Recent Advances in Long Acting PrEP and Novel Drug Delivery Systems

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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 et al. JIAS 2016

Williams et al. Nanomedicine 2013
State of the Field in Long-Acting PrEP: Advanced

A NEW LONG-ACTING PREVENTION METHOD FOR WOMEN COULD HELP PROTECT AGAINST HIV

Dapivirine Ring

Cabotegravir Injectable

Multipurpose Intravaginal Rings

Islatravir (EFdA)

Once-monthly pill

Once-yearly implant
Dapivirine Vaginal 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

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 & PD
  - Extended use (3-month) data in Kenya, Dominican Republic and U.S. pending

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<thead>
<tr>
<th>IND-Enabling</th>
<th>Phase I</th>
<th>Phase II</th>
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<tr>
<td>CONRAD-128 (TFV, TFV/LNG, ~1 month use)</td>
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<td>CONRAD-138 (TFV/LNG) – Results pending late 2019</td>
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<td>MTN-038 (TFV-only) – LPLV Sept 2019</td>
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<td>CDC Kisumu Combined Ring Study (TFV, TFV/LNG) – LPLV Sept 2019</td>
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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 Ellen, Deborah Goldstein, Chester Fisher, Magdalena E Sobieszczuk, 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

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


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)

**Step 1**
- 5 weeks
- Placebo-controlled

**Step 2**
- Up to 185 weeks (3.5 years)
- Injection, every 8 weeks+
- Oral tablet, daily

**Step 3**
- 48 weeks
- Placebo-controlled
- Open-label

**Group A**
- CAB Active
- TDF/FTC Placebo

**Group B**
- CAB Placebo
- TDF/FTC Active

*In Steps 1 and 2, the tablets and the injections will look alike, so staff and participants will not know if they are getting the active or placebo products. In step 3, everyone will be given active TDF/FTC.
+In step 2 the first two injections are four weeks apart and 8 weeks apart thereafter.

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

**Sites in the Study**
- 7 Sites in South Africa
- 1 Site in Zimbabwe
- 5 Sites in Botswana
- 1 Site in Swaziland
- 1 Site in Kenya
- 2 Sites in Malawi
- 3 Sites in Uganda
- 1 Site in Botswana

Courtesy of M. Cohen, IAS 2019
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

**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
Next-Generation: Implantable Drug Delivery Systems

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

Nondegradable Mini-Pump Implant (Intarcia Therapeutics)

Refillable Transdermal Nanofluidic Implant (Houston Methodist Research Institute)

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)
- **Nano- and Microparticle-Based Delivery Systems** (CONRAD, others)
- **"Mini-Pillbox" as Once-Weekly Oral Capsule** (MIT/Harvard)
- **Microarray Needle Transdermal Patch** (PATH, others)
- **Electrospun Nanofibers** (U. Washington, others)
Acknowledgements
Extra Slides
Technology for Drug Delivery

New drug delivery systems: The promise of long-acting ART and ARV-based prevention

Courtesy of Scarsi, AIDS 2018
Antiretroviral Oral Drug Sustained Release Delivery System

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

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