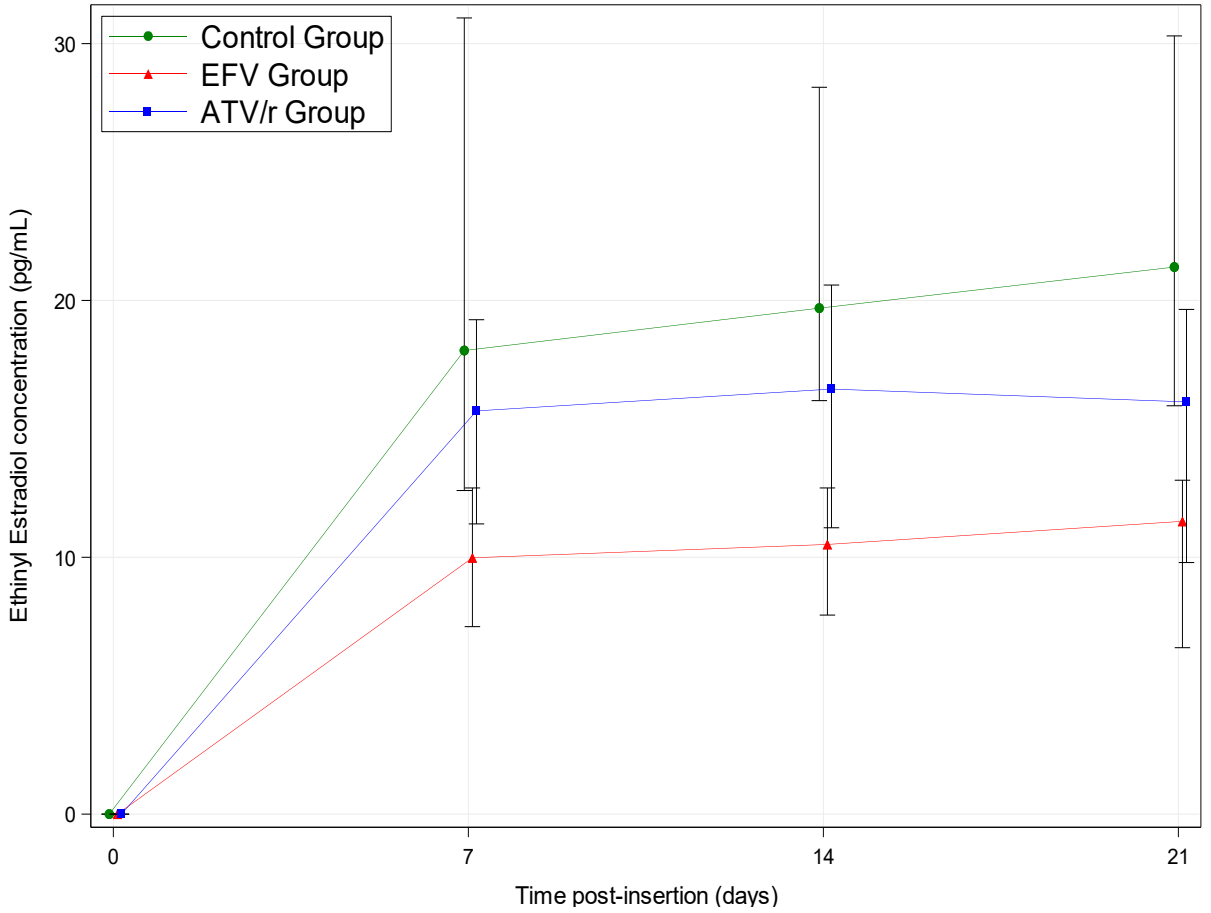
Compared to the control group, EE exposure:

- EFV group: ↓ 53-57%
- ATV/r group: ↓ 29-35%

EE Geometric Mean Ratio (90% CI)		
	EFV: Control Groups	**ATV/r: Control Groups**
Day 7	**0.47*** (0.35, 0.63)	0.68 (0.54, 0.87)
Day 14	**0.45*** (0.34, 0.60)	**0.71*** (0.57, 0.89)
Day 21	**0.43*** (0.33, 0.57)	**0.65*** (0.50, 0.84)

