R4P 2021: Updates on the HIV Prevention Pipeline

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Disclosures

• **Research grants**: Gates, ViiV/GSK, Merck, & Gilead managed by JHU

• **Advisory Board**: Population Council, RTI, PREVENT Program, Gilead, Merck, ViiV/GSK, Orion Biopharma

• **Founding Partner** Priönde Biopharma, LLC

• **US Patents** 10,092,509, 10,646,434 microbicide formulations
Objectives

- Describe benefits of PrEP choices for HIV prevention
- Understand differences of long-acting PrEP
- Discuss ongoing development of on demand PrEP
- Discuss development of multi-purpose prevention technologies (MPTs)
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### Years Ahead in HIV Prevention Research

#### Time to Market

<table>
<thead>
<tr>
<th>Prevention Product</th>
<th>2020</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
<th>2024</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaginal Ring</strong></td>
<td></td>
<td></td>
<td><strong>Probable regulatory approval &amp; early introduction</strong></td>
<td></td>
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</tr>
<tr>
<td>Dapivirine Vaginal Ring</td>
<td>Positive EMA Opinion; WHO Prequalification and Recommendation</td>
<td></td>
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</tr>
<tr>
<td><strong>Long-Acting Injectables</strong></td>
<td></td>
<td><strong>Early JPTIN 003 and 004 results</strong></td>
<td><strong>Possible regulatory approval &amp; early introduction</strong></td>
<td><strong>Efficacy trials of six monthly injectables</strong></td>
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<tr>
<td>Lenacapavir</td>
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<tr>
<td><strong>Dual Prevention Pill</strong></td>
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<td></td>
<td></td>
<td><strong>Possible regulatory approval &amp; early introduction</strong></td>
<td></td>
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<tr>
<td>TDF/FTC/C Combined oral contraceptives</td>
<td></td>
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<tr>
<td><strong>Oral PrEP</strong></td>
<td></td>
<td></td>
<td><strong>Daily oral FTC/TAF efficacy trials in cisgender women</strong></td>
<td><strong>Monthly oral islatravir efficacy trials in MSM, TG women and cisgender women</strong></td>
<td></td>
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<tr>
<td>FTC/TAF</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Ilatravir</td>
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<tr>
<td><strong>Preventive Vaccines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Efficacy trials in all populations</strong></td>
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<tr>
<td>Ad26</td>
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</tbody>
</table>

March 2021
Many Factors Influence Choice

- Effectiveness does not drive all decision-making
- Perception of safety is similarly important
- Control, privacy, convenience, etc. are important, too

CHOICE: Proven Benefit in Contraception

- WHO Systematic Review (231 articles)
- CHOICE associated with better:
  - Contraceptive Uptake
  - Contraceptive Persistence
  - Health outcomes (↓ pregnancies, ↓ STIs)
- CHOICE, as with needs, vary over a lifetime

Why should PrEP be different?

- EACH add’l product option yields 12% increase in contraceptive use
- How much will it be for PrEP?

Gray AL, et al. WHO RHRU 2006

Jain AK, et al. Stud Fam Plan 1989
## More CHOICE, Better Uptake & Persistence

<table>
<thead>
<tr>
<th></th>
<th>Systemic</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td>Injectable (3m) Implant (yrs)</td>
<td>IUD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal ring</td>
</tr>
<tr>
<td><strong>Short Acting</strong></td>
<td>Oral (qd)</td>
<td></td>
</tr>
<tr>
<td><strong>On Demand</strong></td>
<td>Oral (x1 EC)</td>
<td>Barrier Film</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cu IUD (x1 EC)</td>
</tr>
</tbody>
</table>

*EC emergency contraception
Oral F/TDF: 39 Incident, 3 Baseline Infections

- 37/39 infections poor precedent adherence
- Only 2 “adherent” infections, resistance
- 6 (14%) NRTI resistance

TFV-DP ≥1250 fmol/punch
TFV-DP ≥700 - <1250 fmol/punch
TFV-DP ≥350 - <700 fmol/punch
TFV-DP >LLOQ - <350 fmol/punch
TFV-DP BLQ

- First HIV positive visit and first site positive visit
- First site positive visit
- First HIV positive visit
- HIV genotyping test

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- First HIV positive visit and first site positive visit
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Objectives

