

Innovation in HIV Prevention Research Workshop

Cresta Lodge, Harare Zimbabwe

21 and 22 AUG 2019

Recent Advances in Long Acting PrEP and Novel Drug Delivery Systems

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Meredith Clark (PhD)



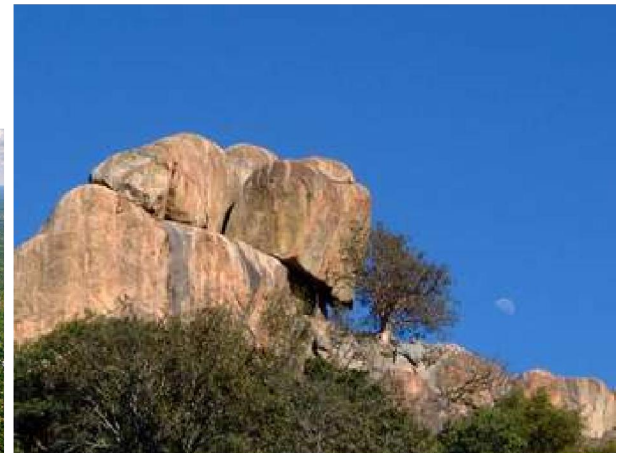
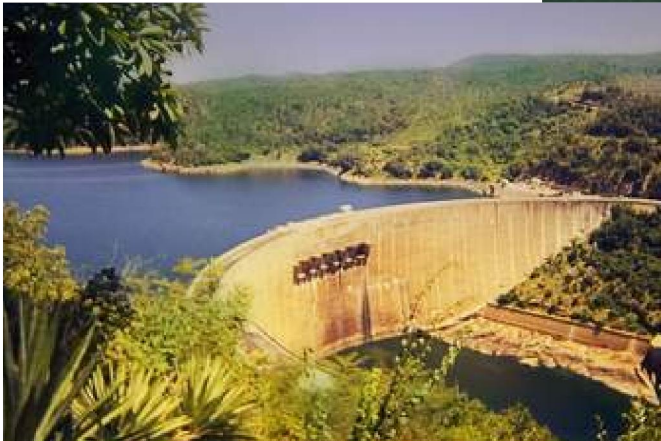
University of Zimbabwe College of Health Sciences - Clinical Trials Research Centre
Saving Lives Through Innovative Research Strategies



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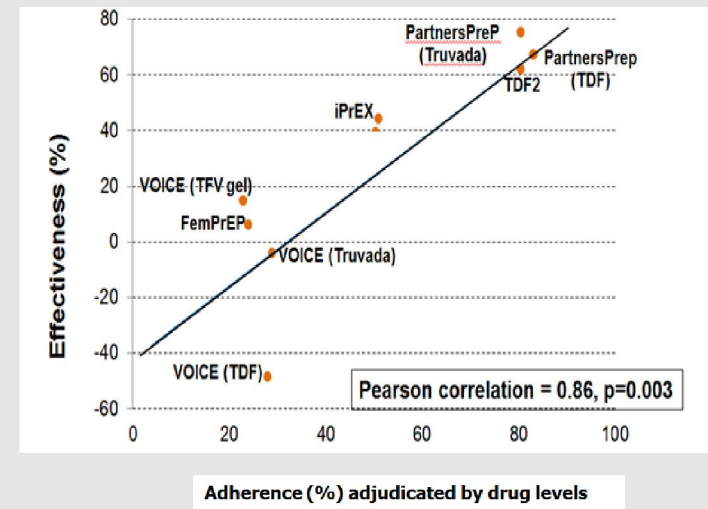


Welcome to Zimbabwe!



Introduction – Oral PrEP

- Shows a clear dose-response relationship of protection and adherence.
- Protection modelled to be 99% when taken 7 days per week as prescribed.
- Modelled data suggest some forgiveness of missed doses for protection against rectal exposures
- **Protection against vaginal exposures is modelled to be much less forgiving of missed doses.**
- Urgent need for PrEP agents that have more convenient dosing schedules.



Abdool Karim, SS IAS,
2014

Longer-acting, systemic HIV prevention products represent a product development priority

Improved product profile = potential for greater adherence

- ❖ Less user-dependent
- ❖ Safer
- ❖ More effective
- ❖ More forgiving
- ❖ More compatible with women's lifestyles (particularly in SSA)
- ❖ Longer duration of protection
- ❖ Fewer follow-up visits to clinic

Drug development strategies to improve favourable characteristics: nano-formulations; prodrugs; devices

Preferences

Luecke EH et al. *Journal of the International AIDS Society* 2016, 19:20875
http://www.jiasociety.org/index.php/jias/article/view/20875 | http://dx.doi.org/10.7448/IAS.19.1.20875

