1. The toolbox of biomedical prevention options
2. Novel Technology by Product Pipeline Stages
   • Discovery
   • Development
   • Delivery
   • @ The Horizon
3. Conclusion- the Science of Choice

Lessons learned
1. The expanding toolbox of biomedical prevention

Options → choices → coverage → impact

Adapted from Sharon Hillier, 2019
Benefits of Product Choice: E.g. for Contraception

• WHO Systematic Review
• 231 articles, limited high quality evidence

• **Increased choice** associated with:
  • Increased contraception uptake
  • Better health outcomes (fewer pregnancy, STIs)

• Women given contraceptive choice continue their chosen method to a greater degree than those denied choices

• Contraceptive needs and choices vary over a women’s reproductive life

**Index of Contraceptive Availability**

12% increase contraceptive prevalence for EACH additional method

*How much will it be for PrEP?*
2. Novel Technologies by Product Pipeline Stages

Adapted from Elizabeth Tolley, 2020

Discovery Stage

It is never too early to engage end-users in the research.
**Implant Capabilities:**
- Sustained, long-acting delivery of API
  - Capable of dual delivery (ARV + Hormone)
- Biodegradable
- Reversible
- Subcutaneous inserted via commercially available trocar
- Discrete
- User-Independent

**Milestones:**
- Demo’ed > 1 year drug release in vitro
- Demo’ed > 6 months constant release in animals
- Demo’ed vaginal efficacy in NHP
- Demo’ed: co-release of hormone and ARV

**Other implants at clinical stage** (non biodegradable):
- TAF implant (OCIS)
- Islatravir implant (Merck)
- Cabotegravir implant (NW U/ ViiV)  www.rti.org

Schlesinger et al. Pharmaceutical Research 2016; Johnson et al. Pharmaceutics, 2019
Preferred User Characteristics (PUC):

Study populations for PUC component:

- Young cis-women and men/male partners, health care providers
- Reproductive aged cis-women (aged 18-30 years)
- Men-who-have-sex-with-women-only (MSW)
- Men-who-have-sex-with-men (MSM)
- Cis-women
- Male youth MSM and MSW (aged 18-24 years)
- MSM, TGW, and cis-women at risk for HIV

Methods Used:
- In-Depth-Interviews
- Focus Group Discussions
- Discrete Choice Experiment (DCE)
- Questionnaire surveys

Krostad et al, AIDS Patient Care and STDs 2019; JIAS 2020, Shapley-Quinn et al, AIDS Conference 2020
### Generation 1

**Subject matter experts, health care providers, key stakeholders, women aged 18-30**

- **Removal of side seam from Gen1, removal of top and bottom seam from Gen2**

### Generation 2

**Removal of side seam from Gen1, removal of top and bottom seam from Gen2**

### Generation 3

**Recommendation for implant compatible with existing trocar**

- **Easily removable contraceptive implant component**

### Generation 4

**Support for independent retrievability to allow for easy return to fertility**

### Questions and Changes

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Who we asked</th>
<th>What the change was</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What do you think about these physical characteristics?</strong></td>
<td>Subject matter experts, health care providers, key stakeholders, women aged 18-30</td>
<td>Removal of side seam from Gen1, removal of top and bottom seam from Gen2</td>
</tr>
<tr>
<td><strong>How long should this implant last?</strong></td>
<td>Subject matter experts, health care providers, key stakeholders, women aged 18-30</td>
<td>NO GO for implants that last &lt;6 months, Multiple rods OK if duration is increased</td>
</tr>
<tr>
<td><strong>How should two indications be delivered?</strong></td>
<td></td>
<td>Easily removable contraceptive implant component</td>
</tr>
<tr>
<td><strong>How should the implant be inserted?</strong></td>
<td>Subject matter experts, health care providers</td>
<td>Implant developed to be compatible with Jadelle trocar (for cost and training reasons)</td>
</tr>
</tbody>
</table>

Krogstad, JIAS 2018; Krogstad, APCSTD 2019; Shapley-Quinn, AIDS 2020 (forthcoming); PATH, Design Recommendations Report: Subcutaneous Implant Applicator 2017
Development Stage

Development

IDEA PHASE

BASIC & preclinical SCIENCE

CLINICAL TRIALS Phases 1-3

Open Label, bridging studies

MPT products
LA-injectables

DEMONSTRATION PROJECTS

PATIENT CARE

CUPID/MTN-045: a 400 couples preference study for MPTs

- 400 couples from Uganda and Zimbabwe
- Discrete Choice Experiment (DCE) with 7 attributes
- Subset of qualitative interviews
- DCE done first individually, then jointly by both
- Ideal product activity for couples under D.O

Informational video (product pipeline)

4 Delivery Forms are evaluated:
Vaginal Ring; Film; Insert and Oral Tablet
International Partnership for Microbicides (IPM)
- HIV PrEP & contraceptive (LNG/DVR) 3-month ring
- MTN-044: Open label Phase 1 with continuous or monthly removal for approximately 90 days (N=24)

CONRAD-128
- TFV/LNG ring for HSV2, HIV & contraception
- **CONRAD-128**: Placebo-controlled RCT phase I trial assessing TFV, TFV/LNG ring for 2 weeks (N=51)

OCIS
- Pod ring delivering TAF/ACV/ENG+EE to prevent HIV, HSV2, contraceptive
- Evaluated in pigtailed macaques (N = 6) over 35 days

Thurman et al, PLOS 2017; Smith et al, PLOS 2017; https://mtnstopshiv.org/research/studies/mtn-044
When you can, bundle your indications.
HPTN 077: Acceptability of CAB-LA

