PrEP Beyond Pills

New Technologies in Biomedical HIV Prevention
As of 1 Oct 2018, Dr. Hurt receives salary support for supervising UNC site activities in a Gilead-funded study of PrEP (DISCOVER).

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The views expressed are not necessarily those of CDC, HRSA, or the NIH.
Objectives

• List three ways in which pre-exposure prophylaxis may be delivered in the future.

• Describe the results of HPTN 083 and what this means for PrEP in the near term.

• Identify the agent currently under investigation as implantable PrEP.

• Explain how broadly neutralizing antibodies work to prevent HIV infections.
## Pregnancy Prevention

### Education & behavior modification

- Condoms
- Rings
- Birth control pill & injection
- "Morning-after pill"
- Spermicide
- Implantable birth control
- Vasectomy/Tubal Ligation

Adapted from HPTN
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Adapted from HPTN
ASPIRE
Monthly dapivirine ring
2629 cis women aged 18-45
Malawi, South Africa, Uganda, Zimbabwe
July 2012 – August 2015

27% lower incidence overall
71 infections on DPV, 97 on placebo (95%CI: 1, 46)

56% lower incidence among participants > 21 years old (95%CI: 31, 71)

61% lower incidence among participants ≥ 25 years old (95%CI: 32, 77)

Younger women didn’t adhere

The Ring Study
Monthly dapivirine ring
1959 cis women aged 18-45
South Africa and Uganda
April 2012 – December 2016

31% lower incidence overall
77 infections on DPV, 56 on placebo
(HR 0.69; 95%CI: 0.49, 0.99)

15% lower incidence among participants ≤ 21 years old
(HR 0.85; 95%CI: 0.45, 1.60)

37% lower incidence among participants > 21 years old
(HR 0.63; 95%CI: 0.41, 0.97)

Open-label extensions
ASPIRE → HOPE
Ring → DREAM

Placebo incidence is estimated

39% lower incidence among 1465 open-label recipients in HOPE
(95%CI: 14, 65)

63% lower incidence among 941 open-label recipients in DREAM
(95%CI: 0.86, 2.33)

https://www.prepwatch.org/nextgen-prep/dapivirine-vaginal-ring/
Where does dapivirine go from here?

- Positive opinion from European Medicines Agency in **July 2020**
- FDA application anticipated in 2020
- Three-month version in development
- Coformulation with levonorgestrel in development
HPTN 083 & 084
Oral FTC/TDF vs Injectable Cabotegravir-LA
MSM & TGW (083) and Cisgender Women (084)
HPTN 083
Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW

December 2016 – May 2020

4566 at-risk persons (target N = 5000)
87.5% MSM 12.4% TGW

50% daily FTC/TDF (n=2284)

50% long-acting injected CAB (n=2282)

37% from US (n=1698)

49.7% of US participants were Black (n=844)

26 median age (IQR 22-32)

HPTN 083
Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW

HIV Incidence

<table>
<thead>
<tr>
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<th>HIV Incidence Rate/100 PY</th>
<th>39 Infections</th>
<th>13 Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAB</td>
<td></td>
<td>1.22</td>
<td>0.41</td>
</tr>
<tr>
<td>n=2244</td>
<td></td>
<td>3187 PY</td>
<td>3202 PY</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n=2250</td>
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CI, confidence interval

52 infections
6389 PY of follow-up

HPTN 083
Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW

52 infections
6389 PY of follow-up


66%
reduced hazard of HIV among CAB recipients,
compared with FTC/TDF
(95% CI: 18%, 62%; p=0.0005)
47 (2.2%) of CAB participants permanently discontinued due to an adverse effect of an injection.

Severity of an injection site reaction was strongly associated with odds of permanently discontinuing.
HPTN 083
Oral FTC/TDF vs Injectable CAB-LA for MSM & TGW

- **All ISRs**
  - N=9221

- **Pain**
  - n=5515 (59.8%)
  - Duration: 3 (2, 5)

- **Tenderness**
  - n=2161 (23.4%)
  - Duration: 3 (2, 6)

- **Other**
  - n=1545 (16.8%)
  - Duration: 4 (2, 7)

*Other injection site reactions include induration, nodule, hematoma, bruising, discoloration, swelling, erythema, itching, warmth, anesthesia, hemorrhage, and abscess

### Unanswered questions

**Is an oral “lead-in” really necessary?**

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<thead>
<tr>
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<th>TOTAL (n=4566)</th>
<th>TDF-FTC (n=2284)</th>
<th>CAB (n=2282)</th>
<th>p-value</th>
</tr>
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<tr>
<td>Participants with grade 3+ AEs, n (%)</td>
<td>1490 (32.7%)</td>
<td>766/2282 (33.6%)</td>
<td>724/2280 (31.8%)</td>
<td></td>
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<tr>
<td>CPK increased</td>
<td>633 (13.9%)</td>
<td>309 (13.5%)</td>
<td>324 (14.2%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Creatinine clearance decreased</td>
<td>348 (7.6%)</td>
<td>190 (8.3%)</td>
<td>158 (6.9%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>152 (3.3%)</td>
<td>76 (3.3%)</td>
<td>76 (3.3%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>152 (3.3%)</td>
<td>75 (3.3%)</td>
<td>77 (3.4%)</td>
<td>0.87</td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>122 (2.7%)</td>
<td>69 (3.0%)</td>
<td>53 (2.3%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Participants with EAEs and SAEs, n (%)</td>
<td>240 (5.3%)</td>
<td>122 (5.4%)</td>
<td>118 (5.2%)</td>
<td></td>
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<tr>
<td>Participant deaths, n (%)</td>
<td>11 (0.24%)</td>
<td>7 (0.3%)</td>
<td>4 (0.2%)</td>
<td></td>
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</table>
Unanswered questions

What about covering the “tail”?

CAB dropped below LLOQ after a median of 10 months among participants assigned male at birth.

15.5 months among participants assigned female at birth.

HPTN 077
What if you could just remove it?

S. Rahima Benhabbour, PhD and Martina Kovarova, PhD

Implants
Islatravir
First-in-class nucleoside reverse transcriptase translocation inhibitor NRTTI
Formerly known as MK-8591 or EFdA

Two mechanisms of action

Essentially, it’s “sticky” and once incorporated, it keeps the entire RT “machine” from ratcheting forward (strong interaction with dNTP binding site of RT)

Markowitz M, Sarafianos SG. Curr Opin HIV AIDS. 2018;13(4):294-299 ← for more on the mechanism of action
Islastravir PO once weekly protects macaques

Islatravir prototype similar to Nexplanon

Islatravir levels predicted to last 1 year

Projected $C_{\text{week52}}$ ISL-TP: ~0.076 pmol/10^6 cells

http://programme.ias2019.org/Programme/Session/167
bnAbs
Breadth & potency of bnAbs are important

How many viruses circulating in transmission networks will the antibody neutralize?
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How many viruses circulating in transmission networks will the antibody neutralize?

How much of an antibody “dose” is required to neutralize viruses?

Very potent

Not potent
Breadth & potency of bnAbs are important

- Open circle: 1st generation mAb
- Filled circle: 2nd generation mAb

CD4 binding site
Apex-specific
High-mannose patch
gp120-gp140 interface
Membrane proximal external region (MPER)
Four bnAbs are the focus of current studies

- Open circle: 1st generation mAb
- Filled circle: 2nd generation mAb
- CD4 binding site
- Apex-specific
- High-mannose patch
- gp120-gp140 interface
- Membrane proximal external region (MPER)
Antibody-Mediated Prevention Study (VRC01)

COMING SOON
Questions?

Please email me!

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