Drug Delivery Systems in Women's Health

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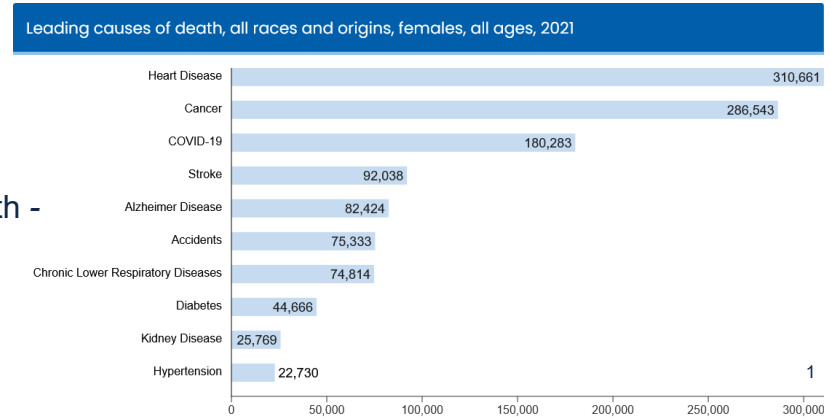
CRS 2025 ANNUAL MEETING & EXPOSITION
PHILADELPHIA, PA
JULY 13-18, 2025

NEXT-GENERATION DELIVERY INNOVATIONS

Women's health: Burden of disease

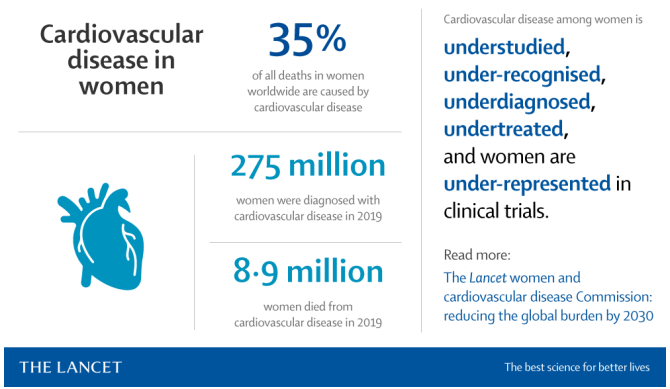
Primary causes of disease in women and unmet needs

- **Cardiovascular disease** (35% of all ♀ deaths; more fatal for women)
- **Cancers** (2.3 million breast cancer diagnoses/year; cervical cancer - *100% preventable, yet ~350k women die from it annually*)
- **Dementia/Alzheimer's** (majority women; fastest rising ♀ cause of death - *tripled 2020-2021*)
- **Autoimmune diseases** (80%+ of patients are ♀; e.g., lupus, MS, RA)
- **Maternal health complications** (esp. in LMIC; 287,000 deaths/year)
- **Reproductive system conditions** (endometriosis, fibroids, PCOS)
- **Mental health** (depression: women 2x as likely as men)



- Several conditions (CVD, depression, autoimmune) **affect women > men**
- Women **spend more years living with disability** (26% more YLD than men)[2]

- Under-diagnosis, under-treatment, less clinical trial data for women
- **Lack of new, targeted, user-centered therapies for many conditions**
- Several research gaps, esp. in pregnant women



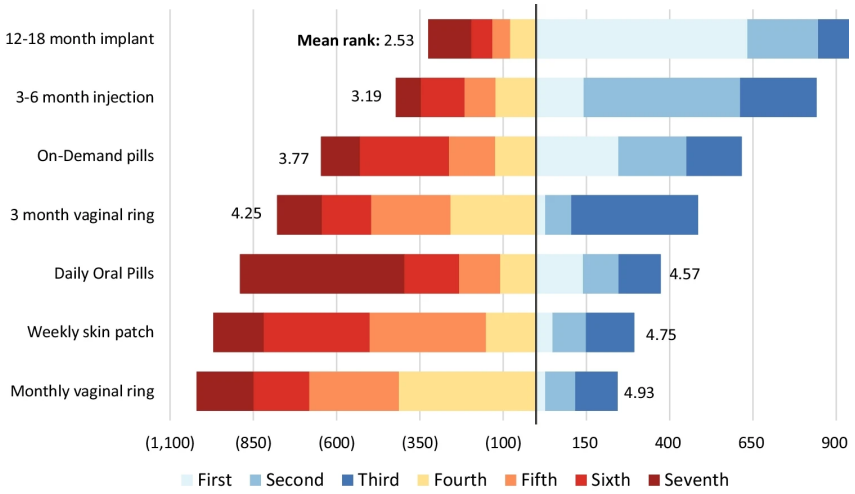
1. CDC Office of Women's Health: Leading Causes of Death in Females; 2. WHO: Global Health Estimates: Life expectancy and leading causes of death and disability; 3. Vogel et al., The Lancet. 2021

Product choice supports better adherence and effectiveness

❖ **Drug Delivery Systems and HIV Prevention:**

- Clinical trials have shown significant improvements in adherence and efficacy for women using LA DDS