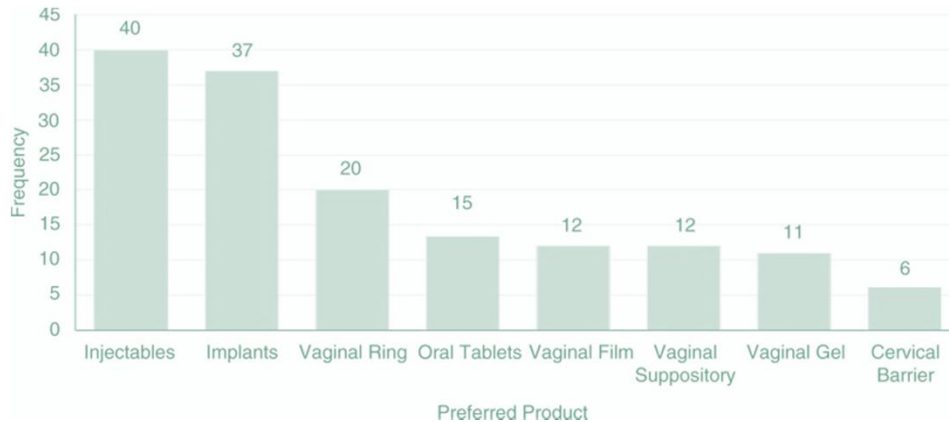


Research article

Stated product formulation preferences for HIV pre-exposure prophylaxis among women in the VOICE-D (MTN-003D) study

Ellen H Luecke^{5,1}, Helen Cheng¹, Kubashni Woeber², Teopista Nakyanzi³, Imelda C Mudekunya-Mahaka⁴ and Ariane van der Straten^{1,5} on behalf of the MTN-003D Study Team

⁵Corresponding author: Ellen H Luecke, 351 California Street, Suite 500, San Francisco, CA 94104, USA. Tel: + (415) 848 1392. (eluecke@rti.org)



Luecke et al. *JIAS* 2016

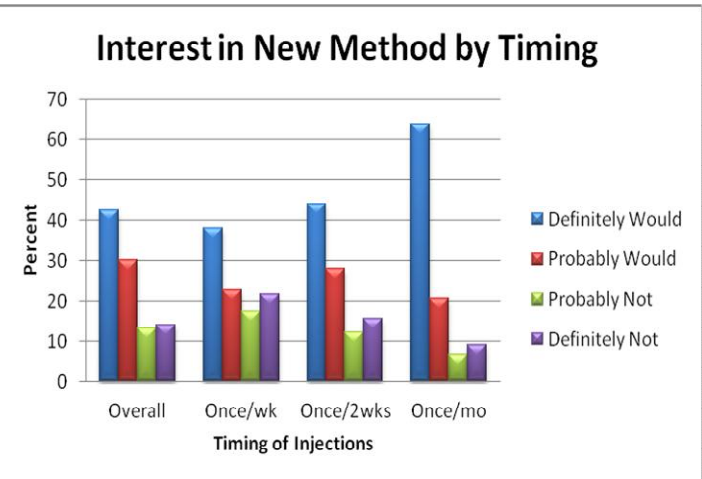


Figure 1. MTN-003D stage 2 HIV prevention potential product formulation discussion card.

RESEARCH ARTICLE

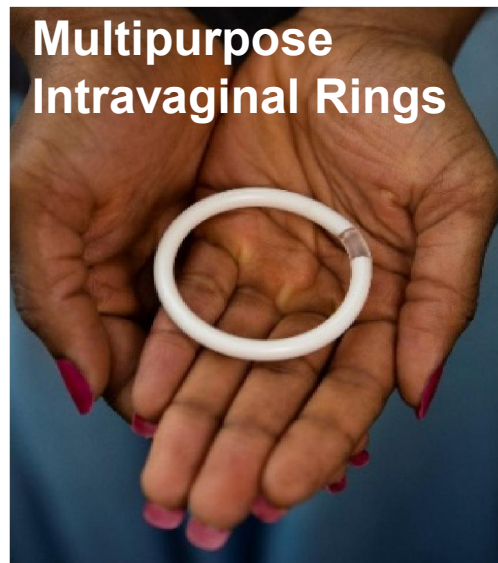
For reprint orders, please contact: reprints@futuremedicine.com

Long-acting parenteral nanoformulated antiretroviral therapy: interest and attitudes of HIV-infected patients



Williams et al. *Nanomedicine* 2013

State of the Field in Long-Acting PrEP: Advanced

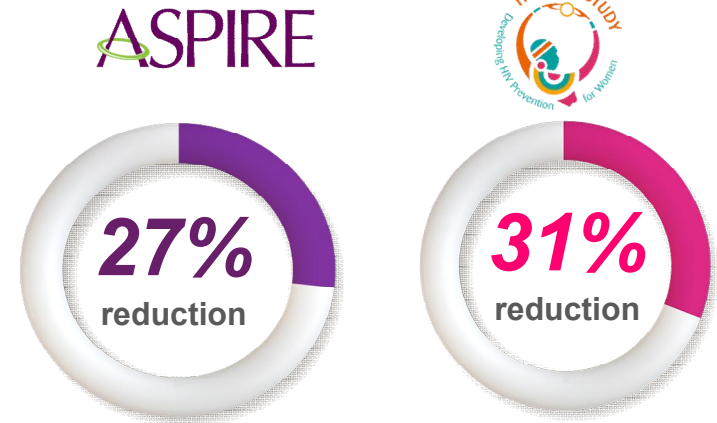


Dapivirine Ring (IPM)



Long-acting PrEP formulated as a flexible silicone ring that slowly releases the antiretroviral dapivirine

