HIV Prevention and Drug Development: Past, Present, Future

May 4, 2019

James E. Cummins, Jr., PhD
Division of AIDS
National Institute of Allergy and Infectious Diseases
National Institutes of Health
The views expressed are those of the presenter and do not necessarily reflect the official policies of the Department of Health and Human Services (HHS), nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

Conflicts of Interest

None to report
In this presentation, the following candidate HIV prevention products will be described:

- None of these products are licensed for HIV prevention, but all have been studied for the prevention of HIV in uninfected individuals at high risk of HIV infection.

- Studies supporting the licensure of Truvada (emtricitabine/tenofovir disoproxil fumarate; FTC/TDF) for pre-exposure prophylaxis (PrEP) will also be described.
Outline of Presentation

- **Introduction**
  - Current HIV statistics
  - Sexual HIV transmission
  - Drug delivery in HIV prevention
  - HIV targets in HIV prevention
  - Timeline for HIV prevention products

- **Past:** Lessons Learned from 1st Generation HIV Prevention Products

- **Present:** Approval of Truvada for Pre-Exposure Prophylaxis and Current Products in Development

- **Future:** Multipurpose Prevention Products and Long-Acting Injectables

- **Conclusions**
Learning Objectives

As a result of this activity, participants will be able to:

- Describe factors that impeded further development of first generation HIV prevention products
- Discuss clinical trial results that supported licensure of Truvada for Pre-Exposure Prophylaxis (PrEP) to prevent HIV infection
- Explain how pharmacokinetic differences between men and women impact dosing of Truvada for PrEP
- Recognize drug-drug interactions between Dapivirine and topical miconazole nitrate
Snapshot of HIV Infections (2016)

In the United States, there were new HIV diagnoses in every state in 2016. According to the Centers for Disease Control and Prevention (CDC):

- **Approximately 1.2 million people** in the United States are living with HIV.
- **More than 39,000 people** in the United States were diagnosed with HIV in 2016.
- **Some populations have higher rates** of HIV infection:
  - Although 37 percent of the U.S. population lives in the South, more than half of new diagnoses (52%) and deaths (49%) among persons diagnosed occur in the South.
  - **African Americans** comprise 12 percent of the total U.S. population, yet were 44 percent of new HIV diagnoses.
  - **Latino men and women**, comprising 18 percent of the population, were 25 percent of all new HIV diagnoses.
  - **Youth ages 13 to 24** accounted for 22 percent of all new HIV diagnoses.
  - **45 percent of PWH** are over the age of 55 and are more likely to face comorbidities of HIV, aging, and/or complications of treatment.

The United Nations General Assembly declared the AIDS pandemic “a global emergency and one of the most formidable challenges to human life and dignity...which undermines social and economic development throughout the world and affects all levels of society—national, community, family, and the individual.” According to the joint United Nations Programme on HIV/AIDS (UNAIDS), in 2016:

- **36.7 million people globally** were living with HIV.
- **1.8 million people** were newly infected with HIV.
- **Approximately 1 million people** died from AIDS-related illnesses.
- **Only 19.5 million people**, slightly more than half (53%) of those living with HIV, were using ART.
- **In 2015, 1.8 million children under 15 years of age** were living with HIV worldwide.
- **An estimated 160,000 children** acquired HIV globally in 2016.

(from CDC & UNAIDS)
Global HIV Infections and 2020 Target


AVAC Report 2018: No Prevention, No End
www.avac.org/report2018
38,739 people received an HIV diagnosis in the U.S.
The annual number of new HIV infections remained stable between 2012 and 2016.
Sexual HIV Transmission

- After sexual exposure, HIV must be blocked within the mucosa to prevent dissemination and establishment of a lymphatic tissue reservoir.

- To prevent sexual transmission, drug concentrations that block HIV infection must be maintained within the mucosa.

