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)

Women need better protection
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
WHY WE NEED AN MPT

• The end user wants an MPT
• Combined products reduce barriers
• Increased synergy of family planning and HIV services
“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...”
THE NIH INVESTMENT STRATEGY

- Truvada as PrEP
- Dapivirine Ring
- HIV Vaccine
- Injectable PrEP
- bNABs
- MPT?

Improving implementation of existing interventions

Discovery of new interventions

Treatment and prevention
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
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?
Co-formulated:
Multiple API formulated into a single dose

Co-administered:
Two independent products used together

Co-packaged:
Two different doses packaged together in a single product for simultaneous co-use
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
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Sustained high TFV-DP levels in CV tissues, compatible with protection in NHP³

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

### IND-Enabling

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Phase I</th>
<th>Phase II</th>
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<tr>
<td><strong>CONRAD-128</strong> (TFV, TFV/LNG, ~1 month use) – <em>Completed 2016</em></td>
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<td><strong>CONRAD-138</strong> (TFV/LNG) – <em>Results pending final analysis</em></td>
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<td><strong>MTN-038</strong> (TFV-only) – <em>Enrollment ongoing</em></td>
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<td><strong>CDC Kisumu Combined Ring Study</strong> (TFV, TFV/LNG) – <em>Enrollment ongoing</em></td>
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- 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
• **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
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
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
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?
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.
IMPACT OF NNRTIS ON IMPLANTABLE LARCS

• Levonorgestrel (Uganda)
  • EFV – 47% decrease in LNG exposure\textsuperscript{1},
  • NVP – no significant change in LNG exposure\textsuperscript{1}

• Etonogestrel (Brazil and Uganda)
  • EFV – 63.4\% (Brazil)\textsuperscript{2} to >80\% (Uganda) decrease in ENG exposure\textsuperscript{2}
  • NVP - no significant change in ENG exposure

\textsuperscript{1}Scarsi KK, et al. CID. 2016. \textsuperscript{2}Vieira CS, et al. JAIDS. 2014; \textsuperscript{3}Chappell, et al. AIDS. 2017
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)
Combined contraceptive vaginal ring
(NuvaRing®: ethinyl estradiol/etonogestrel 15/120 mcg/day)

• **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**
Screening: HIV-RNA; CD4+ cell count

Entry: ENG/EE PK; HIV-RNA; ATV/r or EFV intensive PK assessment

Day 7: ENG/EE PK

Day 14: ENG/EE PK

Day 21: ENG/EE PK; HIV-RNA; ATV/r or EFV intensive PK assessment

Day 28: Safety assessment

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.

CROI 2018, Scarsi
Compared to the control group, EE exposure:
- EFV group: ↓ 53-57%
- ATV/r group: ↓ 29-35%

<table>
<thead>
<tr>
<th>Time</th>
<th>EFV: ControlGroups</th>
<th>ATV/r: ControlGroups</th>
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<tbody>
<tr>
<td>Day 7</td>
<td>0.47* (0.35, 0.63)</td>
<td>0.68 (0.54, 0.87)</td>
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<tr>
<td>Day 14</td>
<td>0.45* (0.34, 0.60)</td>
<td>0.71* (0.57, 0.89)</td>
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<tr>
<td>Day 21</td>
<td>0.43* (0.33, 0.57)</td>
<td>0.65* (0.50, 0.84)</td>
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*Wilcoxon Rank Sum p<0.05
HORMONE PK: ETONOGESTREL

Compared to the control group, ENG exposure:
- EFV group: ↓ 76-79%
- ATV/r group: ↑ 71-79%

<table>
<thead>
<tr>
<th>Day</th>
<th>ENG Geometric Mean Ratio (90% CI)</th>
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<tbody>
<tr>
<td></td>
<td>EFV: Control Groups</td>
</tr>
<tr>
<td>7</td>
<td>0.21* (0.17, 0.27)</td>
</tr>
<tr>
<td>14</td>
<td>0.22* (0.17, 0.29)</td>
</tr>
<tr>
<td>21</td>
<td>0.24* (0.18, 0.32)</td>
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*Wilcoxon Rank Sum all visits p<0.05

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

CROI 2018, Scarsi
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
• 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 ensure 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 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
Acknowledgements

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