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HPTN 083 Study Design

**Screening day and informed consent**

**Step 1**
- Every day for 5 weeks
- CAB

**Step 2**
- Weeks 5 and 9
- TDF/FTC (Every day)
- Every 2 months for approximately 3 years

**Step 3**
- Every day for 1 year
- TDF/FTC

**Group A**
- CAB
- TDF/FTC pill
- Cabotegravir (CAB) injection
- Placebo for TDF/FTC pill
- Placebo for cabotegravir (CAB) injection

**Group B**
- CAB
- TDF/FTC pill
- Cabotegravir (CAB) injection
- Placebo for TDF/FTC pill
- Placebo for cabotegravir (CAB) injection

Landovitz RJ et al. AIDS 2020, #OAXLB0101
CAB-LA vs. F/TDF

HIV Incidence

<table>
<thead>
<tr>
<th>HIV Incidence Rate/100 PY</th>
<th>CAB</th>
<th>F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.37</td>
<td>1.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections</th>
<th>CAB (n = 1614)</th>
<th>F/TDF (n = 1610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 Infections</td>
<td>0.2 (0.06-0.52)</td>
<td>1.86 (1.30-2.57)</td>
</tr>
</tbody>
</table>

Person-yrs

<table>
<thead>
<tr>
<th>Person-yrs</th>
<th>CAB</th>
<th>F/TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1953</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>1939</td>
<td>3204</td>
<td>3187</td>
</tr>
</tbody>
</table>

Hazard ratio 0.32 (0.16, 0.58)  Hazard ratio 0.11 (0.04, 0.32)

Marzinke JID 2021; Delany-Moretlwe R4P 2021 HY01.02
Hazard Ratio is CAB-LA vs. F/TDF, not placebo

Background HIV Risk
- Historically RCT Incidence \textit{CGW} > MSM/TGW

F/TDF adherence
- MSM/TGW v. high; GCW pending

F/TDF adherence-protection differences
- \textit{MSM} adherence less stringent vs. CGW; TGW (GAHT) uncertain

CAB-LA Plasma Pharmacokinetics
- Troughs favors \textit{CGW}; Peaks favor MSM/TGW; AUC similar

CAB-LA Tissue Pharmacokinetics
- \textit{Cervicovaginal} tissue \(\sim 1/6^{th}\) plasma, Colorectal tissue \(\sim 1/10^{th}\) plasma
CAB-LA Concentration Targets

- **NHP Rectal SHIV Challenge**
  - 1x - 3x PA-IC$_{90}$ 97% protective

- **NHP Vaginal SHIV Challenge**
  - >1x PA-IC$_{90}$ 100% protective

- **NHP Vaginal SHIV Challenge**
  - 4x PA-IC$_{90}$ 88% protective

- **Clinical ART Monotherapy**
  - 4x PA-IC$_{90}$ >99% HIV RNA reduction

CAB-LA did not have the same long precedent treatment history as F/TDF & F/TAF to guide PrEP development, albeit with many assumptions about relevance of treatment to prevention doses, but the successful CAB-LA/RPV-LA treatment program proceeded CAB-LA PrEP in informative ways.

Andrews Science 2014; Radzio STM 2015; Andrews STM 2015; Spreen HIV Clin Trials. 2013
Exploring Breakthrough Infections

The shaded area represents time on ART.

BLQ: Below Limit of Quantitation
ND: Not Determined
Exploring Breakthrough Infections

The shaded area represents time on ART.
# Exploring Breakthrough Infections

The shaded area represents time on ART.

- **CAB concentration**
- **CAB injection**
- **First site positive visit**
- **First HIV positive visit**

- **Weeks between first HIV positive visit and the first site positive test**

The shaded area represents time on ART.
Exploring Breakthrough Infections

IN D + 263 IN D + 152,730

0.664

Weeks since enrollment

BLQ 0.166

CAB (mcg/mL)

Viral load

Confirmatory Ab test

Qualitative RNA test

Ag/Ab test

INSTI: G140A, Q148R

Undetectable on TDF/FTC/EFV

6.4W

weeks since enrollment

0 5 10 15 20 25 30 35 40 45 50 55 60 65 70

CAB concentration  CAB injection  First site positive visit  First HIV positive visit