(from *Nature* 2010; 464: 217-23)
Drug Delivery in HIV Prevention

- Systemic Delivery
  - Protects against all potential routes of exposure

- Topical Delivery
  - Protects against mucosal exposure

- Right Drug
- Right Amount
- Right Place
- Right Time
HIV Drug Targets in HIV Prevention

- **Virus itself**
  - Nonoxynol-9

- **Virus attachment**
  - PRO2000

- **Reverse Transcription**
  - Tenofovir
  - Dapivirine
  - Truvada

- **Integration**
  - Cabotegravir

(from *Lancet* 2014; 384: 258-71)
Timeline for HIV Prevention Products

**Systemic Products**
- Truvada (FTC/TDF) pill
  - 2007-2014
- Cabotegravir injection
  - 2016-2022

**Topical Products**
- Nonoxynol-9 gel
  - 1996 - 2000
- PRO2000 gel
  - 2005-2009
- Dapivirine IVR
  - 2012-2016
- Tenofvir gel
  - 2007-2014

**Concept for Topical Microbicide (1990)**

**Antiretroviral Drugs**
- Tenofovir gel
  - 2007-2014
Nonoxynol-9 Gel

- **Drug Class**: Surfactant used as a vaginal spermicide (available in OTC formulations)
- **Mechanism of Action**
  - Interacts with the lipids in the membranes of HIV virions – inhibits HIV *in vitro*
- **Formulation/Dosing**
  - Topical gel (3.5% w/w) applied vaginally with each sex act
- **Clinical Studies**
  - **COL-1492**: Phase 2/3 study in 892 female sex workers (>16 years of age) in Africa and Thailand (1996-2000)
- **Sponsors**: UNAIDS & Columbia Laboratories

Molecular Weight: 616.8
C\textsubscript{33}H\textsubscript{60}O\textsubscript{10}
## Nonoxynol-9 Gel: Clinical Trial Results

### COL-1492 Trial: HIV Incidence per treatment group & frequency of use

<table>
<thead>
<tr>
<th>Nonoxynol-9</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Seroconversions</td>
</tr>
<tr>
<td>376</td>
<td>59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonoxynol-9</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gel Use (#/day)</td>
<td>Seroconversions</td>
</tr>
<tr>
<td>Low (&lt;1.5)</td>
<td>13</td>
</tr>
<tr>
<td>Medium (1.5-3.5)</td>
<td>13</td>
</tr>
<tr>
<td>High (&gt;3.5)</td>
<td>33</td>
</tr>
</tbody>
</table>

(from *Lancet* 2002; 360: 971-77)
Nonoxynol-9 Gel: Conclusions

- The COL-1492 study did not show a protective effect of Nonoxynol-9 gel on HIV transmission in high-risk women.

  - Frequent use of Nonoxynol-9 gel was associated with an increased risk of HIV transmission.
  
  - Frequent use of Nonoxynol-9 gel was associated with epithelial lesions (cervix, vagina, and vulva).

- Development of Nonoxynol-9 gel as an HIV prevention method was discontinued.
PRO2000 Gel

- **Drug Class**: Napthalene sulfonate polymer
- **Mechanism of Action**
  - Inhibits binding of HIV to target cell receptors (gp120 binding to CD4)
- **Formulation/Dosing**
  - Topical gel (0.5% or 2.0% w/w) applied vaginally 1 hr before each sex act
- **Clinical Studies**
  - **HPTN-035**: Phase 2/2b study in 3101 women (≥18 years of age) in Africa and USA (2005-2009)
  - **MDP-301**: Phase 3 study in 9385 women (≥16 years of age) in Africa (2005-2009)
- **Sponsors**: NIH & Endo Pharmaceuticals

Molecular Weight: 5 kDa
### PRO2000 Gel: Clinical Trial Results

#### HPTN-035 Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th></th>
<th>PRO2000</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Seroconversions</td>
<td>HIV incidence per 100 woman-years</td>
<td>n Seroconversions</td>
<td>HIV incidence per 100 woman-years</td>
<td></td>
</tr>
<tr>
<td>PRO2000</td>
<td>764</td>
<td>36</td>
<td>2.7</td>
<td>760</td>
</tr>
<tr>
<td>Placebo</td>
<td>764</td>
<td>36</td>
<td>2.7</td>
<td>760</td>
</tr>
</tbody>
</table>

(from *AIDS* 2011; 25: 957-66)

#### MDP-301 Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th></th>
<th>PRO2000</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n Seroconversions</td>
<td>HIV incidence per 100 woman-years</td>
<td>n Seroconversions</td>
<td>HIV incidence per 100 woman-years</td>
<td></td>
</tr>
<tr>
<td>PRO2000</td>
<td>3156</td>
<td>130</td>
<td>4.5</td>
<td>3112</td>
</tr>
<tr>
<td>Placebo</td>
<td>3156</td>
<td>130</td>
<td>4.5</td>
<td>3112</td>
</tr>
</tbody>
</table>