- Potential for *better adherence*
- Long acting, strong safety profile
- No related resistance
- Discreet -woman-initiated and controlled.
- Easy to use, scalable



Baeten et al., Nel et al., NEJM 2016

HOPE and DREAM results suggest **interest in, adherence to, safety and effectiveness** of the dapivirine vaginal ring when used in an open-label setting. Baeten et al., IAS 2019, Nel et al., SA AIDS 2019

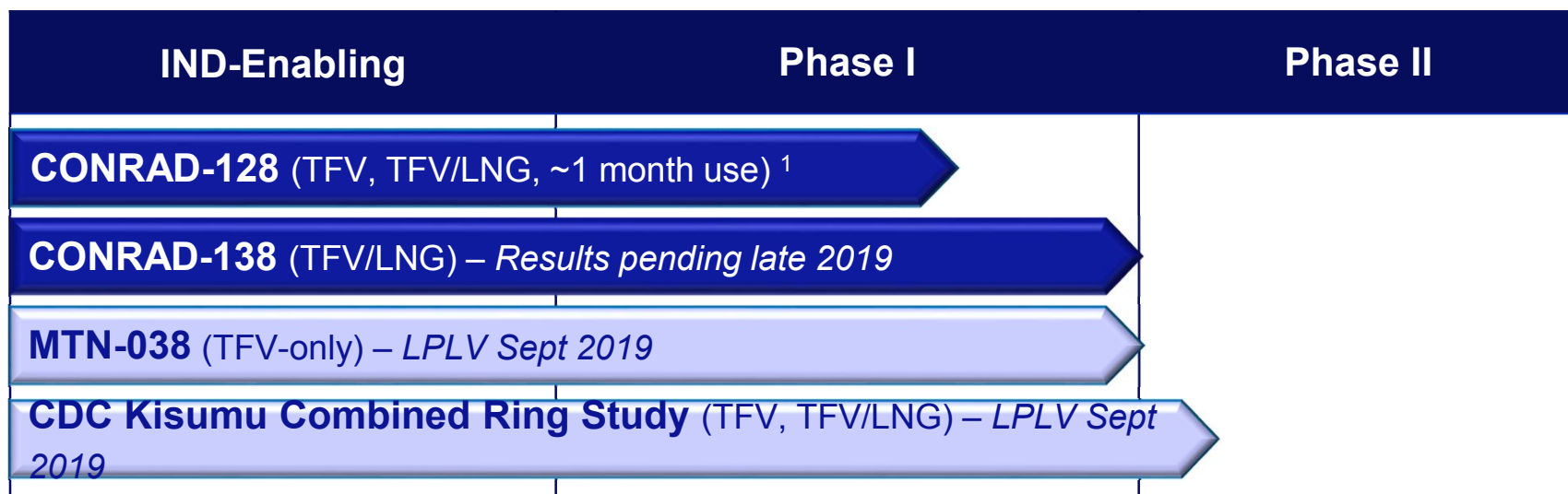
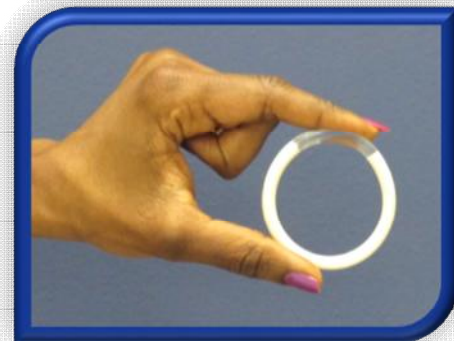


Dapivirine Vaginal Ring is currently under regulatory review by the European Medicines Agency (EMA) through an Article 58 application.



Next-Generation Intravaginal Rings: Tenofovir + Levonorgestrel (CONRAD) – 3 months

- ❖ Most advanced MPT IVRs in the field
- ❖ For protection against HIV, HSV & pregnancy
- ❖ Pharmacologically forgiving if removed for 3 days
 - Promotes increased adherence
 - Supports end-user needs and use patterns
- ❖ Clinical proof-of-concept demonstrated for safety, acceptability, TFV & LNG PK & PD¹
 - Extended use (3-month) data in Kenya, Dominican Republic and U.S. pending



¹ Thurman et al., 2018. PLOS One; Thurman et al. 2019. PLOS One

Cabotegravir Long-Acting Injectable (ViiV) – 2 months



Safety and tolerability of long-acting cabotegravir injections in HIV-uninfected men (ECLAIR): a multicentre, double-blind, randomised, placebo-controlled, phase 2a trial

Martin Markowitz, Ian Frank, Robert M Grant, Kenneth H Mayer, Richard Elion, Deborah Goldstein, Chester Fisher, Magdalena E Sobieszczyk, Joel E Gallant, Hong Van Tieu, Winkler Weinberg, David A Margolis, Krischan J Hudson, Britt S Stancil, Susan L Ford, Parul Patel, Elizabeth Gould, Alex R Rinehart, Kimberly Y Smith, William R Spreen