# Weeks between first HIV positive visit and the first site positive test

The shaded area represents time on ART.
CAB-LA

- 2241 participants
- 16 total infections
- 12 incident infections
- 11 dx’d earlier by RNA testing
- 7/16 resistance-associated mutations
  - 5 ISTI (1 NNRTI) all received CAB-LA IM
    - 1 of 4 baseline - not incident
    - 2 of 3 oral lead-in
    - 2 of 4 on-time injection & expected conc’n
    - 0 of 5 tail
  - 2 NNRTI +/- NRTI

F/TDF

- 2247 participants
- 42 infections
- 39 incident
  - 37/39 poor adherence (<4/wk DBS)
- 13/42 infections resistance
  - 6 NRTI (3 also NNRTI)
  - 7 NNRTI only
Key Findings

- Oral lead-in will be optional in 083 OLE
- CAB-LA can delay detection of infection;
  - Is VL testing necessary with LA, deployable, cost-effective?
- Incident CAB arm infections despite target CAB concentrations;
  - Only 4 pts – v. low 0.4% incidence
  - 3 of 4 prior [CAB] dips (related to virologic test delay?)
- INSTI resistance
  - 38% of infections
  - Seen in active dosing, high [CAB]
  - Not seen in tail-phase infections
- F/TDF arm 37/39 incident infections poor adherence
  - CAB-LA & TDF/FTC highly effective PrEP; CAB-LA superior

Marzinke JID 2021
CAB-LA: What to improve upon?

- **HPT 083 CAB-LA “Failure” Analysis (0.4% incidence)**
  - Pharmacological Effect (25%)
    - 2 unexplained infections (*under evaluation*)
    - 2 infections due to PK variability (*TDM, dose-optimization, PrEP implants*)
  - Virologic diagnosis (25%)
    - 4 missed diagnoses at entry (*cost-benefit of sensitive virologic testing, test in OLE*)
    - 5 cases of resistance (31% of infections) might have been prevented
  - Behavioral (50%)
    - 3 adherence failures in oral lead-in
    - 5 lack of persistence (in 3,204 person-years)

- **Personal Desires & Behavior (50% of infections)**
  - Myriad variables informing adherence/persistence
  - Dislike for needles or find injection site reactions intolerable
  - Dislike systemic drug exposure
  - Lack of commitment to long-term drug exposure
HPTN 077: CAB-LA PK Variability

A Male participants

B Female participants

<table>
<thead>
<tr>
<th>Simple linear regression</th>
<th>Multivariable linear regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean fold-change in t½ (95% CI)</td>
<td>p value</td>
</tr>
<tr>
<td>Sex at birth (female vs male)</td>
<td>1.33 (1.06-1.68)</td>
</tr>
<tr>
<td>BMI (≥ median vs &lt; median)</td>
<td>1.31 (1.06-1.63)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.00 (0.99-1.01)</td>
</tr>
<tr>
<td>Weight (kgf)</td>
<td>1.01 (1.00-1.01)</td>
</tr>
<tr>
<td>Race‡</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.11 (0.82-1.50)</td>
</tr>
<tr>
<td>Non-Hispanic Asian</td>
<td>1.11 (0.40-2.45)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1.30 (0.99-1.72)</td>
</tr>
<tr>
<td>Non-Hispanic or other</td>
<td>0.91 (0.50-1.67)</td>
</tr>
<tr>
<td>Region§</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>1.23 (0.95-1.59)</td>
</tr>
<tr>
<td>Brazil</td>
<td>1.11 (0.83-1.50)</td>
</tr>
<tr>
<td>Current Smoker (yes vs no)</td>
<td>0.80 (0.56-1.13)</td>
</tr>
<tr>
<td>Injections, n</td>
<td></td>
</tr>
<tr>
<td>Cohort 1</td>
<td>1.09 (0.88-1.35)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>0.88 (0.69-1.22)</td>
</tr>
<tr>
<td>Cohort (2 vs 1)</td>
<td>1.02 (0.82-1.28)</td>
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</table>