(from *Lancet* 2010; 376: 1329-37)
PRO2000 Gel: Conclusions

- Although the HPTN-035 study showed a modest protective effect of PRO2000 gel on HIV transmission (~30%) in high-risk women, the results were not statistically significant.
- The MDP-310 study did not show a protective effect of PRO2000 gel on HIV transmission in high-risk women.
- Development of PRO2000 gel as an HIV prevention method was discontinued.
Tenofovir Gel

- **Drug Class**: Nucleoside Reverse Transcriptase Inhibitor (NRTI)

- **Mechanism of Action**
  - Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication

- **Formulation/Dosing**
  - Topical gel (1% w/w) applied vaginally before & after sex (within 12 hr) or applied daily

- **Clinical Studies**
  - **CAPRISA-004**: Phase 2b study in 889 women (18-40 years of age) in Africa (2007-2010)
  - **MTN-003/VOICE**: Phase 2b study in 5029 women (18-45 years of age) in Africa (2009-2012)
  - **FACTS-001**: Phase 3 study in 2059 women (18-30 years of age) in Africa (2011-2014)

- **Sponsors**: CAPRISA, NIH, & CONRAD

**Molecular Weight**: 287.2

\[ \text{C}_9\text{H}_{14}\text{N}_5\text{O}_4\text{P} \]
# Tenofovir Gel: Clinical Trial Results

## CAPRISA 004 Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir Gel</th>
<th>Placebo Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>422</td>
<td>421</td>
</tr>
<tr>
<td>Seroconversions</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>HIV incidence per 100 woman-years</td>
<td>5.6</td>
<td>9.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>0.85 (0.61-1.21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

*(from Science 2010; 329: 1168-74)*

## MTN-03/VOICE Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir Gel</th>
<th>Placebo Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>996</td>
<td>996</td>
</tr>
<tr>
<td>Seroconversions</td>
<td>61</td>
<td>70</td>
</tr>
<tr>
<td>HIV incidence per 100 woman-years</td>
<td>6.0</td>
<td>6.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>0.85 (0.61-1.21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>0.37</td>
<td></td>
</tr>
</tbody>
</table>

*(from N Eng J Med 2015; 372: 509-18)*
# FACTS-001 Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th>Tenofovir Gel</th>
<th>Placebo Gel</th>
<th>Incidence Rate Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Seroconversions</td>
<td>HIV incidence per 100 woman-years</td>
<td>n</td>
</tr>
<tr>
<td>935</td>
<td>61</td>
<td>4.0</td>
<td>934</td>
</tr>
</tbody>
</table>

(from *Lancet* 2018; 18: 1241-50)
Tenofovir Gel: Conclusions

- The CAPRISA-004 study showed a modest protective effect of Tenofovir gel on HIV transmission (~39%) in high-risk women.

- The MTN-03/VOICE* and FACTS-001 studies did not show a protective effect of Tenofovir gel on HIV transmission in high-risk women.

  *Major issue was product adherence: Tenofovir was only detected in 25% of available plasma samples from women using the gel (vs. 83-90% adherence based on product counts and interviews).

- Development of Tenofovir gel as an HIV prevention method was discontinued.
Dapivirine Intravaginal Ring (IVR)

- **Drug Class**: Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

- **Mechanism of Action**
  - Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication

- **Formulation/Dosing**
  - Intravaginal ring (25 mg) worn 28 days

- **Clinical Studies**
  - **MTN-020/ASPIRE**: Phase 3 study in 2629 women (18-45 years of age) in Africa (2012-2015)
  - **IPM-027/The Ring Study**: Phase 3 study in 1959 women (18-45 years of age) in Africa (2012-2016)

- **Sponsor**: International Partnership for Microbicides, Inc.

- **Molecular Weight**: 329.4
  - \(C_{20}H_{19}N_5\)
## Dapivirine IVR: Clinical Trial Results

### MTN-020/ASPIRE Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th>Dapivirine IVR</th>
<th>Placebo IVR</th>
<th>n Seroconversions</th>
<th>HIV incidence per 100 woman-years</th>
<th>n Seroconversions</th>
<th>HIV incidence per 100 woman-years</th>
<th>Effectiveness (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1308</td>
<td>71</td>
<td>3.3</td>
<td>1306</td>
<td>97</td>
<td>4.5</td>
<td>27% (1-46)</td>
<td>0.05</td>
</tr>
</tbody>
</table>


### IPM-027/The Ring Trial: HIV Incidence per treatment group

<table>
<thead>
<tr>
<th>Dapivirine IVR</th>
<th>Placebo IVR</th>
<th>n Seroconversions</th>
<th>HIV incidence per 100 woman-years</th>
<th>n Seroconversions</th>
<th>HIV incidence per 100 woman-years</th>
<th>Hazard Ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1307</td>
<td>77</td>
<td>4.1</td>
<td>652</td>
<td>56</td>
<td>6.1</td>
<td>0.69 (0.49-0.99)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

(from *N Eng J Med* 2016; 375: 2133-43)
The MTN-020/ASPIRE study showed a modest protective effect of Dapivirine IVR on HIV transmission (~27%) in high-risk women.