- **Unacceptable**
  - A lot
  - Somewhat
  - A little

- **Acceptable**
  - A little
  - Somewhat
  - A lot

Cohort 2
- 1st 2 injections 4 weeks apart, then every 2 months, 3 cycles
- 600 mg per 1 injection

**Bar Chart**
- One injection
- Frequency
- Location
- Privacy
- Size or Quantity
- Pain
- Rash reaction
- Side effects
HPTN 083/084: Efficacy of CAB-LA

**HPTN 083:**
- **N=4570 MSM/TGW**
- CAB-LA provided **high efficacy** compared to TDF/FTC
- CAB LA was found to be **statistically superior** to daily oral TDF/FTC for PrEP
- 50 incident HIV infections occurred
  - TDF/FTC arm: 38 incident HIV infections (1.21% incidence rate)
  - CAB arm: 12 incident HIV infections (0.38% incidence rate)
- **Status:** Halted early for efficacy. Moving into OLE

**HPTN 084:**
- **N=3,200 women (aged 18-45 years) in sub-Saharan African who are at risk for acquiring HIV**
- **Status:** ONGOING

*Landovitz RJ et al, AIDS 2020*
Choice, Preference and Use
N=300 AGYW aged 16-21
4 Locations: RSA, Uganda, Zimbabwe
Status: ongoing

All participants use PrEP and the ring – each for 6 months – and then they can choose which to use for another 6 months.

Providing choice is empowering and increases autonomy

Drug level feedback

ACASI/CRFs
Stated preference; Willingness to

Product choice

Qualitative
To explore preference,
• Median age: 19 (IQR 17-21)
• 78% ≥ secondary education
• ½ randomized to incentive arm (counseling at months 2 and 3 about the prior month’s drug level with a 200 Rand, $13, incentive conditioned on TFV-DP > 700), and 1/2 to the standard arm (counseling at months 2 and 3 about the prior month’s drug level without an incentive).
• At 3 months, < half had high adherence (TFV-DP in DBS > 700 fmol/punch)
• The proportions with high adherence decreased from M3 to M6 and M12

Incentives can help, but you also need to lower barriers to use
Lessons learned

1. It is never too early to engage end-users in the research
2. When you can, bundle your indications
3. Strategies that help lower user burden improve effectiveness
4. Providing method choice is empowering and increases autonomy
5. Incentives can help, but you also need to lower barriers to use
The Regulatory Horizon: The Dapivirine Vaginal Ring

PrEP Works if You Take It — Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention

- CAPRISA 004 (tenofovir gel, BAT-24 dosing)
- FEM-PrEP
- IPERGAY (TDF/FTC)
- iPrEx
- Partners PrEP (TDF)
- Partners PrEP (TDF/FTC)
- PROUD (TDF/FTC)
- TDF2
- VOICE (TDF)
- VOICE (TDF/FTC)
- VOICE (tenofovir gel, daily dosing)

Islatravir, NRTTI
formerly known as MK-8591 and EFdA, halts construction of new viral DNA by acting as a defective building block and acting at a later step in the viral replication process
- Can be dosed once a week
- Under investigation as a potent form of post-exposure prophylaxis (PEP), for monthly oral dosing as PrEP, or for even longer which will be given in an implant form (1 year)

Antibody Mediated Prevention (AMP) Study (HPTN 081 and 085)

- Giving people antibodies to see if the antibodies will protect them from getting infected with HIV
- AMP study (phase IIB trial) is the first study testing if antibodies can prevent HIV infections in people

bnAbs

- Rare antibodies that latch on to HIV virus and hinders the virus from attaching to human cells, neutralizing different forms of HIV virus from around the world
- In AMP, a bimonthly infusion of a bnAb called VRCO1 is evaluated as an HIV preventative strategy (N=4,625)
- The goal is to use these antibodies to create new ways to combat HIV infection
- A new phase I trial (HVTN127/HPTN 087) evaluates VRC07-523LS (a longer lasting and more potent bnAB) via infusion, SubQ injection and IM injection
3. More Options → Better Choices: The science of informed choice

More Options → Better choices → increased coverage → higher impact
The science of informed choice

Public Policy

Community

Institutional

Interpersonal

Individual

Access: Delivery and Cost

IEC and Advocacy

HCP endorsement: education & training

Couple counseling; S.O engagement, partner education

Decision tool
Thank you!!

Questions?

Contact: ariane@rti.org
EXTRA SLIDES
DCE is designed to elicit product preferences by examining trade-offs individuals make when choose between alternate product designs.

iPrevent enrolled youth (MSW, MSM, females) in a DCE to determine their preferences for an HIV-prevention products.

**Key Finding:** Duration was the major driver of preference.

### DCE Characteristics

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product form</strong></td>
<td>Implant</td>
</tr>
<tr>
<td><strong>Duration</strong> – how often you will need to a get a dose</td>
<td>One dose every 2 months</td>
</tr>
<tr>
<td><strong>Where it is available</strong></td>
<td>Pharmacy</td>
</tr>
<tr>
<td><strong>Soreness after injection /implant</strong></td>
<td>Mild</td>
</tr>
<tr>
<td><strong>Location of injection/ implant</strong></td>
<td>Bum</td>
</tr>
</tbody>
</table>

3P Adherence Level (Persistors and Non-Persistors): an end-user journey

Adherence Heat Map of Persistors in 3P Study over 12 Months (n=8)

Adherence Heat Map of Non-Persistors in 3P Study over 12 Months (n=14)