# CAB-LA Single Dose Study

<table>
<thead>
<tr>
<th>Protocol</th>
<th>HPTN 083</th>
<th>ViiV/GSK 201767*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>3 mL (600mg)</td>
<td>3 mL (600mg)</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Q 8 wks for 3 years</td>
<td>Single dose</td>
</tr>
<tr>
<td><strong>Injection Site</strong></td>
<td>Ventrogluteal or Dorsogluteal</td>
<td>Ventrogluteal</td>
</tr>
<tr>
<td><strong>Needle Gauge</strong></td>
<td>21, 23, 25 gauge</td>
<td>22 gauge</td>
</tr>
<tr>
<td><strong>Needle Length</strong></td>
<td>BMI &lt;30 - 2.5-3.8 cm</td>
<td>9-15 cm</td>
</tr>
<tr>
<td></td>
<td>BMI &gt;30 - 5.1 cm</td>
<td>with ultrasound guide</td>
</tr>
<tr>
<td><strong>Z tracking</strong></td>
<td>Not specified</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PK Sampling</strong></td>
<td>Plasma</td>
<td>Plasma, RT, RF, VT, CT, CVF</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>No</td>
<td>Day 1, 3, 7</td>
</tr>
</tbody>
</table>

*Fuchs HIV R4P 2021; *2 Site PK intensive study, Hopkins & Pitt*
CAB-LA Single Dose Study

- Median plasma CAB above targets Wk 8 (>4× PA-IC₉₀) & Wk 12 (>PA-IC₉₀)
- Median CAB cervical, vaginal, & rectal tissue >1× PA-IC₉₀ through Wk 4

In vitro 4× PA-IC₉₀ (0.664 µg/mL)
In vitro 1× PA-IC₉₀ (0.166 µg/mL)

Error bars = minimum and maximum CAB concentrations

Fluid LLOQ (0.0000625 µg/mL)
Tissue LLOQ (0.00005 µg/mL)

Weld et al. HIVR4P 2021; Virtual. Slides OA669.
<table>
<thead>
<tr>
<th>Ratio to plasma, geometric mean (95% CI)</th>
<th>Cervical tissue (n=7)</th>
<th>Rectal tissue (n=13)</th>
<th>Cervicovaginal fluid (n=7)</th>
<th>Rectal fluid (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>0.20 (0.16-0.25)</td>
<td>0.10 (0.08-0.11)</td>
<td>0.13 (0.07-0.26)</td>
<td>0.62 (0.31-1.25)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{Wk4}}$</td>
<td>0.16 (0.09-0.26)</td>
<td>0.10 (0.09-0.11)</td>
<td>0.10 (0.04-0.25)</td>
<td>0.55 (0.23-1.28)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{Wk8}}$</td>
<td>0.15 (0.07-0.33)</td>
<td>0.11 (0.09-0.13)</td>
<td>0.09 (0.04-0.23)</td>
<td>0.49 (0.21-1.11)</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{Wk12}}$</td>
<td>0.15 (0.07-0.33)</td>
<td>0.11 (0.09-0.13)</td>
<td>0.09 (0.04-0.23)</td>
<td>0.49 (0.21-1.11)</td>
</tr>
</tbody>
</table>

• Each tissue and fluid matrix had lower CAB $C_{\text{max}}$ and AUC values vs plasma
• Slightly higher ratios seen in cervicovaginal tissue to plasma than rectal tissue to plasma
CAB-LA IM Injection Site MRI Anatomy

- ViiV/GSK Multi-compartment tissue study

Correlates of Depot Location & Plasma PK

Plasma CAB ng/mL

Depot Surface Area mm²

Days

0 7 14 21 28 35 42 49 56 63 70 77 84

r = 0.83

Fuchs. HIV R4P 2021
Implantable ARV-Eluting Devices

- Sustained release of PrEP drugs with constant release over time
- User-independent, subcutaneous implant
- Biodegradable
- Compatible with existing contraceptive implant trocar applicators

<table>
<thead>
<tr>
<th>Formulated drug core</th>
<th>Channels or Permeable membrane</th>
<th>Biological fluid in</th>
<th>Dissolved drug out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolved drug (saturated)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Compatibility with Existing Trocars

- Implanon
- Jadelle

Courtesy Marc Baum & Ariane van der Straten
PK Advantages of Implant vs. Injection

- Flattens peaks & troughs (optimize safety/efficacy)
- Eliminates long PK tail
- Reversibility eliminates oral lead-in
- Requires medical procedure vs. non-MD injection
- Limited by potency & PK of candidate drug
Islatravir Once Yearly Implants

