Where are we with long acting PrEP?

13th International Workshop on HIV Transmission
October 20th, 2018
Leah M. Johnson, PhD
Presentation Outline

- Current PrEP Strategies
- Engineering Factors to Consider for LA PrEP
- LA PrEP Toolbox
  - Implants
  - LA-Injectables
  - Vaginal ring
- Feedback from End-Users
Background: Oral PrEP

- 2012: FDA approval of Truvada™ (FTC 200 mg /TDF 300 mg)
- 2015: WHO recommends offering PrEP for people at substantial risk of HIV (as an additional prevention choice, as part of comprehensive prevention).
- User-adherence is crucial for effective HIV prevention with Oral PrEP
When considering an alternative to an Oral Pill….

Drug Delivery Systems (DDS) are engineered technologies for the targeted delivery and/or controlled release of therapeutic [preventative] agents.

**Drug**

- Properties of Drug
  - Potency
  - Efficacy
  - Solubility

**Delivery System/Formulation**

- Properties of DS/Formulation
  - API delivery rate
  - Duration
  - End-user adoption
  - Drug Stability
PrEP: Drug Delivery Approaches

**On-Demand**
- Vaginal & rectal gel
- Microneedle Patch
- Vaginal film
- Vaginal & rectal inserts

**Long-Acting**
- Injectables
- Implant
- Vaginal ring
General Considerations for PrEP Delivery Approaches

Key Characteristics

- Low user burden; ease of use
- Low burden on existing health systems
- Discretion
- Retrievable/Reversible
- Safe with minimum side effects
- Sustained and constant drug delivery
- Favorable PK profile (e.g., PK tail)
- Adequate levels of ARV for protection
- Cost
### Product Form Factors: Value Added to Field if Successful

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Minimize User Burden</th>
<th>Preference*</th>
<th>Low Systemic Side Effects</th>
<th>Ease of Reversibility</th>
<th>Health system burden</th>
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</thead>
<tbody>
<tr>
<td>Condoms</td>
<td>✗</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Daily oral tablets</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>On demand product</td>
<td>✓ ?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vaginal ring</td>
<td>✓ ?</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Injectable</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Implant</td>
<td>✓</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* HYPOTHETICAL OR ACTUAL: Luecke, JIAS 2016, VDS APC 2017; VDS CROI 2017

*Table adopted from van der Straten and Luecke*
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**Low Daily Dose: Need for Potent APIs**

Potency and PK will support longer duration of products

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>ARV Name</th>
<th>Development Phase</th>
<th>Company</th>
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<tbody>
<tr>
<td>Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)</td>
<td>Rilpivirine (RPV)</td>
<td>• Oral approved</td>
<td>Janssen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase III injectable (with Cab)</td>
<td></td>
</tr>
<tr>
<td>Integrase Inhibitor (INSTI)</td>
<td>Cabotegravir (CAB)</td>
<td>• Phase III Injectable (with RPV)</td>
<td>ViiV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phase III injectable</td>
<td></td>
</tr>
<tr>
<td>Nucleoside/Nucleotide Reverse Transcriptase Inhibitor (NRTI)</td>
<td>Tenofovir alafenamide (TAF)</td>
<td>Oral approved (as F/TAF)</td>
<td>Gilead</td>
</tr>
<tr>
<td></td>
<td>EFdA</td>
<td>Phase I (Oral)</td>
<td>Merck</td>
</tr>
<tr>
<td></td>
<td>GS-9131</td>
<td>Preclinical/Phase I</td>
<td>Gilead</td>
</tr>
<tr>
<td>Capsid Inhibitor</td>
<td>GS-CA1</td>
<td>Preclinical</td>
<td>Gilead</td>
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</table>

Table Adopted from Editorial by Matthew Barnhart: Long-Acting HIV Treatment and Prevention: Closer to the Threshold. Global Health: Science and Practice. 2017 | Volume 5 | Number 2
## LA PrEP Planned Efficacy Trials