- In post hoc analysis, a higher rate of HIV protection (~56%) was observed in women over 21 years of age (CI 31-71; p<0.001) with a higher rate of product adherence (~70%) vs. women <21 years of age.

The IPM-027/The Ring Study showed a modest protective effect of Dapivirine IVR on HIV transmission (~31%) in high-risk women.

- The Dapivirine IVR is the first topical microbicide submitted for regulatory approval by the European Medicines Agency under Article 58. An opinion is expected by mid-2019.
Dapivirine IVR: Drug-Drug Interactions

- An open-label, randomized, cross-over trial was conducted in 36 women (18-40 years of age):
  - Participants used the Dapivirine IVR alone or together with a single dose of miconazole nitrate (1200 mg vaginal capsule).
  - A single dose of miconazole nitrate was administered alone as a third treatment.
  - Washout periods of 3 weeks were included between treatments.

- Dapivirine and miconazole concentrations were determined in plasma and vaginal secretions, and residual Dapivirine levels were assessed in used rings.

(from AIDS Res Hum Retrovir 2014; 30 Suppl 1(S1):A144)
A single vaginal dose of miconazole nitrate:

- Increased the systemic exposure ($C_{\text{max}}$ and AUC) of Dapivirine by 20% at the time of Dapivirine IVR insertion.
- Decreased cervicovaginal fluid levels of Dapivirine up to 14 days post-IVR insertion (decreases of 26% in $C_{\text{max}}$ and 69% in AUC$_{0-24h}$).

- No significant difference was observed between residual levels of Dapivirine in used IVRs with and without concomitant miconazole use, suggesting similar Dapivirine release.

- Dapivirine cervicovaginal fluid levels remained at least 100x higher than the in vitro IC$_{99}$ in cervical tissue (3.3 ng/mL).

(from AIDS Res Hum Retrovir 2014; 30 Suppl 1(S1):A144)
Local and systemic miconazole exposure was increased after co-administration with the Dapivirine IVR (1.4 to 6-fold higher).

Concomitant use of the two products was safe and well-tolerated.

Although these changes are considered unlikely to affect efficacy of either drug, studies are underway to determine the cause (e.g., role of drug transporters).
**Drug Class:** Nucleoside Reverse Transcriptase Inhibitor (NRTI)

**Mechanism of Action**
- Inhibits the activity of reverse transcriptase, a viral DNA polymerase required for HIV replication

**Formulation/Dosing**
- Oral tablet (200 mg FTC/300 mg TDF) taken daily

**Clinical Studies**
- **iPrEx:** Phase 3 study in 2499 MSM and transgender women (>18 years of age) in Americas, Asia, and Africa (2007-2014)
- **Partners PrEP:** Phase 3 study in 4758 uninfected men and women (serodiscordant couples; 18-65 years of age) in Africa (2008-2013)

**Sponsors:** NIH and University of Washington
# Truvada Pill: Clinical Trial Results

## iPrEx Trial: HIV Incidence per treatment group, overall

<table>
<thead>
<tr>
<th></th>
<th>Truvada Pill</th>
<th>Placebo Pill</th>
<th>Effectiveness (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Seroconversions</td>
<td>n</td>
<td>Seroconversions</td>
<td></td>
</tr>
<tr>
<td>1224</td>
<td>36</td>
<td>1217</td>
<td>64</td>
<td>44%</td>
</tr>
<tr>
<td></td>
<td>(15-63)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*from N Eng J Med 2010; 363: 2587-99*

## Partners PrEP Trial: HIV Incidence per treatment group, overall

<table>
<thead>
<tr>
<th></th>
<th>Truvada Pill</th>
<th>Placebo Pill</th>
<th>HIV incidence per 100 person-years</th>
<th>Effectiveness (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Seroconversions</td>
<td>n</td>
<td>Seroconversions</td>
<td>HIV incidence per 100 person-years</td>
<td></td>
</tr>
<tr>
<td>1576</td>
<td>13</td>
<td>1578</td>
<td>52</td>
<td>1.99</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>(55-87)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*from N Eng J Med 2012; 367: 399-410*
Despite the efficacy observed in iPrEx and Partners PrEP, other clinical studies (FEM-PrEP) indicated that low adherence in women was linked to lack of efficacy.