Discover Trial[3]	**Men**	Daily Oral Descovy	**Purpose I Trial**[4]	**Women**	Daily Oral Descovy
High Adherence (98% by pill count; 78-82% by self-report @96 wks)			**Low Adherence** (Only 16% medium/high adherence @52 wks)		
High Efficacy (0.14 infections/100 PY)			**Low Efficacy** (2.02 infections/100 PY)		
HPTN-083[5]	**Men**	CAB-LA	**HPTN-084**[6]	**Women**	CAB-LA
Coverage: 91.5% person-years covered			**Coverage:** 93% person-years covered		
Efficacy: (0.41 infections/100 PY)			**High Efficacy** (0.2 infections/100 PY)		



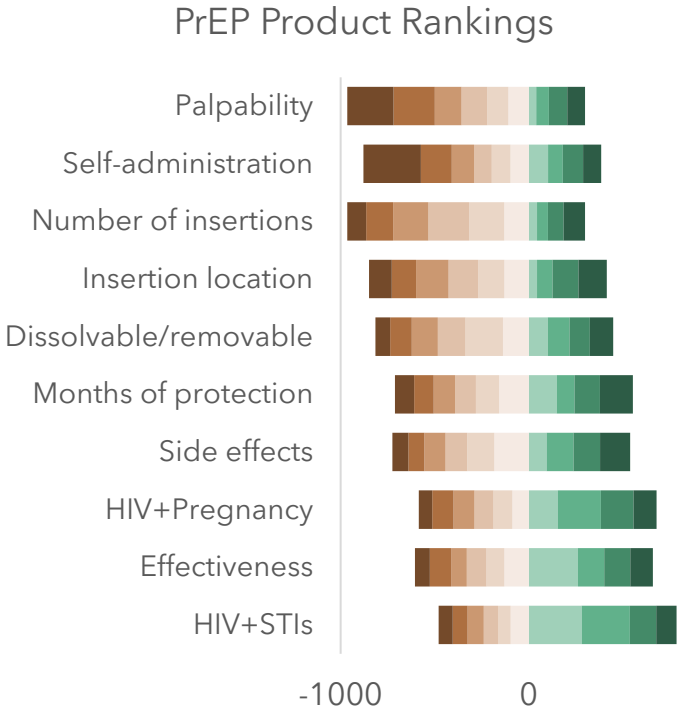
Women's preferences: In the HIV space, women express desire and an **unmet need** for long-acting and on-demand products with flexible pre- or post-coital use and user-control

Montgomery et al., JIAS, 2019; Little et al., AIDS Behav. 2022 & 2024

End user research informs product development

Women's preferences (systemic dosage forms):

- **Discrete choice experiments (DCE)** provide data on product preferences based on trade-offs, highlighting the weight of certain parameters such as dosage form, insertion/injection location, number of injections, dual-protection, and palpability
- **Different demographics** show varied as well as overlapping preferences
- **Choices change with use** of a prototype product



Montgomery et al., JIAS, 2019; Little et al., AIDS Behav. 2022 & 2024

Drug delivery systems in Women's Health R&D

Properly informed and developed DDS tailored to specific API and TPP can:

- Appeal to end users enhancing adherence and persistence
- Facilitate administration
- Deliver API to the target site of action
- Control release
- Preserve/increase stability
- Increase/decrease absorption
- Prolong therapeutic levels
- Mitigate adverse effects and local reactions

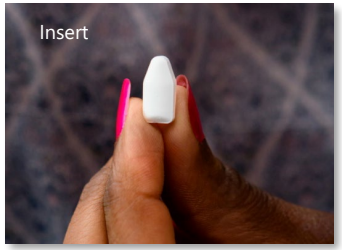
DDS in WH R&D:

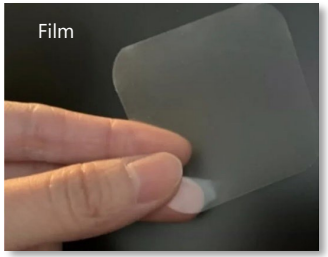
- **FRT drug delivery** (reprod tract)
  - Vaginal rings
  - Inserts, pessaries, films
  - Gels, creams
  - Intra-uterine devices

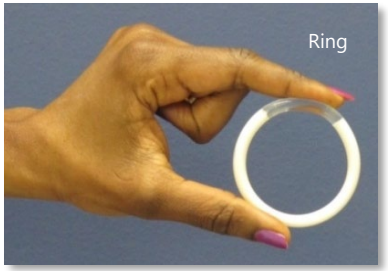
- **Systemic drug delivery**
  - Oral tablets (daily, monthly)
  - Injectables
  - Implants
  - Transdermal patches

Product R&D Portfolio in WH

Drug delivery in the reproductive tract (local) - Examples







Pictured: TFV gel, CONRAD's insert, Rohan Lab's vaginal film, Population Council's ZnAc and Cu rings, Oak Crest's intravaginal ring (IVR), CONRAD's MPT ring, Benhabbour lab's 3D printed IVR, CONRAD's MPT IUS



