Multipurpose Prevention Technologies (MPTs)

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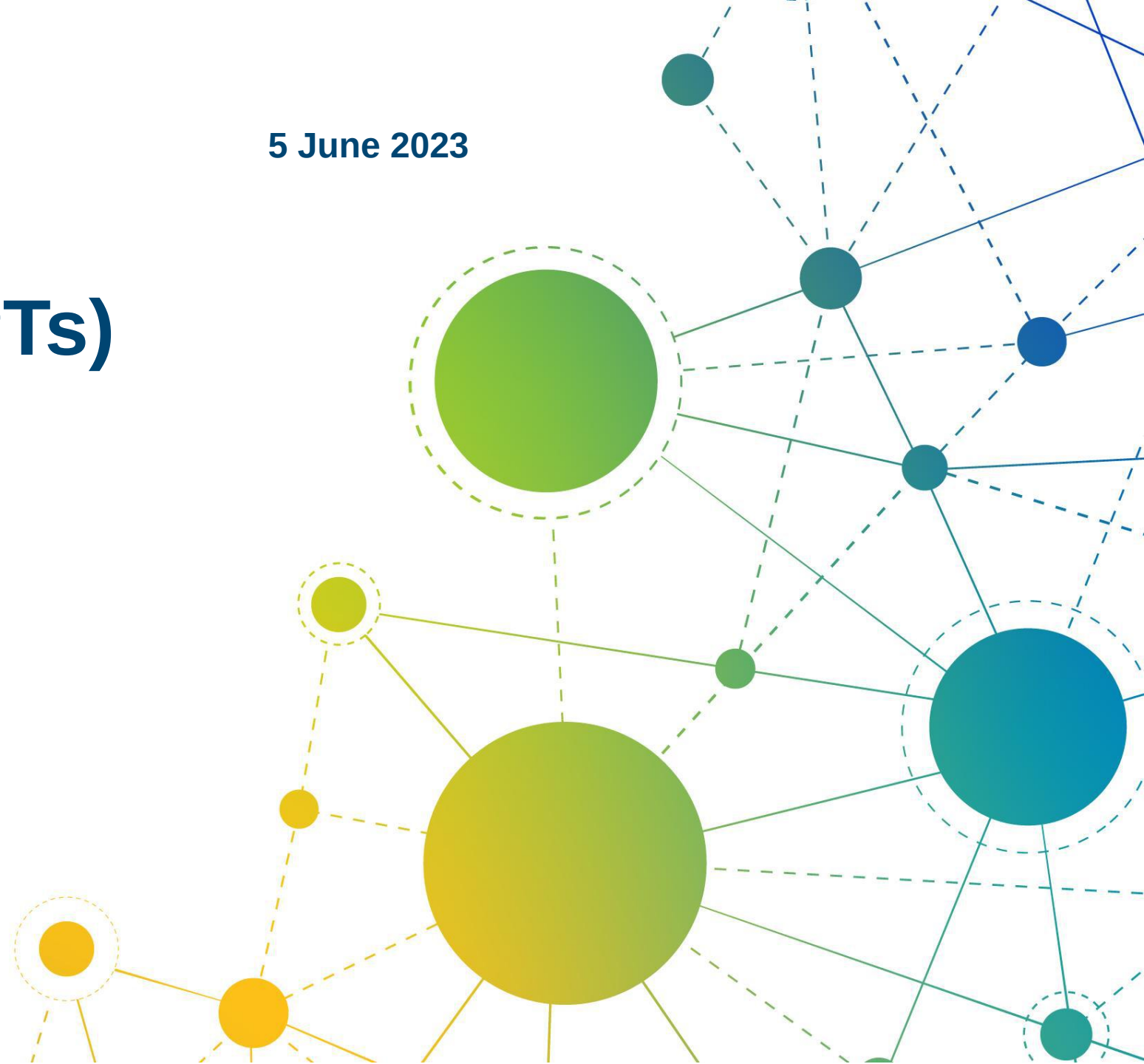
HPTN Annual Meeting