- Radiopaque (barium) implants
- Adverse events less frequent than CAB-LA injection site reactions

Matthews R et al, vCROI March 8, 2021
ISL-TP PBMC PK Dose Proportional

- Mean (SD) ISL-TP PBMC profile overlaid Population PK model median (95% PI)\(^1\)
- 60 mg or 120 mg QM po doses exceeded target concentration with first dose
- P016 ongoing clinical study\(^2\) - Preliminary tissue PK suggest rapid, sustained, and adequate distribution of ISL to target tissue sites comparable to previous ISL studies\(^1\)

ISL, islatravir; PBMCs, peripheral blood mononuclear cells; PK, pharmacokinetics; PI, prediction interval; QM, once monthly; SD, standard deviation; TP, triphosphate.

Lenacapavir Capsid Inhibitor

- Multiple mechanisms of action, pM potency, very long half-life
Lenacapavir Supports q6m SC injection

Begley R et al. Safety and PK of subcutaneous GS-6207, a novel HIV-1 capsid inhibitor. Oral abstract PS13/1. EACS 2020
Merck & Gilead Announce Collaboration

- Islatravir & Lenacapavir
- Long-acting formulations
- Oral & Injectable (SC)
- Requires drug pair with potency & long half-life
- Oral combo trials 2021

Press release March 15, 2021; Smith Collection/Gado/Getty Images & Justin Sullivan/Getty Images
Long-Acting Dapivirine Vaginal Ring

- **Vaginal Ring Design**
  - Silicone matrix ring, 25 mg of dapivirine (NNRTI)
  - Monthly replacement, trivial systemic exposure

- **Two phase III placebo-controlled trials**
  - Well tolerated
  - Reduced HIV incidence ~30%
  - Greater protection (up to 85%) with high adherence

- **OLEs High uptake, better adherence**

- **90-day Ring in Development**

- **EMA favorable scientific review**

Baeten, et al., ASPIRE & Nel, et al., The Ring Study (IPM) NEJM 2016; International Partnership for Microbicides (IPM)
Geometric mean $T_{\text{max}}$ ranged from 16-25 days in plasma and 1-7 days in CVF
Decrease in DPV concentrations 4 hours after ring removal was comparable across arms, in both plasma and CVF

Liu vCROI 2021
Objectives

- Describe benefits of PrEP choices for HIV prevention
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- Discuss development of multi-purpose prevention technologies (MPTs)
On Demand Oral

- **Ipergay – Effective**
  - RCT
    - 2 TDF-FTC 2 - 24 hours before sex
    - 3rd 24 hours after the first dose
    - 4th 24 hours after the 3rd
  - 40% < weekly dosing

- **Prevenir – Popular**
  - Open label,
  - ppts select on demand (54%) or daily (45%);
  - Acquisition Risk 0 (0.0, 0.7) and 0 (0.0, 0.8), no infections in 506 & 443 PY, respectively

Molina NEJM 2015; Molina IAS 2018
On Demand Topical

- CAPRISA 004 TFV Vaginal Gel – Highly effective when used

mITT Analysis

PK-Adjusted Log Reg – 73% RRR

TFV/EVG Topical Inserts (CONRAD)

- Goal:
  - Dual compartment (vaginal & rectal) inserts
  - Discreet, inexpensive
  - On demand,
  - Easy to self-administer

- Tenofovir alafenamide (TAF) & Elvitegravir (EVG)

- Phase 1 FIH Study – Single vaginal dose
  - Genital and systemic safety
  - Multi-compartmental PK
  - Acceptability
  - Mucosal PD in vitro

Thurman HIV R4P Virtual 2021; ¹ Dobard et al. CROI 2019, Abstract #101; Dobard et al. CROI 2020, Abstract #88
CONRAD 146 Study Design

**Product:** Vaginal insert containing TAF/EVG (20 mg/16 mg)

**Participants:** 16 Healthy women, 18 – 50 years old, HIV-1 uninfected, non-pregnant, low STI risk

**Visits:** 4 clinical visits & follow up phone call

**Site:** Eastern Virginia Medical School, Norfolk, VA

**Randomization:**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Dose</th>
<th>Sample Collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>TAF/EVG (20mg/16mg)</td>
<td>4h, 2d, &amp; 7d after dosing</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>TAF/EVG (20mg/16mg)</td>
<td>1d, 3d, &amp; 7d after dosing</td>
</tr>
</tbody>
</table>
Achieved Targets