- Plasma drug concentrations in women indicated that only 24-30% of the women had recently used the product.

Yet, in a cohort of men from iPrEx, plasma drug concentrations indicated that only 28% had recently used the product.

- Subsequent analysis revealed drug exposure consistent with 2-3 doses/week achieved 75-90% protection in men.
A translational pharmacology model was used to predict PrEP outcomes in men and women.

- Measured tissue concentrations (colorectal and female genital tract tissues) of TFV, FTC, and active metabolites (TFVdp and FTCtp)
- Modeled the effective concentration of the active metabolites ($EC_{90}$) for protection against HIV

(from J Infect Dis 2016; 214: 55-64)
## Results from Evaluating Truvada in a Translational Pharmacology Model

<table>
<thead>
<tr>
<th>Factor Evaluated</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFVdp concentration in tissues</td>
<td>10x higher in colorectal vs. cervicovaginal tissues</td>
</tr>
<tr>
<td>Endogenous nucleotides (that compete for active metabolites)</td>
<td>7-11x lower in colorectal vs. cervicovaginal tissues</td>
</tr>
<tr>
<td>Model predictions</td>
<td>&gt;98% of the population achieved protective tissue exposure by the third daily dose of FTV/TDF</td>
</tr>
<tr>
<td>Minimum adherence (i.e., # doses/week) required to protect tissue</td>
<td>2 of 7 doses/week (28%) protected colorectal tissue vs. 6 of 7 doses (85%) required to protect cervicovaginal tissue</td>
</tr>
</tbody>
</table>

*(from J Infect Dis 2016; 214: 55-64)*
Time to protection as determined by pharmacokinetic/pharmacodynamic simulations for colorectal tissue and lower female genital tract tissue

Percentage of the population achieving effective drug concentrations (EC$_{90}$ ratios) with 1-7 doses/week of FTC, TDF, and TDF-FTC stratified by tissue type

(from J Infect Dis 2016; 214: 55-64)
Truvada Pill: Differences in Men and Women

(continued)

Time to protection as determined by pharmacokinetic/pharmacodynamic simulations for colorectal tissue and lower female genital tract tissue

Percentage of the population achieving effective drug concentrations (EC\textsubscript{90} ratios) with 1-7 doses/week of FTC, TDF, and TDF-FTC stratified by tissue type

(from J Infect Dis 2016; 214: 55-64)
Predictions from Evaluating Truvada in a Translational Pharmacology Model

<table>
<thead>
<tr>
<th>Model Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td>The maximal percentage of the population achieved EC$_{90}$ ratios by the third daily dose of TDF+FTC</td>
</tr>
<tr>
<td>Consistent use (7 doses/week) will achieve EC$_{90}$ ratios in 100% of the population in both tissue types</td>
</tr>
<tr>
<td>Only 65% of the population using 2 doses/week achieved target exposure in FGT tissue but &gt;95% using 2 doses/week achieved target exposure in colorectal tissue</td>
</tr>
</tbody>
</table>

(from J Infect Dis 2016; 214: 55-64)
**Truvada Pill: Conclusions**

- The iPrEx study showed a modest protective effect of Truvada pill on HIV transmission (~44%) in high-risk men and transgender women.

- The Partners PrEP showed a high protective effect of Truvada pill on HIV transmission (~75%) in high-risk men and women.

- iPrEx and Partners PrEP participants with measurable drug levels (i.e., the most adherent) had ~90% decreased chance of HIV infection.

- Based on these studies, in 2012 the U.S. FDA approved Truvada pill for PrEP to reduce the risk of sexually acquired HIV infection in adults at high risk.

- A translational pharmacology model indicates that women should adhere to the daily Truvada regimen to maintain maximum protection against HIV infection.
Multipurpose Prevention Technologies (MPTs) are an innovative class of products that deliver varied combinations of HIV prevention, other sexually transmitted infection (STI) prevention, and contraception.

