The case for multipurpose prevention technologies (MPTs) in the space of HIV/STI prevention (Px) and family planning (FP)/contraception

Products in development: categories, current pipeline and examples

R&D and regulatory gaps

Main takeaway messages

No conflicts to declare – Member of CONRAD (part of MATRIX consortium)
What is a multipurpose prevention technology (MPT)?

- **Public health impact**
  - 218m women with unmet need for contraception
  - >300m new STIs annually
  - ~1.5m individuals acquired HIV in 2021; in SSA, 63% are women and girls

- **Definition**
  - Multipurpose prevention technologies, or MPTs, are products designed to simultaneously prevent HIV, other STIs, and/or unintended pregnancy (def. by The Initiative for MPTs)
  - MPTs by FDA: multi-indication/function or combination products

- **Categories**
  - By delivery system: topical and systemic
  - By indication: combinations of HIV, contraception, non-HIV STIs
The case for developing an MPT

• Satisfies **concurrent needs** (eg. FP & HIV Px) in large population of people

• In multiple surveys, women and men have indicated their **preference** for an MPT, a “two in one product”

• MPTs would facilitate **uptake** (convenience, reduction of stigma) and **integration** of FP and HIV/STI services

• Potential for **cost-effectiveness** and cost-savings in certain populations and areas

• **Development and approval** processes are more complicated

• **Dosing** must be synchronized; typically cannot terminate one component separately

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Ipsos Report, 2014

Little et al, 2023
## Current MPT pipeline

### Preclinical
- Vaginal ring
- Vaginal insert
- Rectal insert
- Vaginal gel
- Rectal gel
- Enema
- Vaginal film
- Oral pill
- Long-acting injectable
- Micro-array patch
- Implant

### Phase I
- Vaginal ring
- Vaginal insert
- Rectal insert
- Vaginal gel
- Rectal gel
- Enema
- Vaginal film
- Oral pill
- Long-acting injectable
- Micro-array patch
- Implant

### Phase II
- Vaginal ring
- Vaginal insert
- Rectal insert
- Vaginal gel
- Rectal gel
- Enema
- Vaginal film
- Oral pill
- Long-acting injectable
- Micro-array patch
- Implant

### Phase III
- Vaginal ring
- Vaginal insert
- Rectal insert
- Vaginal gel
- Rectal gel
- Enema
- Vaginal film
- Oral pill
- Long-acting injectable
- Micro-array patch
- Implant

### Phase IIib/IV
- Vaginal ring
- Vaginal insert
- Rectal insert
- Vaginal gel
- Rectal gel
- Enema
- Vaginal film
- Oral pill
- Long-acting injectable
- Micro-array patch
- Implant

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### The Preclinical MPT Pipeline by Indication Combination