Presentation Highlights

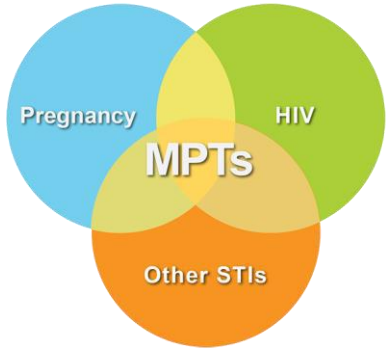
- The case for multipurpose prevention technologies (MPTs) in the space of HIV/STI prevention (Px) and family planning (FP)/contraception
- Products in development: categories, current pipeline and examples
- R&D and regulatory gaps
- Main takeaway messages

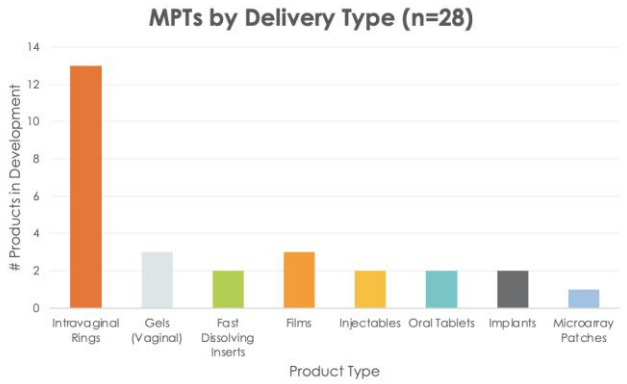
- No conflicts to declare – Member of CONRAD (part of MATRIX consortium)

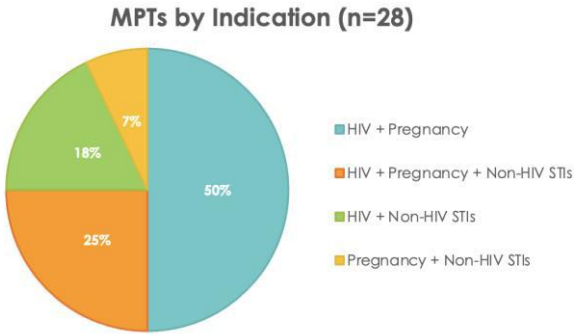
What is a multipurpose prevention technology (MPT)?

HPTN HIV Prevention Trials Network

- **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







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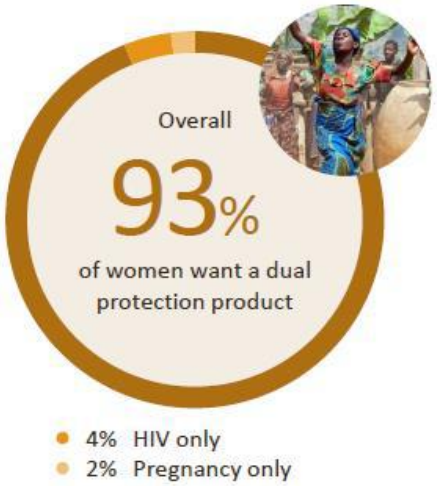
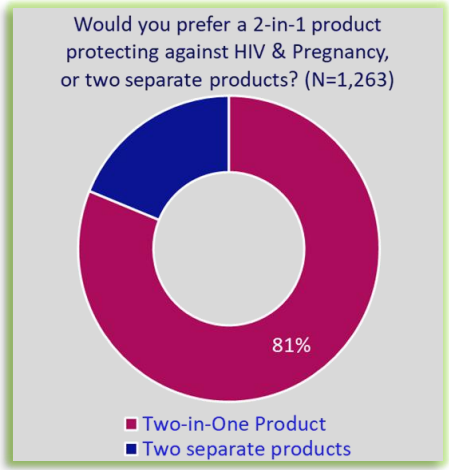
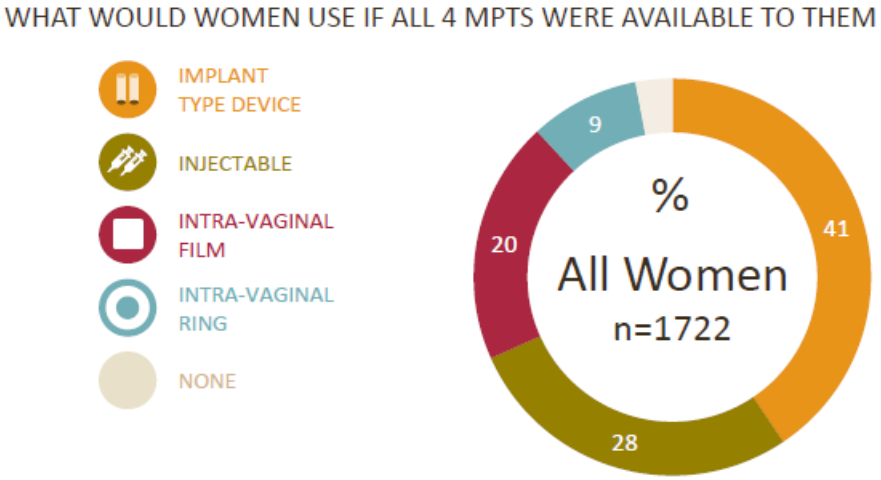
The case for developing an MPT