Table adopted from AVAC infographic, “The Years Ahead in Biomedical HIV Prevention Research”

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Implant</td>
<td>TBD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LA Injectable (Cabotegravir)</td>
<td>Phase IIb/III (HPTN 083)</td>
<td></td>
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<td>TBD</td>
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<td>[HPTN 083]</td>
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<tr>
<td></td>
<td>[Phase 2b/3 LA Cab vs. Daily Oral TDF/FTC in HIV-Uninfected Cisgender Men and Transgender Women]</td>
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<tr>
<td></td>
<td>Phase III (HPTN 084)</td>
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<tr>
<td></td>
<td>[Phase 3 LA Cab vs. Daily Oral TDF/FTC for PrEP in HIV-Uninfected Women]</td>
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<tr>
<td>Vaginal Ring (Dapivirine)</td>
<td>Phase IIib (MTN025)</td>
<td></td>
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<tr>
<td></td>
<td>[HOPE]</td>
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<td></td>
<td>[Open-label, once-monthly dapivirine vaginal ring, ~1400 women]</td>
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<tr>
<td></td>
<td>Phase IIib (IPM 032)</td>
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<td></td>
<td>[DREAM]</td>
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<tr>
<td></td>
<td>[Open-label, once-monthly dapivirine vaginal ring, ~1100 women]</td>
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</tr>
</tbody>
</table>
Efforts towards a PrEP Implant
Implant Attributes
- Systemic Delivery of API
- Zero-Order release
- User-independent
- Provider administered
- Discrete
- SubQ inserted with trocar
- Removable
- Biodegradable

**Late Breaker Oral Presentation**: van der Straten (Gatto et al.,) “Development of an End-user Informed Tenofovir Alafenamide (TAF) Implant for Long-acting (LA)-HIV Pre-exposure Prophylaxis (PrEP)”

- **KEY FINDINGS**:
  - 63D rabbit study with trocar-inserted implants, showing sustained levels of plasma TAF, TFV and PBMC TFV-DP and full retrievability of implants

**Poster Presentation**: Johnson (Girouard et al.,) “A subcutaneous biodegradable implant for sustained delivery of tenofovir alafenamide (TAF) for HIV pre-exposure prophylaxis (PrEP).”

- **KEY FINDINGS**:
  - Sustained release was demonstrated for > 4 months with selected formulation;
  - Shelf-stability after 6-months of accelerated storage conditions.
PrEP Implant Developments: Refillable Implant

**Implant Attributes**
- Transcutaneous refillable implant
- Nanochannel Delivery Implant (NDI)
- Implant with silicone ports for transcutaneous refilling
- Implant filled with either TAF, FTC
- Rhesus Macaque study with sustained release of TAF, FTC for 83 days
- TDF-DP predicted protective levels at Day 3.

*Based on post-hoc analysis of iPrEx study, 40fmol/10^6 PBMCs taken as TFV-DP concentrations associated with EC_{90} in MSM.

PrEP Implant Developments: EFdA Implant

Implant Attributes

- Matrix style
- EFdA implants in rodents & NHP achieved sustained drug release at clinically relevant drug concentration for greater than 6 months.

PrEP Implant Developments: Silicone TAF Implant

Implant Attributes
- TAF delivered at 0.92 mg day\(^{-1}\) \textit{in vitro}
- Tested in beagle dogs over 40 days for PK and preliminary safety.
- TFV-DP in PBMCs (median, 512 fmol/10\(^6\) cells over the first 35 days) were 30x higher than those associated with HIV-1 PrEP efficacy in humans.
- At R4P: PD09.03 - Multispecies, \textit{In Vivo} Evaluation of Subdermal Implants Delivering Tenofovir Alafenamide: Of Mice, Dogs and Sheep. Marc M Baum, Oak Crest Institute of Science, United States and P24.17

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Efforts towards a LA Injectable for PrEP