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Delivery Method</th>
<th>Product Developer</th>
<th>Stage of Development</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV &amp; Pregnancy</td>
<td></td>
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<tr>
<td>Cabogestral/Levonorgestrel Long-Acting MPT (Vaginal)</td>
<td>Injectable</td>
<td>CONRAD</td>
<td>Advanced Preclinical</td>
<td>HIV, Pregnancy</td>
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<tr>
<td>ERSP-01 – Prospects Intrauterine Film</td>
<td>Vaginal Ring</td>
<td>Magee-Womens Research Intl., &amp; Pitt Univ. of Pittsburgh</td>
<td>Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>Human Contraceptive Antibody (mAbs) + MPA + NVP</td>
<td>Intravaginal Ring [IVR]</td>
<td>Merck</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>Inhibitor (FVIII) + Pregnanediol/Dehydroepiandrosterone (DHEA)</td>
<td>Intravaginal Ring [IVR]</td>
<td>University of North Carolina, Chapel Hill</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>IMPT Microarray Patch</td>
<td>Microarray Patch</td>
<td>PATH, Queen’s University Belfast</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>STI-Impedance Probe (type Impedance/STI ring)</td>
<td>Intravaginal Ring [IVR]</td>
<td>Population Council, Oak Crest Institute of Science</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>Subcutaneous Contraceptive – HIV Implant Engineered for Long-Acting Delivery (DOLIC®) device</td>
<td>Implant</td>
<td>Research Triangle International (RTI)</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>Ultra-Long-Acting MPT in Intravenous Implant</td>
<td>Injectable</td>
<td>University of North Carolina, Chapel Hill</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy</td>
</tr>
<tr>
<td>HIV &amp; Other STIs</td>
<td></td>
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<tr>
<td>mife 2CT – TDF (IV)</td>
<td>Intravaginal Ring [IVR]</td>
<td>Microbicides, Oak Crest Institute of Science, Planet Biotechnology, Inc., University of Massachusetts</td>
<td>Advanced Preclinical</td>
<td>HIV, Gonorrhea</td>
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<tr>
<td>Estriol (EC)/Denoyn (ETN)</td>
<td>Vaginal Film</td>
<td>Inst. for Research &amp; Innovation in Health (IRSI), University of Porto</td>
<td>Advanced Preclinical</td>
<td>HIV, HIV-1, HIV-2</td>
</tr>
<tr>
<td>Contraception, HIV, &amp; Other STIs</td>
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<tr>
<td>Contraceptive – Progesterone Long-Acting (Spinal)</td>
<td>Intravaginal Ring [IVR]</td>
<td>University of North Carolina, Chapel Hill</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy, HIV-2</td>
</tr>
<tr>
<td>Non-Hormonal Contraceptive MPT Containing G2-Griffithson (Q2GPT)</td>
<td>Vaginal Insert</td>
<td>Population Council</td>
<td>Early Preclinical</td>
<td>HIV, Pregnancy, HIV-1, HIV-2, Gonorrhea, Chlamydia</td>
</tr>
<tr>
<td>Novel pill as a Non-Hormonal Contraceptive MPT</td>
<td>Intravaginal Ring [IVR]</td>
<td>Population Council, Queen’s University Belfast, Wellcome Trust Cambridge College</td>
<td>Pre-research, pre-phase 1, clinical</td>
<td>HIV, Pregnancy, HIV-2, Gonorrhea, Chlamydia</td>
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<tr>
<td>Non-CPDL</td>
<td>Vaginal Gel</td>
<td>Yaro Pharmaceuticals</td>
<td>Advanced Preclinical</td>
<td>HIV, Pregnancy, HIV-2, Gonorrhea, Chlamydia</td>
</tr>
</tbody>
</table>

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- Many technologies in different R&D stages. Visit AVAC and IMPT website for full list and more information.
Examples of MPTs in development
Systemic delivery – Dual Prevention Pill

- Viatris developing **co-formulated oral tablet with 28-day regimen** (TDF/FTC [HIV Px] + LNG/EE [contraception])
- Bioequivalence study to compare bioavailability of co-formulated tablet to TDF/FTC and LNG/EE separately ongoing
- File for regulatory approval possible in 2024
- Could be packaged in a blister pack – like combined oral contraceptives (COCs) and unlike the classic “rattling PrEP pill bottle”; two colors
- End-user research and market preparation underway
- HPTN 104: adherence to DPP vs separate products (TVD, COC)
- Introduction in Africa (SA, Zim, Kenya, first) planned for 2025
- Longer term, Population Council/Medicines360 to develop F/TAF-based DPP (F/TAF + LNG/EE)
Examples of MPTs in development
Systemic delivery – CAB/LNG injectable hydrogel

• **Novel biodegradable injectable depot** releasing cabotegravir (CAB) and levonorgestrel (LNG) for long-acting (LA; 3-6 months) dual prevention of HIV acquisition and pregnancy

• Fully biodegradable GRAS **hydrogel material with shear-thinning properties** enables high drug loading and low injection volume

• **End-user feedback** from literature and CONRAD’s DCEs demonstrate a high preference for a two-in-one product

• **Health care system impact:** reduced number of clinic visits (synchronized); reduced cost, time, and monitoring; improved integration with FP services/programs; reduced stigma

• **First-in-class MPT injectable** builds on 2 proven & marketed drugs; expedites product dev and reduces liability

• **Leverages ongoing preclinical development** of CAB-only (MATRIX) and LNG-only and CAB/LNG (NIH Horizon, 3-month TPP) in hydrogel depot platform