- 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





Little et al, 2023



Ipsos Report, 2014

Current MPT pipeline

HIV + other STIs	HIV + other STIs + Contraception	HIV + Contraception	Contraception + other STIs
10	4	11	3

IMPT for Reproductive Health

The Preclinical MPT Pipeline by Indication Combination

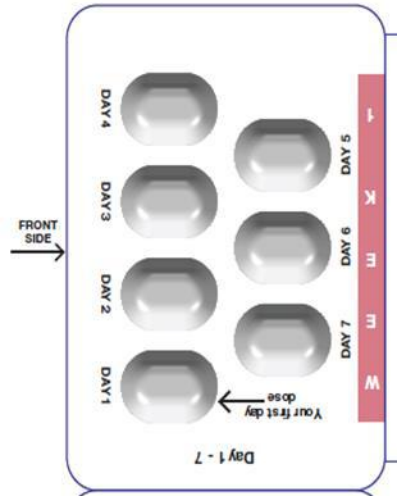
Product Name	Delivery Method	Product Developer	Stage of Development	Indications
HIV & Pregnancy				
Cabotegravir/Levonorgestrel Long-Acting MPT Injectable	Injectable	CONRAD	Advanced Preclinical	HIV, Pregnancy
EFdA-P + Progestin Intravaginal Film	Vaginal Film	Magee-Women's Research Inst. & Fndn., University of Pittsburgh	Early Preclinical	HIV, Pregnancy
Human Contraceptive Antibody (HCA) + VRC01 + N6 IVR	Intravaginal Ring (IVR)	MUCCOMMUNE LLC	Advanced Preclinical	HIV, Pregnancy
Islatravir (EFdA) + Etonogestrel/Ethinyl Estradiol 3D Printed IVR	Intravaginal Ring (IVR)	University of North Carolina, Chapel Hill	Early Preclinical	HIV, Pregnancy
MPT Microarray Patch	Microarray Patch	PATH, Queen's University Belfast	Early Preclinical	HIV, Pregnancy
90-day Pod-type Etonogestrel/Ethinyl Estradiol/QGriffithsin (EEQ) IVR	Intravaginal Ring (IVR)	Population Council, Oak Crest Institute of Science	Early Preclinical	HIV, Pregnancy
Novel mAb contraceptive + Tenofovir Disoproxil Fumarate (TDF) IVR	Intravaginal Ring (IVR)	Oak Crest Institute of Science, Univ. of North Carolina, Chapel Hill	Early Preclinical	HIV, Pregnancy
Subcutaneous Contraceptive + HIV Implant Engineered for Long-Acting Delivery (SCHIELD) device	Implant	Research Triangle International (RTI)	Early Preclinical	HIV, Pregnancy
Ultra-Long-Acting MPT In-situ Forming Implant (ISFI)	Injectable In-situ Forming Implant	University of North Carolina, Chapel Hill	Early Preclinical	HIV, Pregnancy
HIV & Other STIs				
mAb 2C7 + TDF IVR	Intravaginal Ring (IVR)	MassBiologics, Oak Crest Institute of Science, Planet Biotechnology, Inc., University of Massachusetts	Advanced Preclinical	HIV, Gonorrhea
Tenofovir (TFV)/Efavirenz (EFV) Nanoparticles-in-film	Vaginal Film	Inst. For Research & Innovation in Health (i3S), University of Porto	Advanced Preclinical	HIV, HSV-1, HSV-2
Pregnancy, HIV, & Other STIs				
Dapivirine + Pritelivir + Levonorgestrel 3D Printed IVR	Intravaginal Ring (IVR)	University of North Carolina, Chapel Hill	Early Preclinical	HIV, Pregnancy, HSV-2
Dolutegravir + Rilpivirine + Acyclovir + Ethinyl Estradiol + Etonogestrel IVR	Intravaginal Ring (IVR)	Auritec Pharmaceuticals	Advanced Preclinical	HIV, Pregnancy, HSV-2
Non-hormonal Contraceptive MPT Containing Q-Griffithsin (QGRFT)	Vaginal Insert	Population Council	Early Preclinical	HIV, Pregnancy, HSV-2, BV, Chlamydia, Gonorrhea
Novel IVR as a Non-Hormonal Contraceptive MPT	Intravaginal Ring (IVR)	Population Council, Queen's University Belfast, Weill Cornell Medical College	Pre-formulation, pre-Phase 1, Non-clinical	HIV, Pregnancy, HSV-2, Gonorrhea, Chlamydia, BV
Yaso-GEL	Vaginal Gel	Yaso Therapeutics	Advanced Preclinical	HIV, Pregnancy, HSV-2, HPV, Gonorrhea