CONRAD PORTFOLIO

VAGINAL DELIVERY – INSERTS & RINGS

Vaginal Insert for On-Demand Protection

- Would provide women with a **additional DDS option** – **event-driven product**

Inserted by user into the **vagina before sex**

Proven API in **simple, scalable low-cost formulation** (may be combined with other APIs)

Highly discreet, portable and easy-to-use

To **prevent HIV, unplanned pregnancy (and potentially other STI)** when applied vaginally

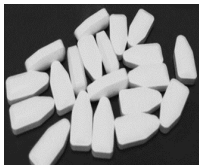
For **all women at risk,** especially **AGYW** having infrequent or clustered sex

- ✓ **Fewer doses and side effects** expected than oral/systemic products
  - *Low systemic exposure → drug where and when you need it → Potential future OTC*

Key Features

+ **Product characteristics** → iterative design (in vitro, rats, NHP, humans), small, portable, solid dosage form; FDA-approved, safe & low-cost excipients
+ **Manufacturing** → simple / robust direct-compression with limited number of processing steps
+ **Physicochemical attributes** → a balance of fast disintegration (for immediate drug release) and mechanical integrity (better handling and packaging feasibility of the final product)
+ **Stability** → no cold chain storage or distribution required; projected shelf life of >2 years if stored ≤30°C/65%RH
+ **Scale-up development** → successfully translated to clinical manufacturing; readily transferrable to LMICs
+ **Preclinical efficacy** → demonstrated protection against SHIV in NHP model with vaginal (PrEP and PEP) and rectal (PrEP; PEP ongoing) insert administration

TAF/EVG and Platform Insert Evolution



COMPLETED

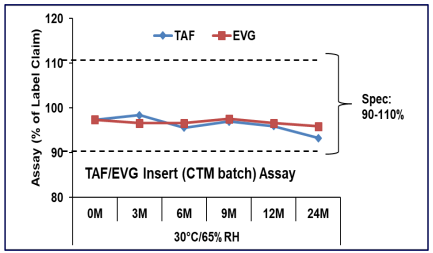
- QUATRO → High acceptability (vaginal & rectal application)
- MTN 035 (DESIRE) → High acceptability (vaginal & rectal application)
- CONRAD 146 → Safe & well tolerated; High levels of EVG & TFV-DP in tissues; Low systemic exposure; Potent antiviral inhibition in fluid/tissues challenged ex vivo
- MTN 039 → Safe & well tolerated; High levels of EVG & TFV-DP in tissues; Low systemic exposure; Potent antiviral inhibition in fluid/tissues challenged ex vivo

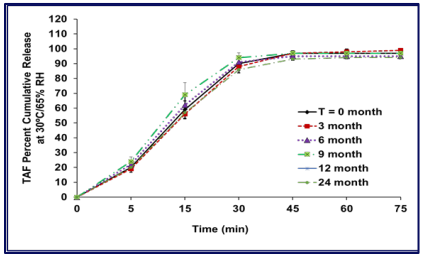
CONRAD 117
User acceptability pointed to improvements in formulation and design

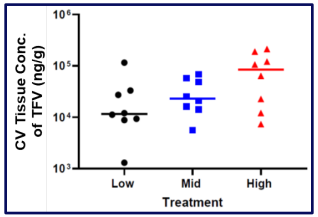
CONRAD 134
Performed to select an insert with greater user acceptability

Bullet shape selected for use in clinical studies

ONGOING
- MATRIX-001
- RITE-PrEP







Agrahari et al., J Contr Release 2025; Peet et al., Pharmaceutics, 2024

TAF/Elvitegravir Topical Inserts

On-Demand (PrEP or PEP) MPT for HIV & HSV Prophylaxis

CONRAD

- **Fills important unmet need in HIV & MPT method mix**
  - Flexible on-demand, PrEP or PEP
  - For vaginal or rectal use
  - Low systemic drug exposure
  - Economical; easy to manufacture
  - Discreet, highly portable, easy to self-administer
- **Preclinical & Clinical Proof-of-Concept demonstrated**
  - NHP SHIV challenge (vaginal PEP/PrEP, rectal PrEP) [1]
  - CONRAD-146 *(FIH **vaginal** PK/PD, single dose)* [2]
  - MTN-039 *(FIH **rectal** PK/PD, single and double dose)* [3]
- **Expanded Phase I studies completed** *(MATRIX-001, RITE-PREP)*
  - Data under analysis