- Vaginal insert safe & acceptable
- Concentration Targets
  - High tissue concentrations of TFV-DP (> 1000 fmol/mg) & EVG (> 1 ng/mg)
  - Durable up to 72 hours post use
- Modeled PD supports MPT activity against HIV-1 and HSV-2
On Demand & Behaviorally-Congruent PrEP

- *Behaviorally-congruent* medicates product already in common use

- Common health fortification of existing products
  - Fluoridated drinking water & toothpaste
  - Calcium & vitamin fortified bread
  - Vitamin A & D fortified milk

- PrEP-medicated Sexual Lubricants
  - Very high levels (>85%) of sexual lubricant use among MSM
  - Modest levels among women, but higher among FSW (>60%)

- PrEP-medicated Douches
  - High levels of anal douching among MSM (>80%)
  - Not well studied among women, but modest to high among FSW (22-56%)
## Rectal Microbicide Candidates

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Formulation</th>
<th>Insertion</th>
<th>B-C</th>
<th>Toxicity</th>
<th>Acceptable</th>
<th>Explant</th>
<th>NHP</th>
</tr>
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<tbody>
<tr>
<td><strong>F/TDF</strong></td>
<td>NRTI</td>
<td>tablet</td>
<td>oral</td>
<td></td>
<td>minor</td>
<td>High</td>
<td>0.6</td>
<td>RV</td>
</tr>
<tr>
<td>UC781</td>
<td>NNRTI</td>
<td>gel</td>
<td>applicator</td>
<td>none</td>
<td>High</td>
<td>reduced</td>
<td></td>
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<tr>
<td>TFV VF</td>
<td>NRTI</td>
<td>gel</td>
<td>applicator</td>
<td></td>
<td>AE's</td>
<td>Modest</td>
<td>0.3-0.5</td>
<td>RV</td>
</tr>
<tr>
<td>TFV RGVF</td>
<td>NRTI</td>
<td>gel</td>
<td>applicator</td>
<td></td>
<td>none</td>
<td>Modest</td>
<td>0.7-0.8</td>
<td>R</td>
</tr>
<tr>
<td>TFV RF</td>
<td>NRTI</td>
<td>gel</td>
<td>applicator</td>
<td></td>
<td>none</td>
<td>High</td>
<td>1.0</td>
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<tr>
<td>TFV</td>
<td>NRTI</td>
<td>liquid</td>
<td>bottle</td>
<td>x</td>
<td>none</td>
<td>High</td>
<td>1.6</td>
<td>R</td>
</tr>
<tr>
<td>DPV</td>
<td>NNRTI</td>
<td>gel</td>
<td>applicator</td>
<td></td>
<td>none</td>
<td>High</td>
<td>1.3</td>
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<td>lubricant</td>
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<td>R</td>
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<td>applicator</td>
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<td>CCR5</td>
<td>gel</td>
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<td>R</td>
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<tr>
<td>OB-002H</td>
<td>CCR5</td>
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<td>applicator</td>
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<td>Q-GRFT</td>
<td>binding</td>
<td>douche</td>
<td>bottle</td>
<td>x</td>
<td>analysis</td>
<td>analysis</td>
<td>analysis</td>
<td>(V)</td>
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<tr>
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<td>NRTI/ISTI</td>
<td>insert</td>
<td>manual</td>
<td></td>
<td>ongoing</td>
<td>ongoing</td>
<td>ongoing</td>
<td>V</td>
</tr>
</tbody>
</table>

MOA, mechanisms of action; B-C, behaviorally-congruent; Explant ex vivo HIV challenge; NHP macaque
Objectives

- Describe benefits of PrEP choices for HIV prevention
- Understand differences of long-acting PrEP
- Discuss ongoing development of on demand PrEP
- Discuss development of multi-purpose prevention technologies (MPTs)
Multipurpose Prevention Technologies (MPT)

- **Concept:**
  - HIV risk associated with other health risks
    - Sexually transmitted infections
    - Pregnancy
  - Co-formulation enhances adherence
    - Behavioral-congruence w/ existing contraceptive practice