Articles

ECLAIR: the potential for long-acting pre-exposure prophylaxis
See page e331

Articles

Survival of patients starting antiretroviral therapy 1996–2013
See page e349

Articles

The effect of criminalisation of drug use on HIV programmes
See page e357

Lancet HIV. 2017 Aug;4(8):e331-e340



Safety, tolerability, and pharmacokinetics of long-acting injectable cabotegravir in low-risk HIV-uninfected individuals: HPTN 077, a phase 2a randomized controlled trial

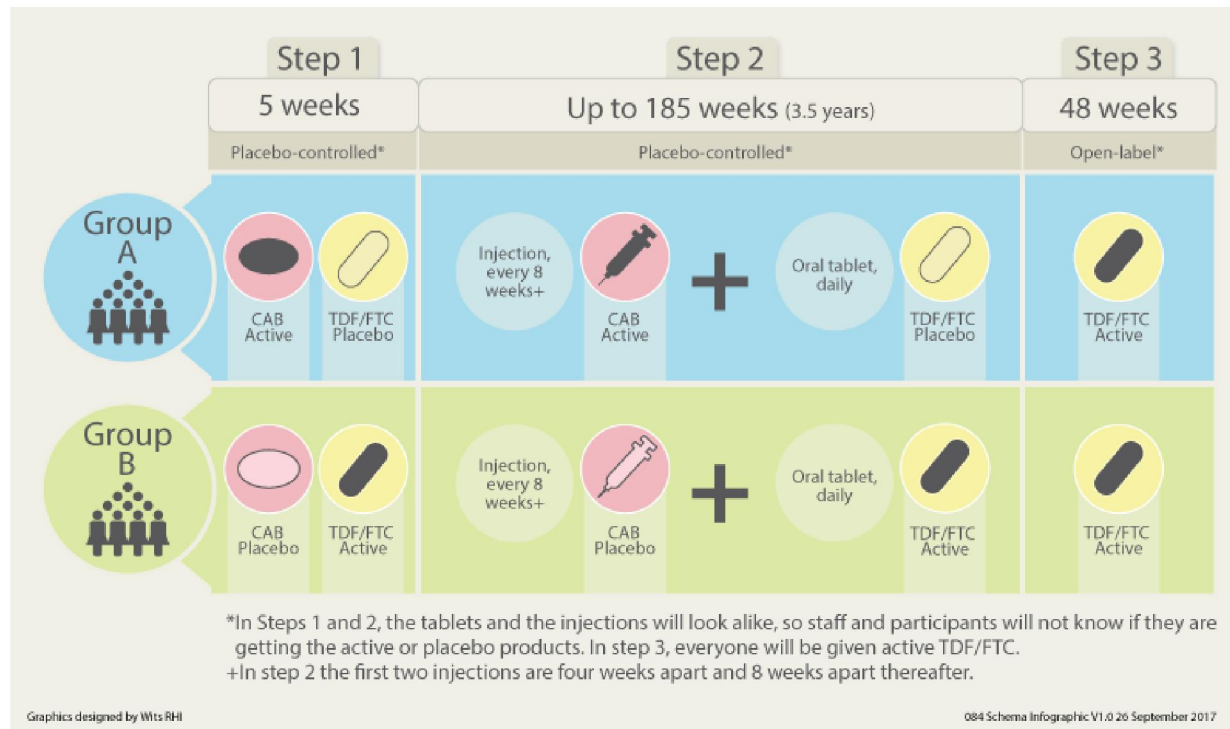
Landovitz RJ, Li S, Grinsztejn B, Dawood H, Liu AY, Magnus M, Hosseinipour MC, Panchia R, Cottle L, Chau G, Richardson P, Marzinke MA, Hendrix CW, Eshleman SH, Zhang Y, Tolley E, Sugarman J, Kofron R, Adeyeye A, Burns D, Rinehart AR, Margolis D, Spreen WR, Cohen MS, McCauley M, Eron JJ

Published by the Public Library of Science ISSN 1549-1277

PLoS Med. 2018 Nov 8;15(11):e1002690

HPTN 083 and 084: Phase 3 for CAB LA PrEP ongoing

Objective: To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)



- 27 US sites
- 11 South American Sites
- 4 Asian sites
- 1 African site

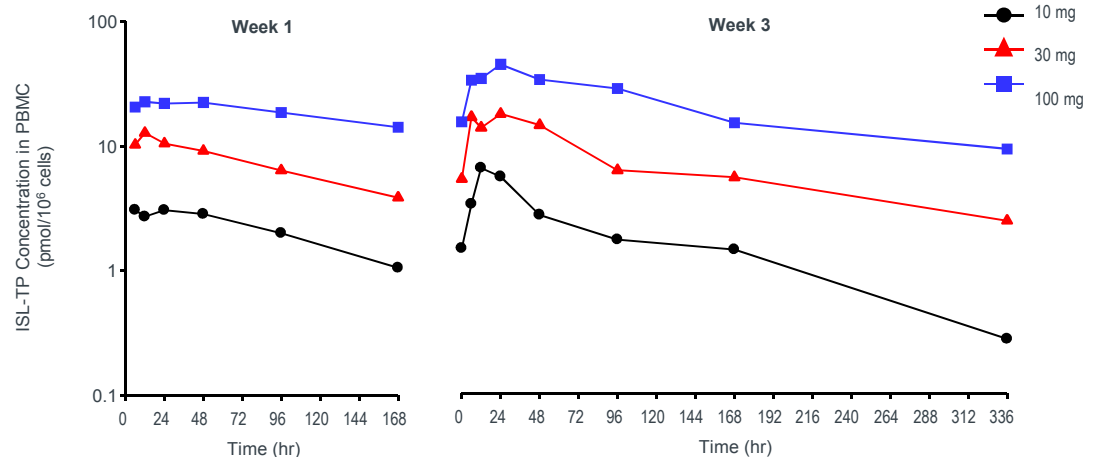


Islatravir (EFdA, MK-8591, Merck)