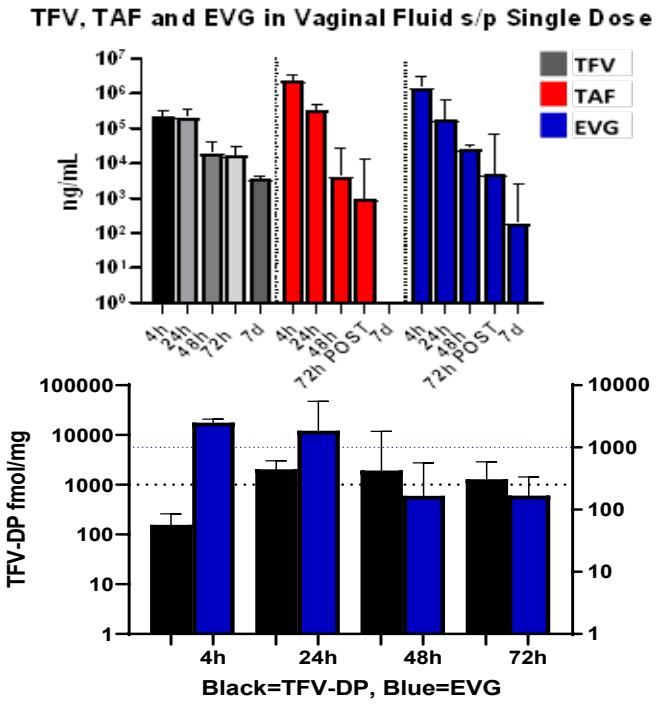
[1] Dobard et al., 2022; Makarova et al., 2022, Makarova et al., 2023; [2] Thurman et al. 2023; [3] Riddler et al. 2024 (MS under review)

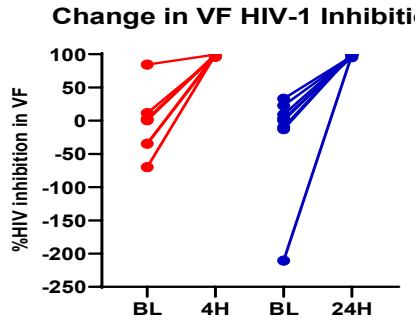
Clinical Proof-of-Concept in FIH Studies

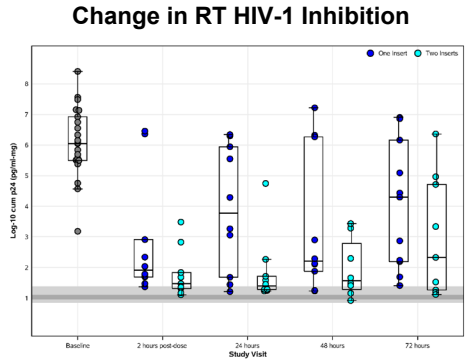
CONRAD 146 (single vaginal dose), MTN 039 (single or double rectal dose) – HIV Prevention (TAF/EVG)

- **Findings consistent across both studies:**
- TAF/EVG insert was **safe, acceptable and well-tolerated**
- **High local concentrations** of TFV/TFV-DP, TAF and EVG in CV or rectal fluids and tissues
- **Low plasma exposure** compared to oral dosing
- **Modeled pharmacodynamics supports** antiviral activity against **HIV-1 and HSV-2** (vaginal) **for up to 24** (vaginal) **or 72 hours** (rectal) compared to baseline

Data from CONRAD-146, FIH vaginal PK/PD, single dose study







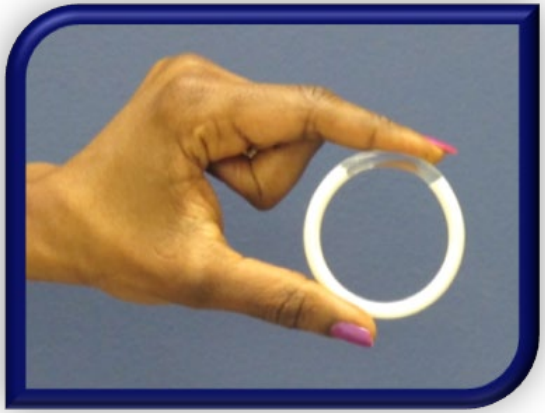
CONRAD
LEADERS IN GLOBAL HEALTH INNOVATION

MTN
microbicide trials network

Thurman et al., Front. Cell. Infect. Microbiol. 2023; Riddler et al. J. Infect Dis. 2024

Tenofovir/Levonorgestrel Intravaginal Ring

Value Added Long-Acting Contraceptive MPT (cMPT)