• **Next steps:** POC in NHPs (CDC), IND-enabling, FIH study in women, and SSA AGYW/key stakeholders (MATRIX-USAID); US AGYW/TGP DCE/Phase I (Project Horizon & ATN-NIH)
Examples of MPTs in development

Topical delivery – TFV/LNG vaginal ring

- 3-month IVR for protection against HIV, HSV & pregnancy (TFV/LNG)
  - Most advanced MPT IVRs in the field (6 clinical trials completed)
- No cold chain storage required
  - 3 year shelf life demonstrated
- Clinical proof-of-concept demonstrated for safety, acceptability, TFV & LNG PK & PD\(^1\)
  - Pharmacologically forgiving; extended protection after removal
  - Minimal impact on menstrual bleeding patterns
- Roadmap for scale up & automated manufacturing
- Effectiveness trials (pending funding)
Examples of MPTs in development
Topical delivery – TFV/LNG IVR clinical development

❖ **CONRAD 128 – first in women study (US, Dom. Rep.)**

❖ **CONRAD 140 – PK/PD modeling study (US)**
Ouattara et al., JAIDS 2022

❖ **CONRAD 138 – TFV/LNG expanded use (US, Dom. Rep)**
Thurman et al., PLoS One 2022; Thurman et al., FCIMB 2022; Tolley et al., J Womens Health 2022

❖ **MTN 038 – TFV expanded use (US)**
Liu et al., JIAS 202 (submitted)

❖ **KCRS (CONRAD 144) – first in Africa study (Kenya)**
Dabee et al., Sci Rep 2022; Mugo et al., Front RH 2023 (Submitted)

❖ **Quatro – placebo acceptability study (SAfrica, Zimbabwe)**
Montgomery et al., JIAS 2019; Weinrib et al., AIDS Behav. 2020; Browne et al., AIDS Behav. 2020; Musara et al., AIDS Behav. 2021

❖ **Karoo and Kalahari HCD research**
Packaging, messaging, educational materials/training needs

Thurman et al., PLoS One 2022
Examples of MPTs in development
Topical delivery – DPV/LNG vaginal ring

• **Features:** extension of dapivirine (DPV) 1-mo. silicone ring

• **Composition:** DPV and LNG in ethylene vinyl acetate (EVA) core/sheath ring

• **Duration:** three months per ring

• **Salient preclinical/clinical data:**
  • Two Phase I trials in silicone ring demonstrated no safety concerns and plasma levels were achieved
  • Ring was reformulated to reduce expulsions; no safety concerns in ongoing Phase IB of the reformulated ring

• **Next steps in development:**
  • Relative bioavailability study for DPV to bridge DPV ring data
  • Phase II/III contraceptive efficacy program
  • The DPV-LNG ring could have a significant impact on reducing HIV among women in sub-Saharan Africa
Examples of MPTs in development
Topical delivery – Non-ARV/NHC vaginal ring

- Highly innovative IVR design for the sustained delivery of an antiviral peptide in combination with a nonhormonal contraceptive
- One drug per cassette (grey) allows for independently controlled release; designed for cost-effective manufacturing
- Developed as 28-day product, with 90-day as follow-up option
- Peptide effective against HIV in vivo; also active against HSV and HPV; contraceptive blocks sperm motility and capacitation, does not affect menstruation
- IND-enabling efforts under way; placebo IVR multicentered clinical study (MATRIX-003) starting in summer 2023
Examples of MPTs in development
Topical delivery – DPV/LNG vaginal film

- **Dual purpose vaginal film** for contraception & HIV prevention
- **Bioerodible vaginal film** platform contains dapivirine, an anti-HIV drug and levonorgestrel, a contraceptive
- Designed to provide protection from HIV and unintended pregnancy for **1 month**
- Women can **insert** the film themselves
- Currently in **preclinical** studies; placebo clinical study (MATRIX 002) in preparation stages
- **Planned IND submission** and Phase 1 clinical study in 2024/2025
Examples of MPTs in development
Topical delivery – GRFT fast-dissolving insert

• **Features:** non-ARV, on-demand, user-controlled, dissolves in women’s natural vaginal secretions, potential for vaginal and rectal use

• **Composition:** Griffithsin (protein/lectin isolated from the red algae with broad antiviral activity) in carrageenan vehicle