A First-in-Class Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI) With Multiple Mechanisms of Action

Oral Pill

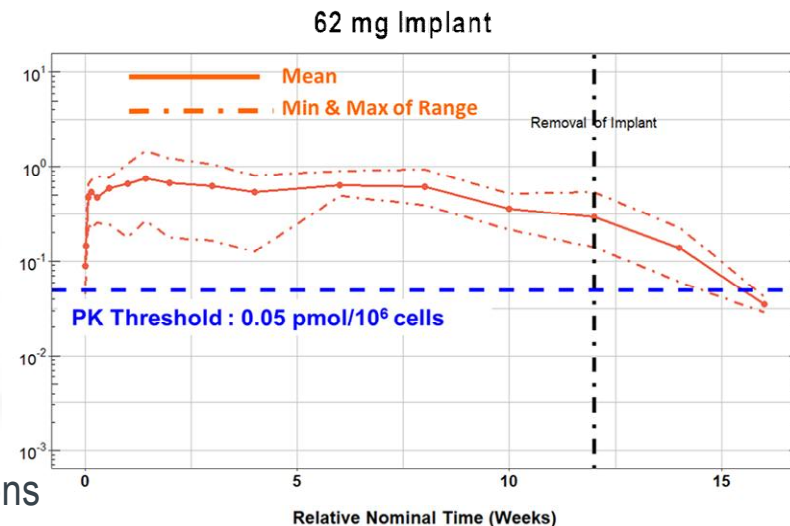
- Once-monthly
- Clinical status: Phase 1/2



Grobler CROI 2016

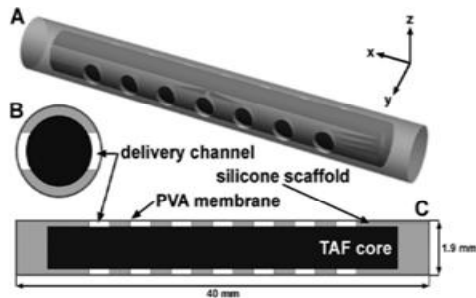
Subdermal Implant

- ISL implant based on Implanon®/Nexplanon®
 - Uses same polymer
 - Removable (not bioerodible)
- Able to use Nexplanon® applicator
- Potential to last at least 1 year
- In Phase 1: generally well tolerated, with no discontinuations due to an AE and no severe implant-related AEs

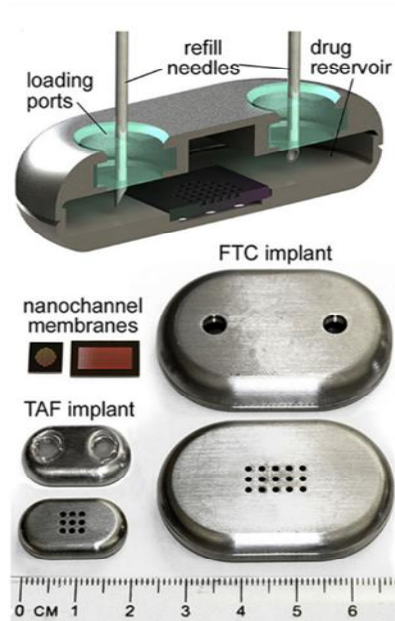


Matthews et al. IAS 2019

Next-Generation: Implantable Drug Delivery Systems



Nondegradable Pod-Type TAF Implant
(Oak Crest Institute of Science)



Refillable Transdermal Nanofluidic Implant
(Houston Methodist Research Institute)



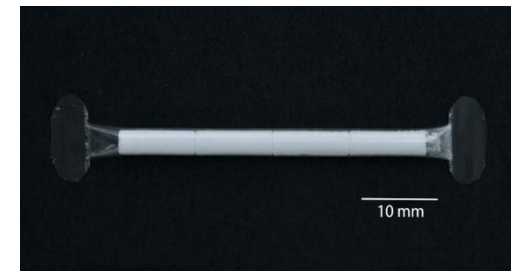
Nondegradable Mini-Pump Implant
(Intarcia Therapeutics)



Biodegradable Reservoir TAF Implant
(RTI International)