- **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

HPTN HIV Prevention Trials Network

- 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)



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Dual Prevention Pill Consortium

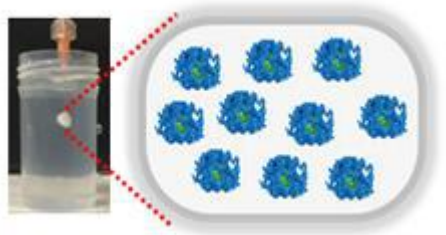
Project Partners:

AVAC
CLINTON HEALTH ACCESS INITIATIVE
Mann Global Health
POPULATION COUNCIL
VIATRIS

Examples of MPTs in development
Systemic delivery – CAB/LNG injectable hydrogel

HPTN HIV Prevention Trials Network

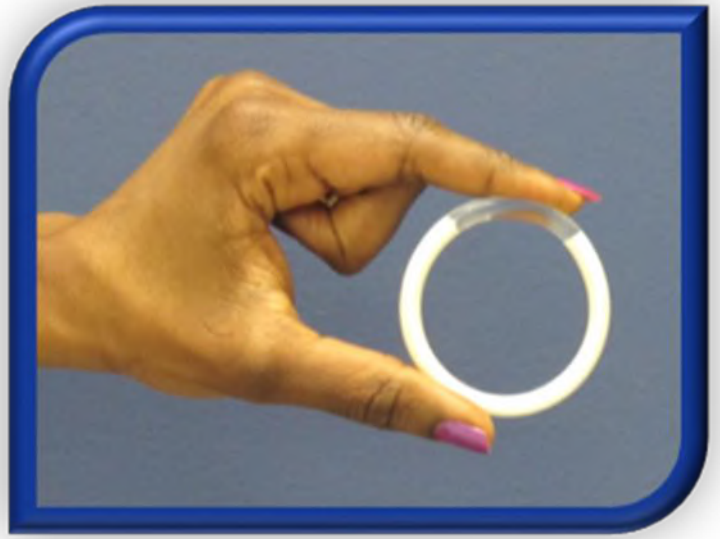
- **Novel biodegradable injectable depot** releasing cabotegravir (**CAB**) and levonorgestrel (**LNG**) for long-acting (LA; 3-6 months) dual prevention of HIV acquisition and pregnancy
- Fully biodegradable GRAS **hydrogel material with shear-thinning properties** enables high drug loading and low 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)

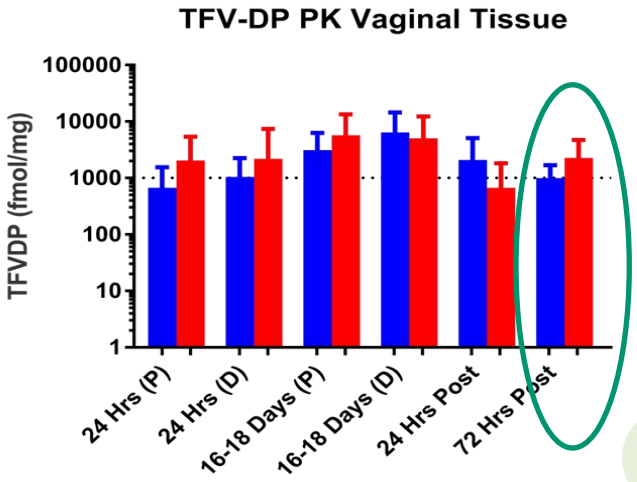


CONRAD NIH Project Horizon PEPFAR U.S. President's Emergency Plan for AIDS Relief USAID FROM THE AMERICAN PEOPLE MATRIX