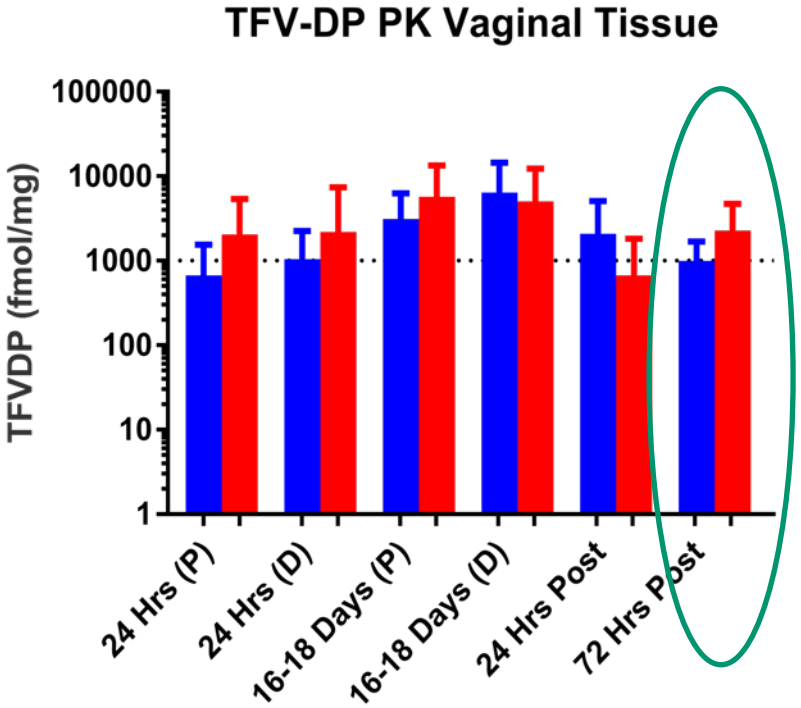
- First-in-Class MPT
- Promotes increased adherence and forgiveness
- No cold chain storage
- Enrich product choice
- Support end-user needs and use patterns
- Scalable & automatable manufacture process
- Clinical proof-of-concept demonstrated

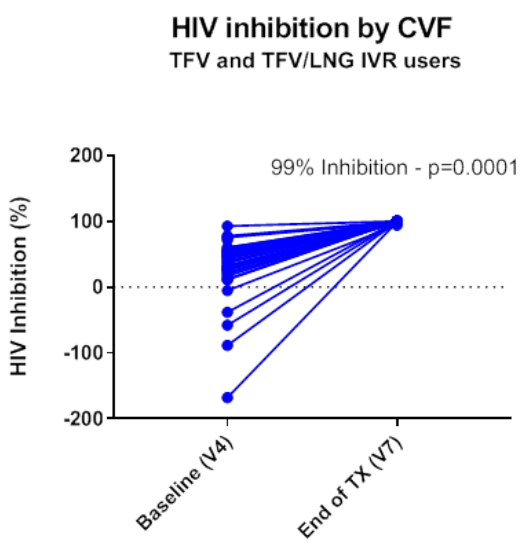
Innovative polyurethane reservoir design tightly
Most advanced cMPT in the field
Designed for protection against HIV, HSV, and pregnancy

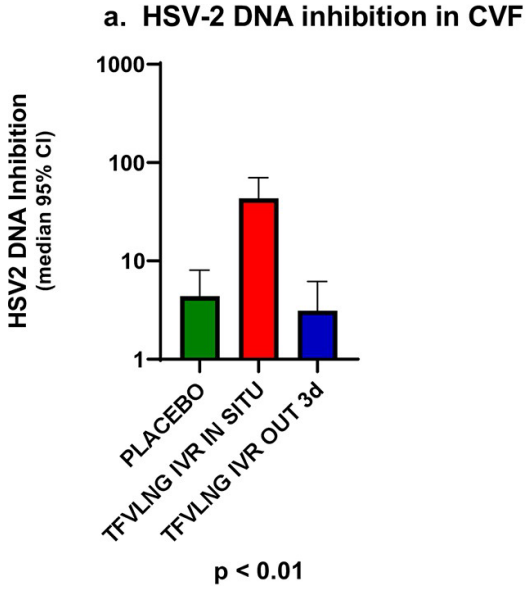
Thurman et al., 2018. PLOS One; Thurman et al. 2019. PLOS One; Thurman et al. 2022. PLOS One; Mugo et al. 2023. Frontiers in RH