- **MPT IVRs – phase I / early phase II**
  - Dual Purpose Pill (DPP)
  - Tenofovir / levonorgestrol ring
  - Dapivirine / levonorgestrol ring

- **Development trade-offs?**
# MPTs in Development & Ring Technology

<table>
<thead>
<tr>
<th>MPT Type</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IIIb/IV</th>
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</thead>
<tbody>
<tr>
<td>Vaginal ring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal insert</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rectal insert</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal gel</td>
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<td></td>
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<tr>
<td>Rectal gel</td>
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<td></td>
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</tr>
<tr>
<td>Encrena</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal film</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral pill</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting injectable</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Micro-array patch</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>

- **HIV + other STIs:**
  - Total: 10

- **HIV + other STIs + Contraception**:
  - Total: 4

- **HIV + Contraception**:
  - Total: 11

- **Contraception + other STIs**:
  - Total: 3

---

Adapted from: The initiative for MPTs (mPT): Practical Development Guidance; Technical Advisory Group (TAG); 2021.Perspectives Report
90-Day DPV/LNG Vaginal Ring PK

Dapivirine Cervicovaginal Fluid
t₁/₂: 0.4 days (IQR 0.3-0.9)

Levonorgestrel Cervicovaginal Fluid
t₁/₂: 0.2 days (IQR 0.2-0.2)

Median concentration, ng/g

Days from initial vaginal ring insertion

DPV, Continuous use
DPV, Cyclic use

LNG, Continuous use
LNG, Cyclic use

Achilles. MTN-044/IPM 053/CCN019. HIV R4P 2021
90-Day MPT VR Conclusions

- Periodic removals likely w/ user-controlled rings as with many contraceptives
- Plasma drug concentrations above target w/ continuous use
  - [LNG] ≅ use of effective LNG-based contraceptives
  - [DPV] ≅ use of 25mg DPV ring
- Drug clearance is rapid from vaginal fluid
- Periodic removals did not impact
  - Safety—no toxicities observed
  - Vaginal bleeding profiles
- Frequent expulsions forced reformulation to less stiff ring

Gaps: Which compartments & concentrations critical for PrEP?
  - Plasma, vaginal fluid, and/or tissue concentrations?
Pregnancy & HIV Prevention

Uganda (N=200)

Pregnancy prevention

Top 3 methods
- Male condom (only): 25%
- Injectable: 23%
- Implant: 15%

HIV prevention

Top 3 methods
- Male condom: 68%
- Male circumcision: 49%
- Other: 15%

Zimbabwe (N=200)

Pregnancy prevention

Top 3 methods
- Male condom: 80%
- Male circumcision: 16%
- Other: 16%

HIV prevention

Top 3 methods
- Oral pills: 59%
- Implant: 20%
- Male condom (only): 8%
**Interest in Dual Purpose Prevention**

*Thinking about your current circumstances, would you prefer to use a “2 in 1” or two separate products?*

- **Ease of use:** 1 thing to remember instead of 2
- **Framing:** Avoid topic of HIV prevention with partner by saying product is just for family planning
- **Access burden:** Fewer clinic visits

- **Side effects:** Simultaneous use of two medicines
- **Pregnancy desire necessitates product switch**
- **Drug volume:** Too much in the body

No differences by sex.
Ideal Product Activity: Couple Preferences

**Form**
- Oral tablet: 58% (Uganda), 73% (Zimbabwe)
- Vaginal ring: 12% (Uganda), 12% (Zimbabwe)
- Vaginal insert: 21% (Uganda), 10% (Zimbabwe)
- Vaginal film: 10% (Uganda), 6% (Zimbabwe)

Vaginal product: 44% UGA, 27% ZIM

**Duration**
- Use before sex:
  - Uganda: 11% (4%)
  - Zimbabwe: 1% (10%)
- Use daily:
  - Uganda: 35% (6%)
  - Zimbabwe: 3% (6%)
- Use weekly:
  - Uganda: 35% (46%)
  - Zimbabwe: 52% (35%)
- Use every 2-3 months:
  - Uganda: 51% (88%)
  - Zimbabwe: 49% (7%)

**How vagina feels during sex**
- No changes: 51% (88%)
- Vagina feels wetter: 49% (7%)
- Vagina feels drier: 0% (6%)

- Uganda: No changes (51%), Vagina feels wetter (49%), Vagina feels drier (6%)
- Zimbabwe: No changes (88%), Vagina feels wetter (7%), Vagina feels drier (6%)
Ideal Product Activity: Couple Preferences