- **Integrase Strand Transfer Inhibitor (InSTI)**
- **Oral Tablet and LA Nanosuspension**
- **Nanocrystals of Pure Parent Compound**
- **Produced via wet-bead milling (~200nm)**
- **Formulation with mannitol, polysorbate-20, PEG$_{3350}$, water**
- **Suspension for IM Use**


**Cabotegravir**

**Rilpivirine**

- **Non-Nucleoside RT Inhibitor**
- **Oral Tablet and LA Nanosuspension**
- **Nanocrystals of Pure Parent Compound**
- **Produced via wet-bead milling (~200nm)**
- **Formulation typically with poloxamer 338**
- **Suspension for IM use**
- **Requires cold chain storage**
<table>
<thead>
<tr>
<th>API</th>
<th>Trial Name</th>
<th>Trial Phase</th>
<th>Status</th>
<th>Trial Design</th>
<th>Participants</th>
<th>Treatment Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV</td>
<td>HPTN 076</td>
<td>2</td>
<td>Complete</td>
<td>Controlled, Placebo, Randomized, Double-Blind</td>
<td>132 HIV uninfected women (18-45)</td>
<td>RPV oral daily 4 weeks; RPV IM at 8 week intervals, 40 weeks</td>
</tr>
<tr>
<td></td>
<td>MWRI-01</td>
<td>1</td>
<td>Complete</td>
<td>Randomized, Open-Label</td>
<td>36 HIV uninfected women and men</td>
<td>RPV IM 1200 mg or 600mg</td>
</tr>
<tr>
<td>CAB</td>
<td>HPTN 084</td>
<td>3</td>
<td>Ongoing</td>
<td>Controlled, Randomized, Double-Blind</td>
<td>~3200 uninfected women (18-45)</td>
<td>IM CAB, 2X, 4 weeks apart + every 8 weeks</td>
</tr>
<tr>
<td></td>
<td>HPTN 083</td>
<td>2b/3</td>
<td>Ongoing</td>
<td>Controlled, Randomized, Double-Blind</td>
<td>~4500 HIV uninfected cisgender men &amp; transgender women who have sex with men</td>
<td>IM CAB, 2X, 4 weeks apart + every 8 weeks</td>
</tr>
<tr>
<td></td>
<td>HPTN 077</td>
<td>2a</td>
<td>Ongoing</td>
<td>Controlled, Randomized, Double-Blind</td>
<td>~200 HIV uninfected women + men (18-65)</td>
<td>CAB (or placebo) injection every 12 weeks</td>
</tr>
<tr>
<td></td>
<td>ÉCLAIR</td>
<td>2a</td>
<td>Complete</td>
<td>Controlled, Placebo, Randomized, Double-Blind</td>
<td>127 HIV uninfected men (18-65)</td>
<td>CAB (or placebo) injection 3X, 12 weeks</td>
</tr>
</tbody>
</table>

Did not include oral lead-in information or oral coverage of PK tail in this table.

Thank you to Dr. Alex Rinehart (ViiV Healthcare) for feedback on this slide
Efforts towards the Vaginal Ring

International Partnership for Microbicides

CONRAD
Leaders in Reproductive Health and HIV Prevention

PrEP Vaginal Ring

MTN Microbicide Trials Network

Einstein
Albert Einstein College of Medicine

Oak Crest Institute of Science
The Dapivirine Ring: Phase III Studies

- Poly(dimethylsiloxane) PDMS (i.e., silicone) ring
- Matrix configuration with 25 mg dapivirine
- Dimensions: 56 mm outer diameter, 7.7 mm cross-sectional diameter
- New insertion every 4 weeks