CONRAD-128 Study: First-in-Women Study

Tenofovir PK & PD

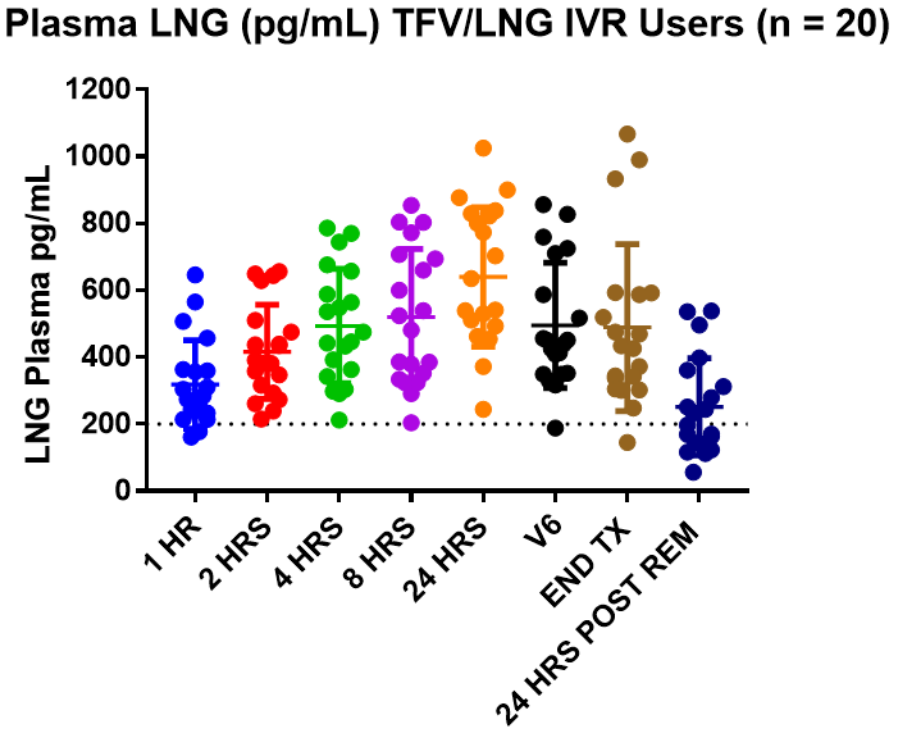






Blue Bars: TFV IVR (n=20) Red Bars: TFV/LNG IVR (n=20)

CONRAD-128 Study: First-in-Women Study
LNG PK & PD



Contraceptive Surrogates:

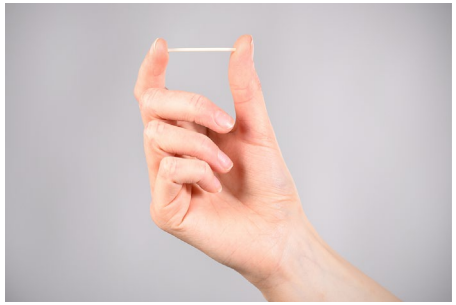
- Anovulation (P4 measured at day of ring removal)
- Cervical Mucus Score < 10/15
- Abnormal/Poor sperm penetration

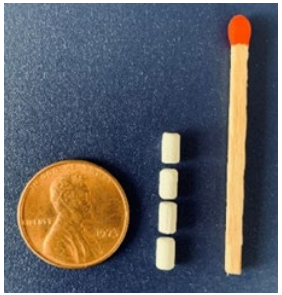
# of TFV/LNG IVR users met:

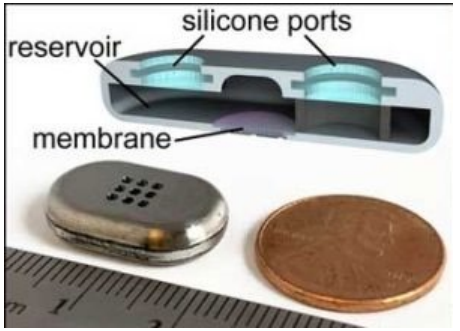
- 1 criterion = 100%
- 2 criteria = 95%

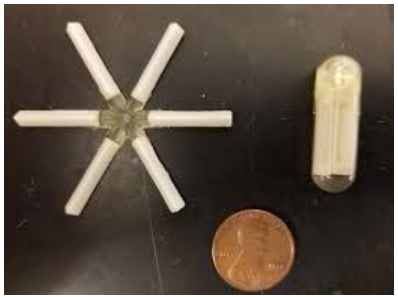
Product R&D Portfolio in WH

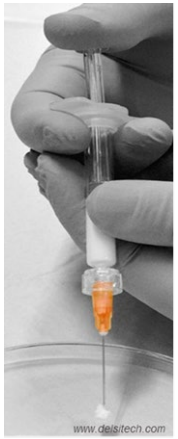
Systemic drug delivery - Examples

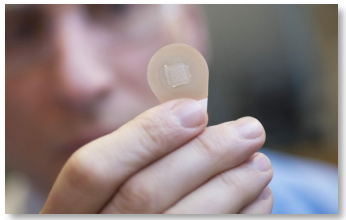




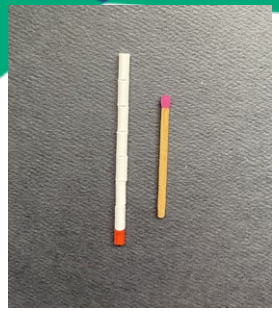


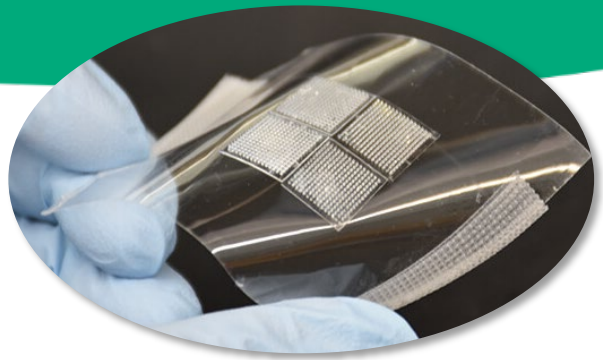


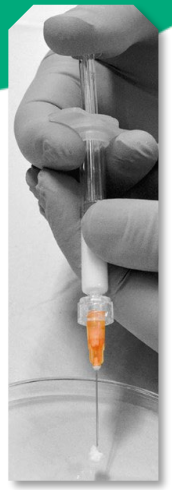




Pictured: Seasonale® OC tablets, DPP, Nexplanon® implant, CONRAD's LNG pellets, Grattoni Lab's refillable nanochannel implant, Lyndra's monthly OC, a LA injectable, hydrogel depot, Ortho Evra transdermal patch, Prausnitz's microneedle patch