**Effect on Menses**
- Bleeding may be heavier: 55% (Uganda), 47% (Zimbabwe)
- Spotting or bleeding between menses: 46% (Uganda), 53% (Zimbabwe)

**Return to Fertility**
- Immediate: 34% (Uganda), 50% (Zimbabwe)
- 3 months after stopping use: 35% (Uganda), 37% (Zimbabwe)
- 6 months after stopping use: 32% (Uganda), 14% (Zimbabwe)

**Type of Protection**
- Protects against all ways of getting HIV: 99% (Uganda), 98% (Zimbabwe)
- Only protects against HIV during vaginal sex: 2% (Uganda), 2% (Zimbabwe)
## Comparing PrEP Efficacy, NNT, Resistance

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>P-YR</th>
<th>PPTs</th>
<th>Infect’s</th>
<th>ACT Incid</th>
<th>PL Incid</th>
<th>RRR mITT</th>
<th>RRR on Rx</th>
<th>NNT</th>
<th>ACT Resist</th>
<th>PL Resist</th>
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<tbody>
<tr>
<td>iPrEx</td>
<td>F/TDF</td>
<td>3324</td>
<td>2499</td>
<td>36</td>
<td>2.2</td>
<td>3.9</td>
<td>44 (15, 63)</td>
<td>92 (40, 99)</td>
<td>59</td>
<td>2 (6%)</td>
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<tr>
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<td>F/TDF</td>
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<td>2247</td>
<td>42</td>
<td>1.2</td>
<td>-</td>
<td>-</td>
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<td>6</td>
<td>6 (14%)</td>
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<tr>
<td>IPERGAY</td>
<td>F/TDF prn</td>
<td>216</td>
<td>199</td>
<td>2</td>
<td>0.9</td>
<td>6.6</td>
<td>86 (40,98)</td>
<td>100 ( )</td>
<td>18</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Discover</td>
<td>F/TDF</td>
<td>4386</td>
<td>2665</td>
<td>15</td>
<td>0.3</td>
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<td>-</td>
<td>4</td>
<td>21%</td>
<td>-</td>
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<tr>
<td>Discover</td>
<td>F/TAF</td>
<td>4370</td>
<td>2670</td>
<td>7</td>
<td>0.2</td>
<td>- *47 (19, 115)</td>
<td>-</td>
<td>-</td>
<td>0 (0%)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HPTN 083</td>
<td>CAB</td>
<td>3204</td>
<td>2241</td>
<td>16</td>
<td>0.4</td>
<td>- *68 (42, 84)</td>
<td>-</td>
<td>-</td>
<td>5 (31%)</td>
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<tr>
<td>Partners</td>
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<td>~2600</td>
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<td>90 (56, 98)</td>
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<td>3.1</td>
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<td>67</td>
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<td>1610</td>
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<td>-</td>
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<td>Ring Study</td>
<td>DPV</td>
<td>2805</td>
<td>1959</td>
<td>56</td>
<td>4.1</td>
<td>6.1</td>
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<td>50</td>
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<td>67 (23, 84)</td>
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<td>8 (12%)</td>
<td>10</td>
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<td>1953</td>
<td>1614</td>
<td>4</td>
<td>0.2</td>
<td>- *89 (68,96)</td>
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<td>-</td>
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*Compared to F/TDF*
## More CHOICE, Better Uptake & Persistence

<table>
<thead>
<tr>
<th></th>
<th>Systemic</th>
<th>Vaginal</th>
<th>Rectal</th>
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<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td>Oral (1m)</td>
<td>Vaginal ring (1m-3m)</td>
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<tr>
<td></td>
<td>Injectable (2m)</td>
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<td></td>
<td>Implant (1yr)</td>
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<tr>
<td><strong>Short Acting</strong></td>
<td>Oral (qd)</td>
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<tr>
<td><strong>On Demand</strong></td>
<td>Oral (2+1+1)</td>
<td>Barrier Gel, Film, Insert</td>
<td>Barrier Insert Lubricant (BC) Douche (BC)</td>
</tr>
</tbody>
</table>
Questions?
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