***Wilcoxon Rank Sum p<0.05**

Figure: Median (interquartile range) EE concentrations (pg/mL) in each group



HORMONE PK: ETONOGESTREL

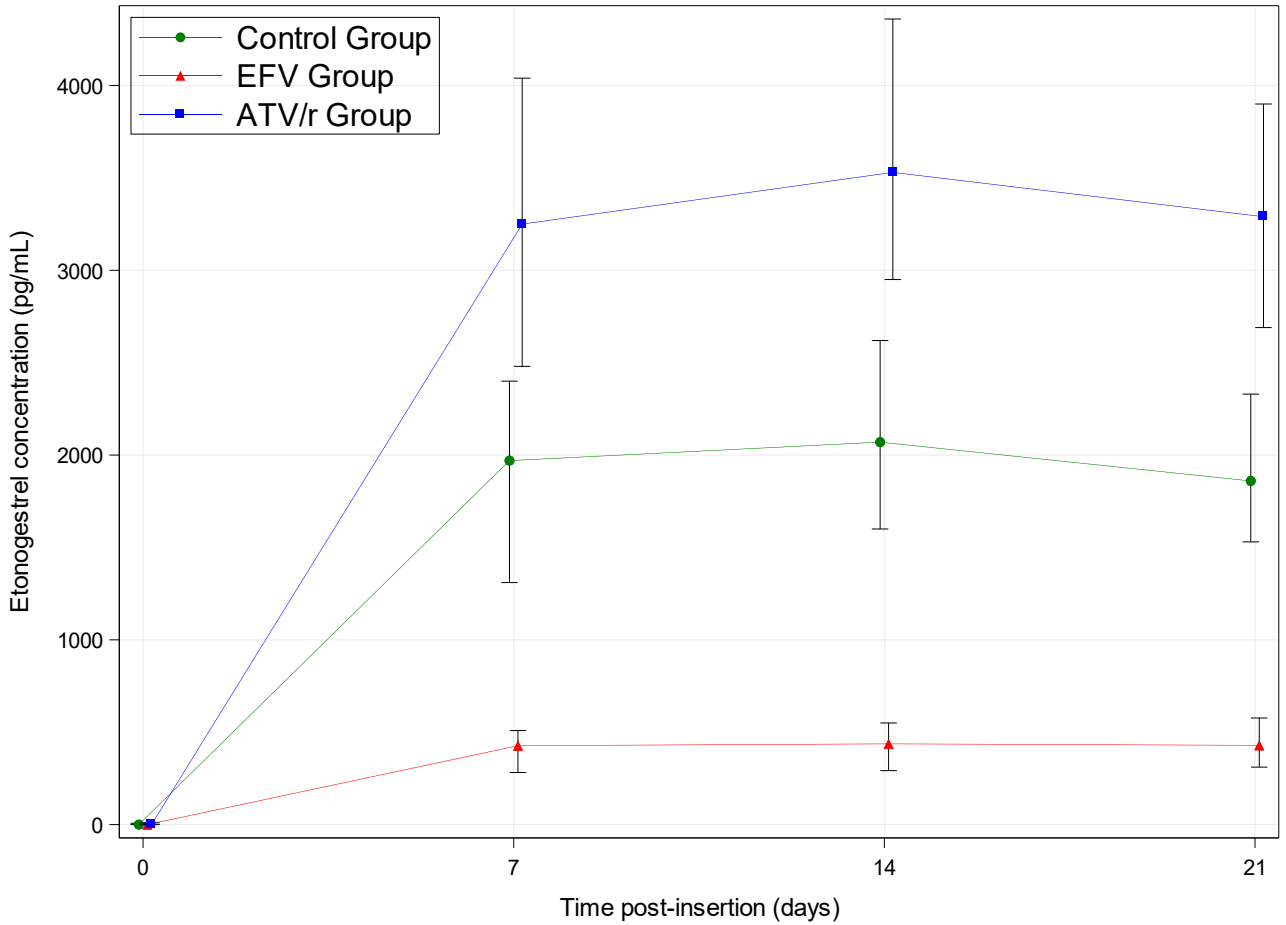
Compared to the control group, ENG exposure:

- EFV group: ↓ 76-79%
- ATV/r group: ↑ 71-79%

ENG Geometric Mean Ratio (90% CI)		
	EFV: Control Groups	**ATV/r: Control Groups**
Day 7	**0.21*** (0.17, 0.27)	**1.71*** (1.41, 2.06)
Day 14	**0.22*** (0.17, 0.29)	**1.79*** (1.44, 2.23)
Day 21	**0.24*** (0.18, 0.32)	**1.74*** (1.38, 2.20)

***Wilcoxon Rank Sum all visits p<0.05**

Figure: Median (interquartile range) ENG concentrations (pg/mL) in each group



CONCLUSION: INTERACTIONS CAN GO BOTH WAYS

- Serum concentrations of vaginally delivered contraceptive hormones are also significantly impacted by CYP-mediated interaction with orally administered antiretrovirals and could undermine contraceptive efficacy
- ARVs can impact hormones and vice versa:
  - ATV/r-based ART decreased EE concentrations 29-35%, yet increased ENG concentrations by 71-79%
  - EFV-based ART decreased EE by 53-57% and ENG concentrations by 76-79%
  - EFV (13-36%) and RTV (34-41%) concentrations were decreased after 21 days of continuous vaginal ring (ENG/EE) contraceptive use

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What are the urgent scientific questions?

- LARCs are extremely effective- does the contraceptive component of an MPT have to be as effective at preventing unintended pregnancies as implants and IUDs?
- Will the hypothetical advantages of MPTs vs products provided separately for each indication be realized? Will MPTs really increase uptake of prevention? Both social/behavioral and implementation research needed.
- Can benchmarks for which MPTs should move forward be developed to esure investments are targeted to the highest priority products?
- Drug drug interactions between ARVs and hormones including contraceptives of increasing scientific concern.
  - Need high quality PK studies of both hormones and ARVs integrated integrated early in the development pathway

Why I believe in MPTs even though there are many challenges

- Because I am a fierce supporter of empowering women to protect themselves from HIV and unplanned pregnancy
- Because our study participants and women in community forums continue to tell us they want an ‘all in one product’ for family planning and HIV prevention.
- Because it will be a catalytic bridge between reproductive health and HIV prevention in women

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