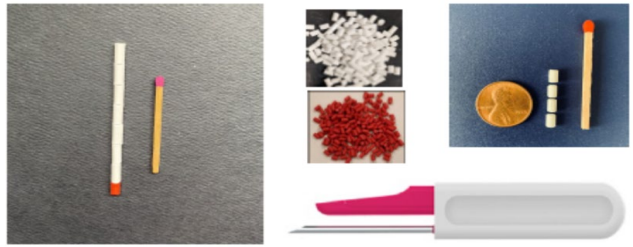
CONRAD PORTFOLIO

SYSTEMIC DELIVERY – BD PELLETS, INJECTABLE DEPOT, MN PATCH

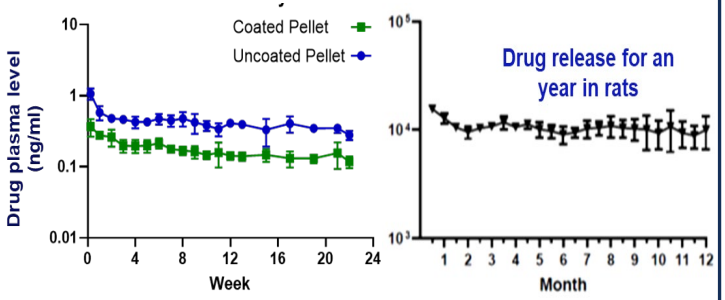
Bioresorbable Pellet-based Implant Platform for Long-Term Controlled Drug Release

- **Bioresorbable:** No need for pellet removal; can be removed for a short duration (1-3 months) if medically warranted
- **Drug loading & controlled/extended-release:** Provides a high (up to 95% per pellet) drug loading; supports sustained and controlled drug release for up to 2 years
- **Flexible dose adjustment:** Highly suitable DDS for long-acting antiretroviral (ARV) delivery, alone or in combination with other ARVs, or contraceptive (MPT)
- **User-friendly insertion:** Single subdermal insertion of multiple pellets, akin to an injectable depot
- **Manufacturing:** Small size, uses a simple, readily scalable, low-cost manufacturing process with FDA-approved excipients
- **Storage & stability:** No need for cold-chain storage or distribution

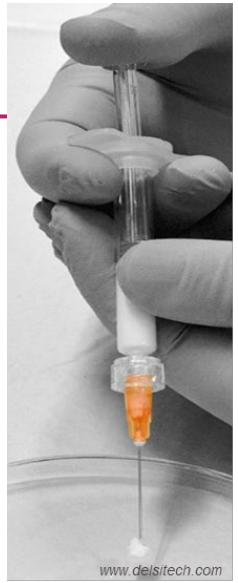
Biodegradable Pellet-based Implants



Drug release controlled by core and coating compositions of the pellets

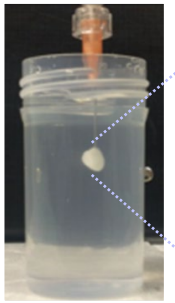


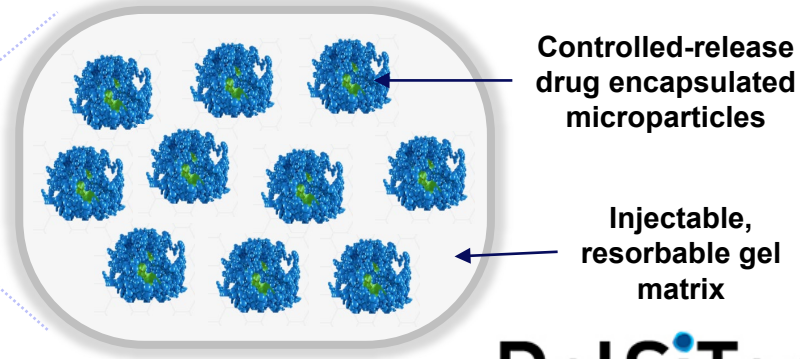
Long-Acting Injectable Hydrogel Depot



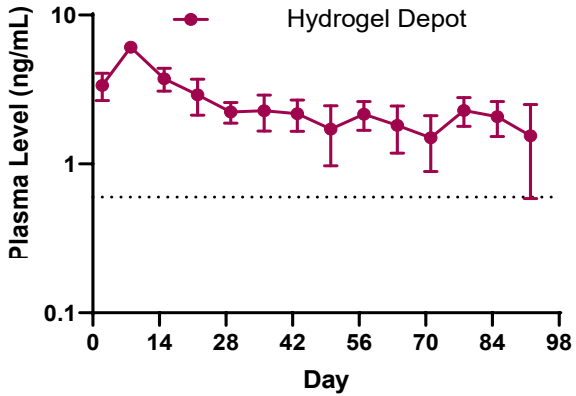
In situ gel forming depot platform

- Natural, FDA-recognized GRAS material
- Thixotropic gel is injectable & fully biodegradable
- Drug release tuned by controlling depot erosion
- Uses small gauge needle (~25 G) & smaller volume (1-2 mL)
- Can accommodate controlled-release of at least two ARVs or MPTs