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)**



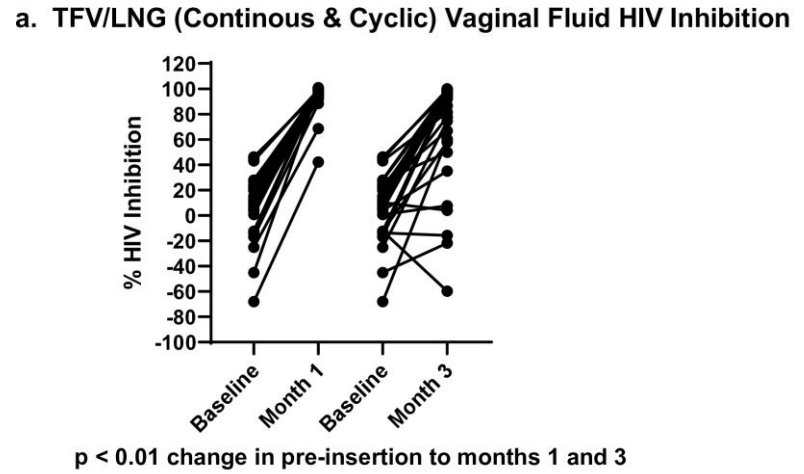


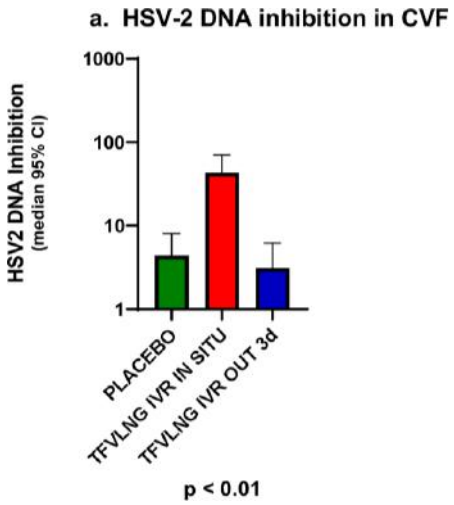
Thurman AR et al., PLoS One 2018

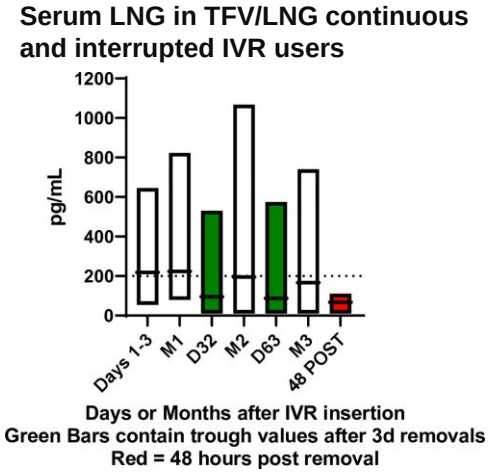
Examples of MPTs in development
Topical delivery – TFV/LNG IVR clinical development

HPTN HIV Prevention Trials Network

- **CONRAD 128 – *first in women study (US, Dom. Rep.)***
  Thurman et al., PLoS One 2018, 13(6): e0199778; Thurman et al., PloS One 2019, 14(5) e0217229
- **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

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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

HPTN HIV Prevention Trials Network

- 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

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Examples of MPTs in development
Topical delivery – DPV/LNG vaginal film

HPTN HIV Prevention Trials Network

- **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

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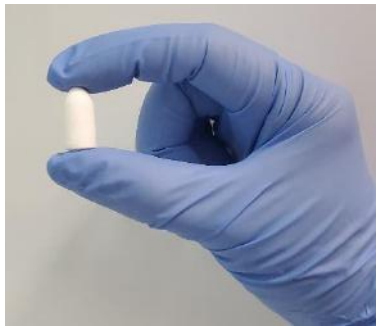
Examples of MPTs in development
Topical delivery – GRFT fast-dissolving insert