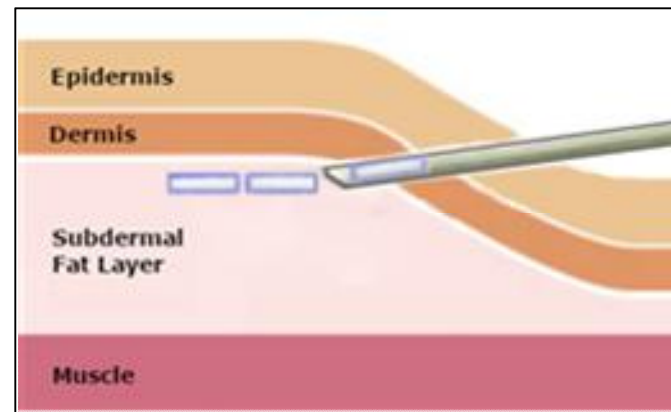
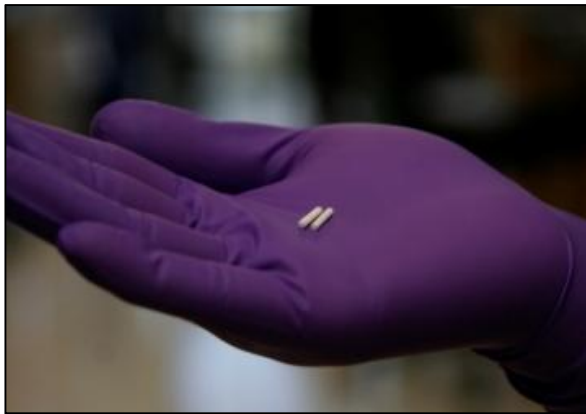
Subdermal Pellet System
(CONRAD)



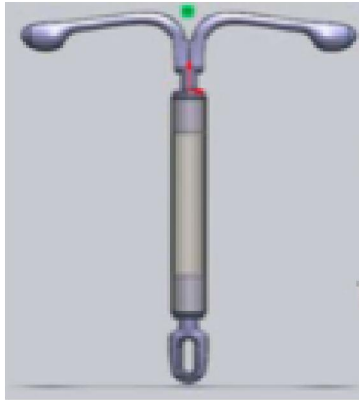
Nondegradable Reservoir CAB Implant
(SLAP HIV-Northwestern University)

CONRAD's Subdermal Pellet System

- + Target 6-12 month delivery of cabotegravir
- + Single subdermal insertion via low-cost device
- + No need for removal (biodegradable) → *Akin to injectable depot*
- + Flexible dosing (development; clinical)
- + Suitable for busy, limited-resource clinics
- + Manufacture & Scalability similar to oral coated pills → *Lower cost*



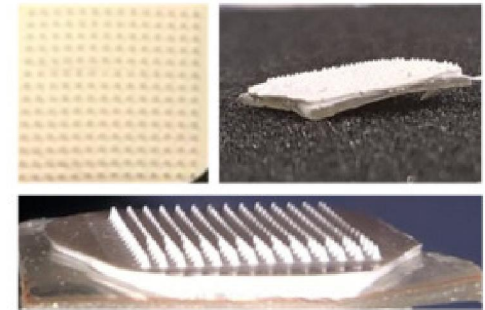
Other Novel Drug Delivery Systems in Preclinical Development Pipeline



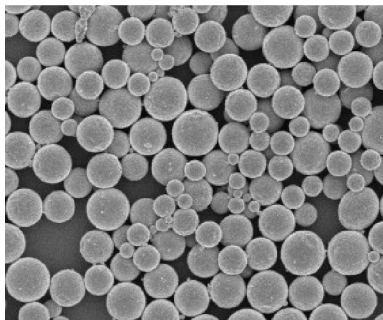
MPT Intrauterine System
(CONRAD)



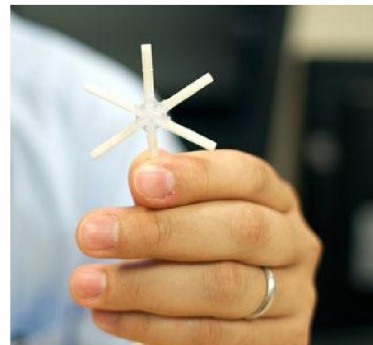
Injectable Depot Systems
(UNC, CONRAD, others)



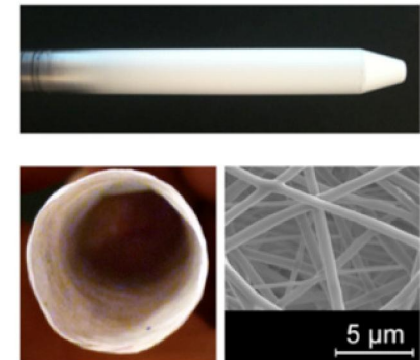
Microarray Needle Transdermal Patch
(PATH, others)



**Nano- and Microparticle-Based
Delivery Systems**
(CONRAD, others)



“Mini-Pillbox” as Once-Weekly Oral Capsule
(MIT/Harvard)



Electrospun Nanofibers
(U. Washington, others)