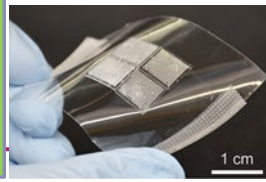




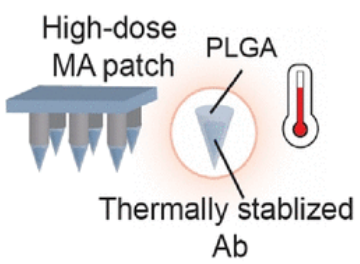
DelSiTech

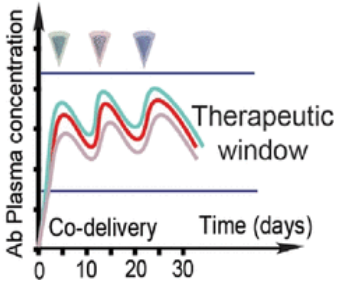


Transdermal MA Patch for Long-term ARV or Antibody (bnAb) Release

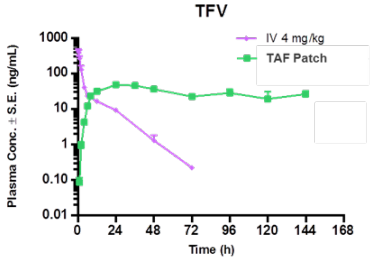


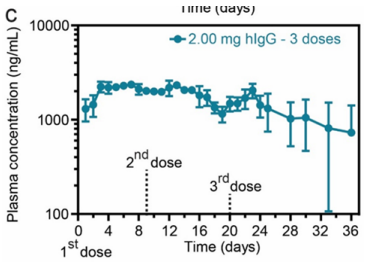
+ Minimally invasive, self-administrable
+ Benefits to supply chain, storage & distribution
+ Powder-filling drug loading method
+ High drug loading & tightly controlled, long-term release capability





+ PLGA-based core-only or core-shell microarrays
+ Sustained release of TAF via MA patch
+ Antibody stabilization via combination of excipients
+ Highly-controlled immediate or time-delayed release of ARVs and/or bnAbs for long-term prevention or treatment





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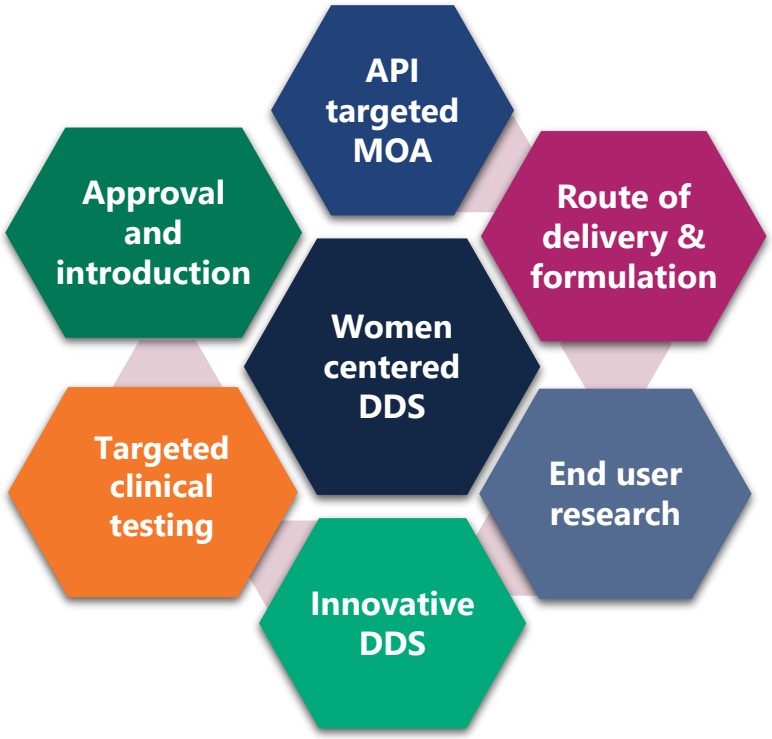
Summary and Conclusions



- Women's health biomedical interventions are in need of renewed innovative R&D efforts and the development of new DDS that are women centered
- Drug delivery can be local, within the reproductive tract, or systemic; vaginal drug delivery is underutilized
- Early incorporation of end user research in product development to define product attributes (TPP)
- Multiple DDS for a variety of WH indications are in development covering immediate and controlled API release for up to several months
- Innovative ways to control drug release and extend duration and early feedback from women, the end user, are essential to the successful introduction of new products in women's health

Acknowledgements

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