• **Duration:** 8+ hours after insertion

• **Salient preclinical/clinical data:**
  o 80% protection (SHIV) in Rhesus macaques; 100% (HPV) and 60% (HSV-2) protection in mice
  o High therapeutic index and lack of safety concerns in Phase 1; toxicity index is expected to be low
  o No systemic drug levels detected in first-in-human gel study further minimizing concerns for toxicity

• **Next steps in development:**
  o NHP dose-finding study; bridging (gel to FDI) toxicology studies
  o Phase 1 trials
Examples of MPTs in development
Topical delivery – TAF/EVG fast-dissolve insert

❖ **TAF/EVG FDI:** on-demand (PrEP or PEP) dual-compartment MPT for HIV & HSV prophylaxis (dual prevention product)

❖ **Fills important unmet need in HIV & MPT method mix**
  - Flexible on-demand, PrEP or PEP
  - For vaginal or rectal use
  - Low systemic drug exposure

❖ **Developed iteratively with end user input throughout PD process**
  - Discreet, highly portable, easy to self-administer, rapidly dissolving
  - Economical; easy to manufacture at scale; transferable

❖ **Preclinical & Clinical Proof-of-Concept demonstrated**
  - SHIV challenge studies in NHPs (vaginal PEP/PrEP, rectal PrEP)¹
  - First-in-human, single administration, vaginal and rectal, long-lasting PK and ex vivo modeled (PD) anti-HIV and anti-HSV data²

❖ **Next clinical studies**
  - MATRIX 001: extended safety, PK/PD assessment after repeated vaginal application (MATRIX)
  - RITE: extended safety, PK/PD assessment after repeated rectal application (CDC/Emory)

¹Dobard et al., EBioMedicine 2022; Makarova et al., EBioMedicine 2022;
²Thurman et al., FCIMB 2023; Riddler et al., CROI 2023
Examples of MPTs in development
Topical delivery – TAF/EVG insert – NHP and clinical data

Vaginal PrEP or PEP (4h), single dose - NHP

Vaginal applic (CONRAD 146), PK/PD single dose – FIH women

Rectal PrEP (4h), double dose - NHP

Dobard et al., EBioMedicine 2022; Makarova et al., EBioMedicine 2022; Thurman et al., FCIMB 2023; Riddler et al., CROI 2023
MPT R&D and regulatory gaps

- Early **end-user and stakeholder input** on modifiable product attributes
- Reliable **in vitro/in vivo correlation** (IVIVC) models to predict release rates for at least two actives
- Validated **preclinical models**, with correlation to human PK/PD
- Criteria, **benchmarks and IND-enabling guidance** to properly develop and select lead MPT candidates in preclinical stage
- Standard **clinical trial design** and clinical development pathway
  - FIH design? Endpoints?
  - POC for both indications? One or two studies?
- **Regulatory requirements** for approval
- **Scale up** and manufacturing
- **Business case** and cost-effectiveness
- **Implementation** and introduction needs
MPTs can be a game changer

Discreet  Convenient  Autonomy  Highly acceptable
Easier to adhere  Overcome stigma  Enhancing sex
Minimize clinic visits

Lisa Haddad, 2022, HPTN Annual Meeting
Takeaway messages - MPTs

- **Overlapping needs** for HIV/STI prevention and FP/contraception
- **MPTs/dual prevention products highly preferred** by people desiring more than HIV prevention (eg. contraception); especially AGYW; offering more choices (higher uptake), more agency and empowerment (higher adherence/continuation)
- Women prefer **highly effective** products with minimal side effects; could be long-acting (>3 mos.) or event-driven
- MPTs can help **integrate services** for FP and HIV/STI prevention
- **Systemic dosage** forms (eg. DPP, LA injectable depot and implants) provide high protection against all routes of transmission; high levels of systemic drug exposure
- **Topical dosage** forms (eg. inserts, film, rings) provide concentrated protection in one compartment with low systemic exposure
- **Product development** is more complex with more challenges and uncertainties
- **Regulatory pathway** for approval of multiple indications requires clarification and guidance
- MPTs represent the **next frontier** in HIV/STI prevention and FP/contraception
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