- **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:**
  - 80% protection (SHIV) in Rhesus macaques; 100% (HPV) and 60% (HSV-2) protection in mice
  - High therapeutic index and lack of safety concerns in Phase 1; toxicity index is expected to be low
  - No systemic drug levels detected in first-in-human gel study further minimizing concerns for toxicity
- **Next steps in development:**
  - NHP dose-finding study; bridging (gel to FDI) toxicology studies
  - Phase 1 trials

Examples of MPTs in development
Topical delivery – TAF/EVG fast-dissolve insert

HPTN HIV Prevention Trials Network

- **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 data[2]
- **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)

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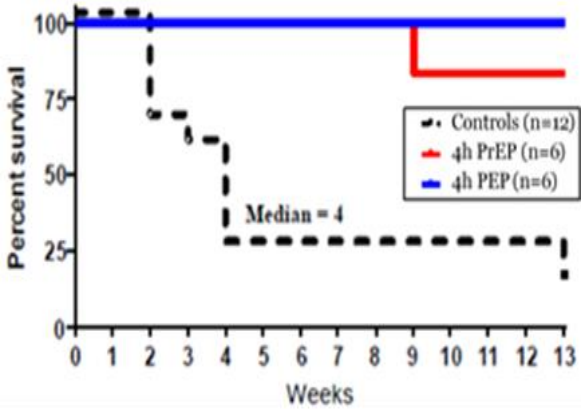
[1]Dobard et al., EBioMedicine 2022; Makarova et al., EBioMedicine 2022;
[2]Thurman et al., FCIMB 2023; Riddler et al., CROI 2023

MATRIX

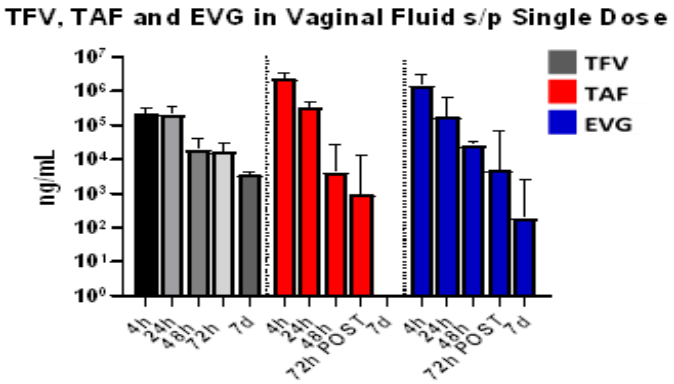
Examples of MPTs in development
Topical delivery – TAF/EVG insert – NHP and clinical data

HPTN HIV Prevention Trials Network

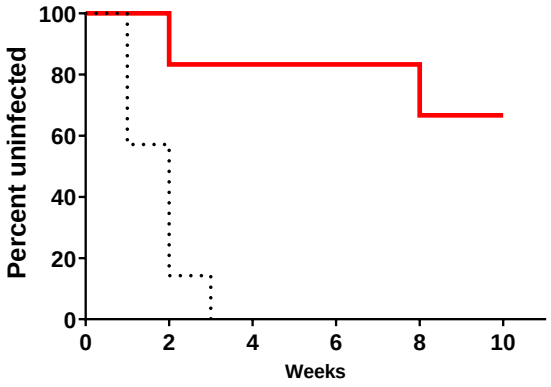
Vaginal PrEP or PEP (4h), single dose - NHP

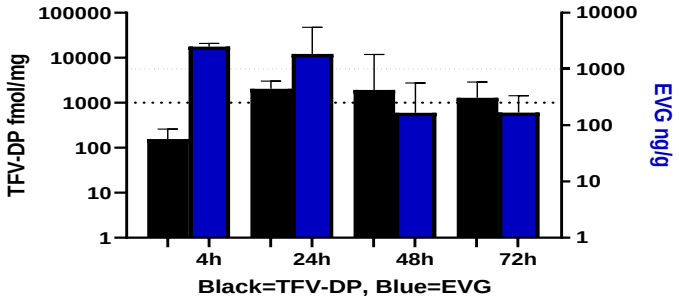


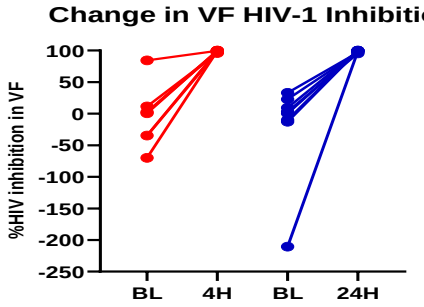
Vaginal applic (CONRAD 146), PK/PD single dose – FIH women