<table>
<thead>
<tr>
<th>API</th>
<th>Name</th>
<th>Phase</th>
<th>Status</th>
<th>Trial Design</th>
<th>Participants</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapivirine Ring + Oral FTC/TDF</td>
<td>MTN042</td>
<td>3B</td>
<td>Planned</td>
<td>Randomized, Open-Label</td>
<td>750 HIV uninfected, pregnant women (18-45)</td>
<td>Up to 30 weeks (safety and efficacy)</td>
</tr>
<tr>
<td>Dapivirine Ring</td>
<td>MTN-025 (HOPE)</td>
<td>3B</td>
<td>Ongoing</td>
<td>Open-Label extension</td>
<td>~1400 HIV uninfected women (18+)</td>
<td>Monthly replacement, total 12 months</td>
</tr>
<tr>
<td>IPM032 (DREAM)</td>
<td>MTN-020 (ASPIRE)</td>
<td>3B</td>
<td>Ongoing</td>
<td>Open-Label extension</td>
<td>1100 HIV uninfected women (18+)</td>
<td>Monthly replacement, total 12 months</td>
</tr>
<tr>
<td>MTN-020 (ASPIRE)</td>
<td>IPM027 (Ring Study)</td>
<td>3</td>
<td>Complete</td>
<td>Randomized, Double-Blind, Placebo-Controlled</td>
<td>2629 HIV uninfected women (18-45 yr)</td>
<td>Monthly replacement, Asked to use ring for minimum 12 months</td>
</tr>
<tr>
<td>IPM027 (Ring Study)</td>
<td></td>
<td></td>
<td>Complete</td>
<td>Randomized, Double-Blind, Placebo Controlled</td>
<td>1959 HIV uninfected women (18-45)</td>
<td>Monthly replacement, Asked to use ring for 24 months</td>
</tr>
</tbody>
</table>
HIV Open-label Prevention Extension (HOPE) (i.e., MTN-025) is a multi-site, open-label, randomized, Phase 3B trial.

- Will assess the continued safety and adherence to a dapivirine vaginal ring.
- Enrollment ~1400 women.
- Interim data (CROI 2018) suggested ring reduced risk of HIV by >50%.

Open-label, randomized, Phase 3B trial to assess long-term safety and adherence to a dapivirine vaginal ring.

- To assess adherence to the use of the 25 mg dapivirine Vaginal Ring-004 inserted at monthly (4-weekly) intervals.
- Enrollment ~1100 women.
- Interim data (CROI 2018) suggested ring reduced risk of HIV by 50%.


Vaginal Rings with Other APIs

**Truvada “Pod Ring”** (Oak-Crest/Auritec)
- Phase I pilot study – Safety, PK, and acceptability of pod-IVRs delivering 3 different ARV regimens: 1) tenofovir disoproxil fumarate (TDF) only, 2) TDF and emtricitabine (FTC), and 3) TDF, FTC, and maraviroc (MVC)**

**TFV and TFV/LNG Ring** (CONRAD)
- Phase 1 study (CONRAD A13-128)
- Achieved high local concentrations, compatible with HIV protection and contraceptive efficacy; CONRAD A15-138 study)***

**TDF Ring** (Einstein/Montefiore)
- Goal: safety, PK with TDF ring when used for 84 consecutive days by sexually active women
- Phase 1 – early termination
- Genital ulcerations observed with sustained TDF in sexually active women, but not in abstinent women.****

**DPV and DPV/LNG 3-month Ring** (IPM)
- FIH Phase 1 study (MTN-030), safety and PK
- Results to be presented at R4P (Safety and Pharmacokinetics of Dapivirine and LNG Vaginal Rings for Multipurpose Prevention of HIV and Pregnancy. Achilles S. Abstract# OA12.02LB)

**References**


**Keller MJ, et al. CROI abstract#1059LB; March 4-7, 2018.**
What does the End-User Say?

End-User Feedback to Guide Future Uptake

Instead of powder, make it a liquid or gel inside to look less like a “street” drug.

Make outside casing look less like “plastic” – more natural.

Have an option for a shorter duration device first as a “test period” for side effects.

Make it thinner, smaller to be more discreet.

Include a monitoring mechanism so you could know when your device is “finished”.

Make a single implant for combined HIV prevention and contraception.

Change the color to something exciting like pink.

14 FGDs among 105 young women & men in South Africa

Acknowledgments

* Thanks to Zach Demkovich for help preparing these slides

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