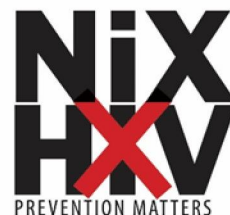
Acknowledgements



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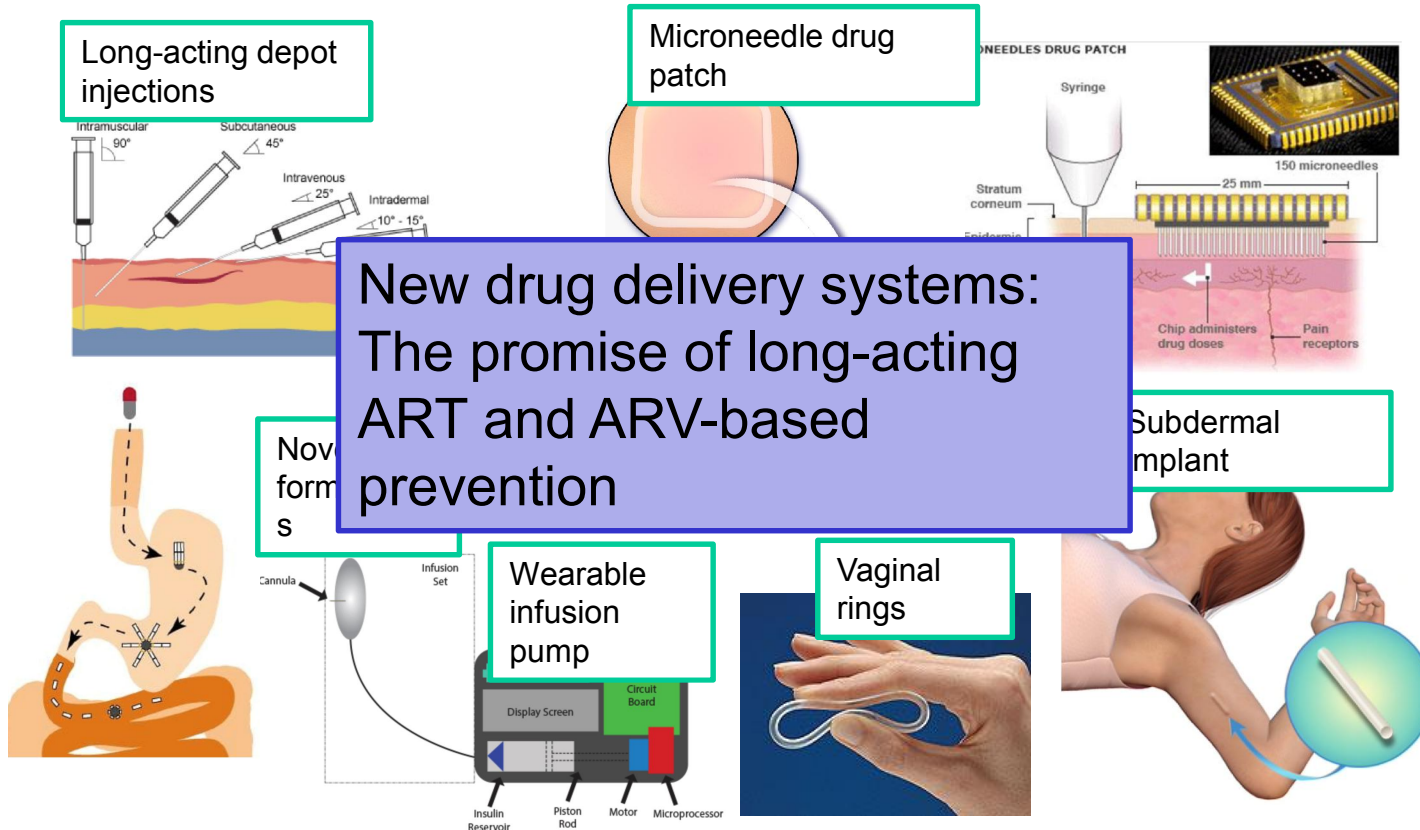