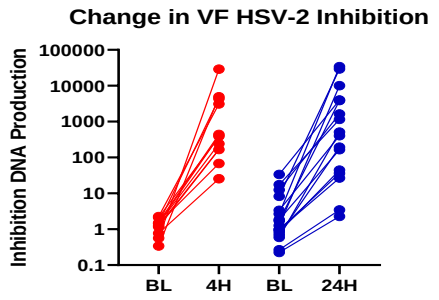


Rectal PrEP (4h), double dose - NHP

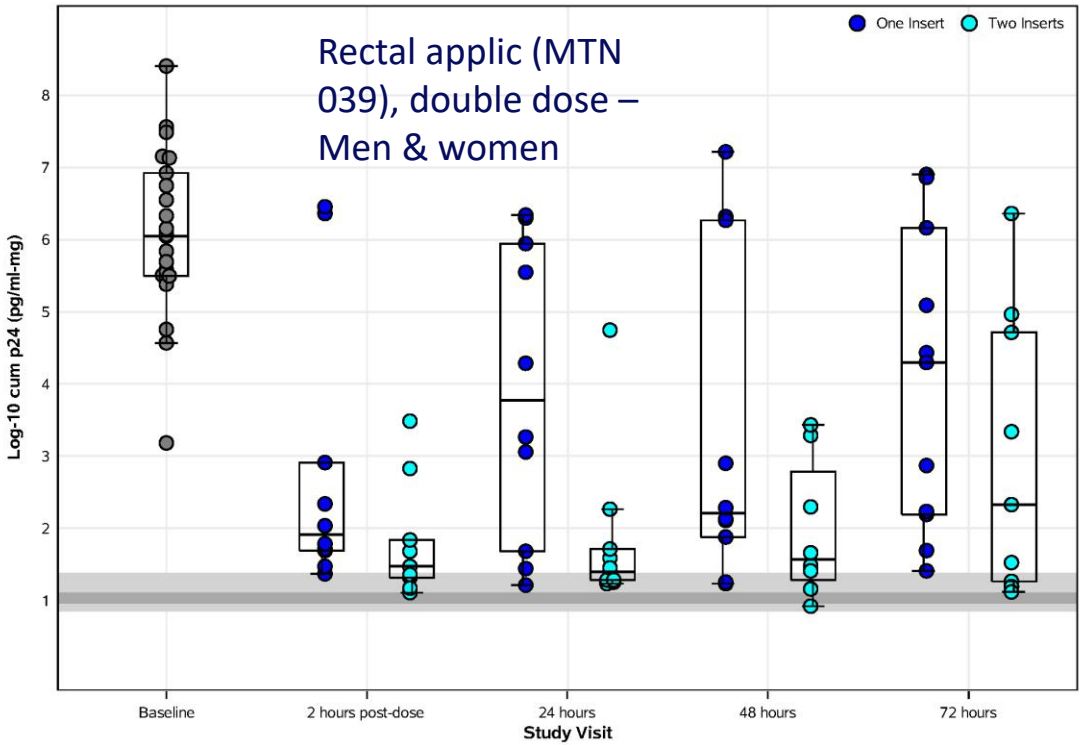








Rectal applic (MTN 039), double dose – Men & women



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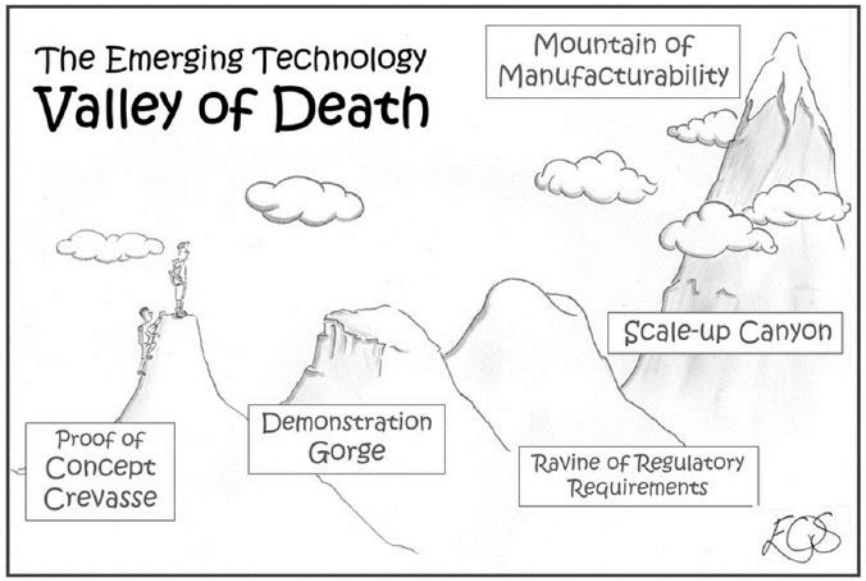
Dobard et al., EBioMedicine 2022; Makarova et al., EBioMedicine 2022; Thurman et al., FCIMB 2023; Riddler et al., CROI 2023

MPT R&D and regulatory gaps

HPTN HIV Prevention Trials Network

- 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



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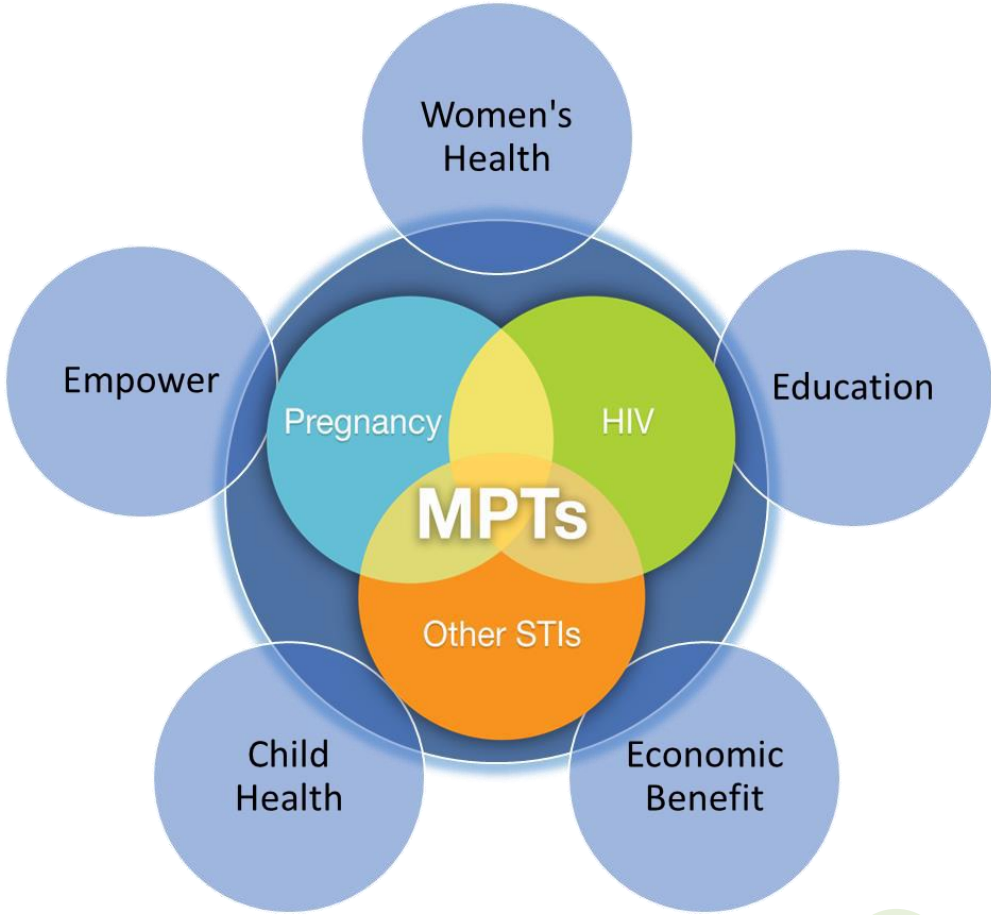
MPTs can be a game changer

Discreet Convenient Autonomy Highly acceptable

Easier to adhere Overcome stigma Enhancing sex

Minimize clinic visits



Lisa Haddad, 2022, HPTN Annual Meeting

Minnis A, et al.. Sexual and Reproductive Health Matters 2021; 29(1):1-15

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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- AVAC (https://www.avac.org/)

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