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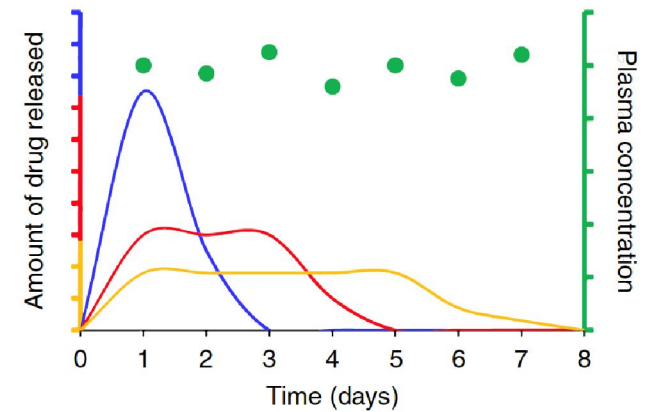
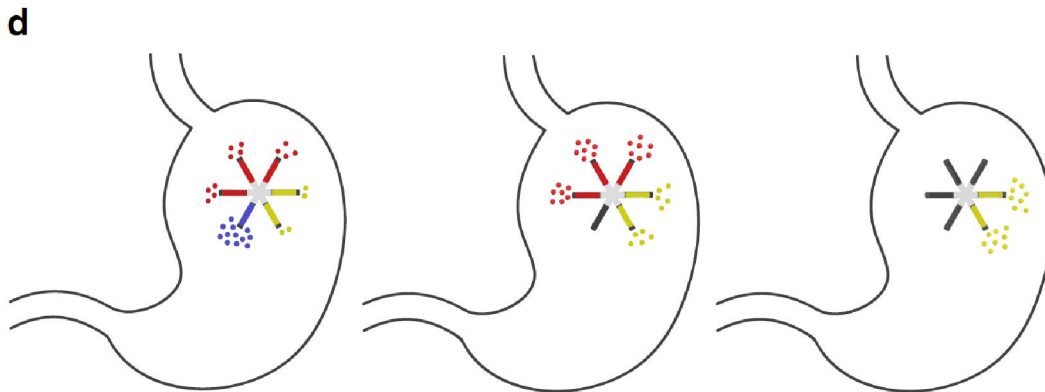
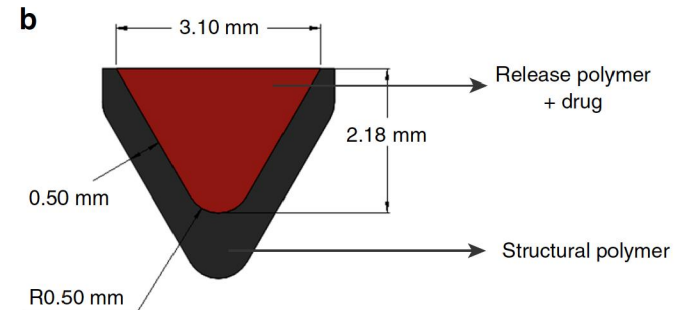
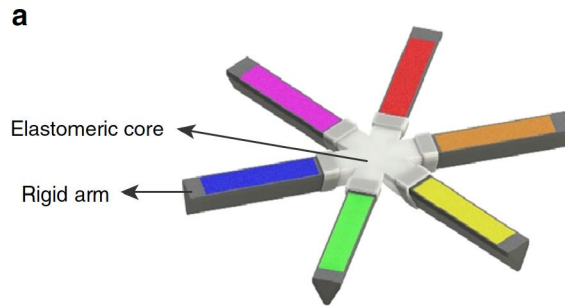
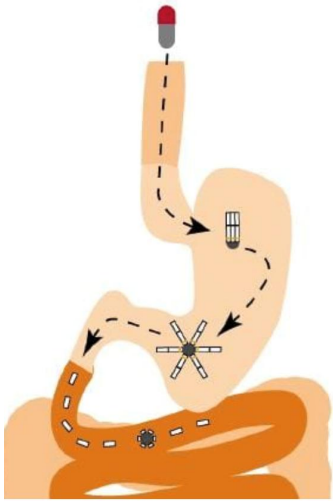
Extra Slides

Technology for Drug Delivery



Courtesy of Scarsi, AIDS 2018

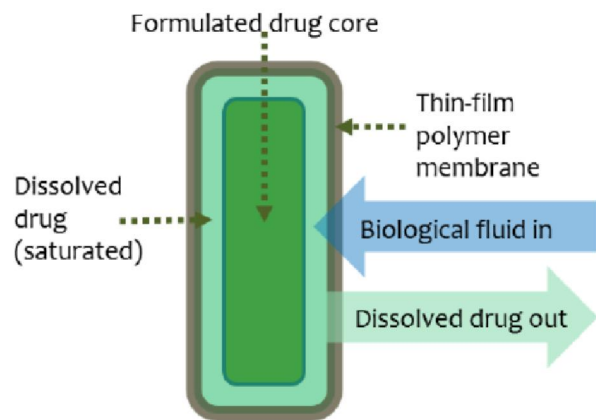
Antiretroviral Oral Drug Sustained Release Delivery System



Kirtane A, et al. Nature Communications 2018. Courtesy of Scarsi AIDS 2018

Next-Generation: Implantable Thin Film Polymer Device (TFPD)

- User-independent, **biodegradable**, subcutaneous implant
- Sustained release of PrEP drugs with constant release over time
- Compatible with existing trocar applicators
- Target TFPD size ranges from 2-2.5mm diameter x 40mm length

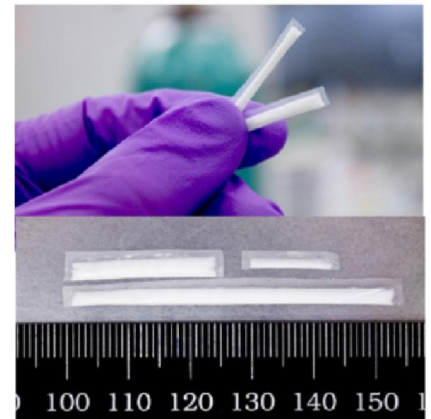


Compatibility with Existing Trocars

Implanon



Jadelle



Courtesy Ariane van der Straten

Possible* LA Formulation (Dis)Advantages

- User independent method improves adherence (v. *oral, topical*)
- Less social & logistical challenges of pills, tablets, & gels (v. *oral, topical*)
- Steady concentration (v. *oral, topical, injectable*)
- One dose (*may*) distribute to vagina and rectum (v. *one topical dose*)
- Very long term implant protection (v. *injectable*)
- Removable implant allows reversal – toxicity, period of risk (*v. injectable*)
- Removable implant avoids long tail (resistance risk) (*v. injectable*)
- Biodegradable implant avoids removal procedure (*v. non-biodegradable*)
- *Clinician administration (increased cost)* (v. *oral, topical*)
- *Sustained systemic exposure (AE's & ISR's)* (v. *topical*)

**assumes implantable, injectable efficacy*