MPTs in development include:

- Longer-acting vaginal rings
- Fast-dissolving films and tablets
- Innovative and effective gels
- Injectables that combine contraception and protection against infection
- Nanofiber delivery systems

Product adherence may be higher for products with multiple indications.
# Future: Multipurpose Prevention Technologies

(continued)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Delivery Modes</th>
<th>Mechanisms of Action</th>
<th>Dosage &amp; Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV*</td>
<td>Diaphragm*</td>
<td>Anti-microbial*</td>
<td>Oral daily*</td>
</tr>
<tr>
<td>Candida</td>
<td>Film*</td>
<td>Anti-fungal</td>
<td>Oral on-demand Gel*</td>
</tr>
<tr>
<td>Chlamydia*</td>
<td>Implant</td>
<td>Anti-viral*</td>
<td>Systemic sustained*</td>
</tr>
<tr>
<td>Gonorrhea*</td>
<td>Injection*</td>
<td>Barrier*</td>
<td>Topical daily*</td>
</tr>
<tr>
<td>HIV*</td>
<td>Intrauterine Device</td>
<td>HC *</td>
<td>Topical on-demand*</td>
</tr>
<tr>
<td>HPV*</td>
<td>Oral pill*</td>
<td>Non-HC*</td>
<td>Topical sustained</td>
</tr>
<tr>
<td>HSV*</td>
<td>Ring (Non-IVR)</td>
<td>Probiotic</td>
<td></td>
</tr>
<tr>
<td>Pregnancy*</td>
<td>Ring (IVR)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syphilis</td>
<td>Tablet*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichomoniasis</td>
<td></td>
<td><em>Currently being tested in human clinical trials.</em></td>
<td></td>
</tr>
</tbody>
</table>

(from MPTs: An Introductory Factsheet. 2016. AVAC)
Future: Long-acting Injectables

- Long-acting injectables are an innovative class of products in which an antiretroviral drug (ARV) is delivered by an injection and persists within the body for an extended period of time.

- For HIV prevention, the goal is to develop an injectable-only regimen that would minimize adherence requirements.

- Ideal products should contain a potent ARV with a long half-life that allows for less frequent dosing.

- Preclinical data and studies in nonhuman primates indicated that Cabotegravir was an ideal candidate when formulated as a long-acting injectable.
Cabotegravir Long-Acting Injection

Protective Levels of Cabotegravir in a Rhesus Macaque Model of Infection

Plasma concentrations of Cabotegravir (CAB) within each dose group (10, 30, & 50 mg/kg) compared to the predicted concentration at 50 mg/kg following two IM injections in rhesus macaques.

(Presented at CROI 2015, Seattle, WA, Poster 966LB)

Rate of SIV infection within various ranges of CAB plasma concentrations. The numbers above the bars represent the number of infections/number of challenges within a plasma concentration range, percentages indicate the infection rate (+/- 95% CI).
Drug Class: Integrase inhibitor

Mechanism of Action
- Inhibits integrase, an HIV enzyme required for HIV integration and replication

Formulation/Dosing
- Long-acting injectable: 600 mg (3 mL) every 8 weeks

Clinical Studies (Ongoing):
- HPTN-083: Phase 2b/3 study in 4500 MSM and transgender women (>18 years of age) in the USA (2016-2022)
- HPTN-084: Phase 3 study in 3200 women (18-45 years of age) in Africa (2017-2022)

Sponsor: NIH
Conclusions

- Lack of efficacy and potential toxicity impeded further development of the 1st generation of HIV prevention products (PRO2000 gel and Nonoxynol-9 gel).

- Despite modest efficacy in one clinical trial, lack of product adherence in larger studies impeded further development of Tenofovir gel.

- The Dapivirine IVR is the first topical microbicide submitted for regulatory approval by the European Medicines Agency under Article 58.

  - Drug-drug interactions between Dapivirine and miconazole are currently being investigated.
Conclusions (continued)

- Truvada pill is the only product approved by FDA for PrEP to reduce the risk of sexually acquired HIV infection in adults at high risk.

  - Available clinical trial data and modeling studies indicate that women should follow the recommended daily Truvada regimen to maintain protection against HIV.

- MPTs offer an innovative approach to combine HIV/STI prevention with contraception – with a product profile that may drive uptake and adherence.

- Long-acting injectables may offer a dosing regimen that minimize adherence requirements by allowing less frequent dosing.
Acknowledgments

Supported by NIAID Contract: HHSN272200800020C, "Non-human Primate Models to Evaluate Therapeutic Strategies and Topical Microbicides for HIV”

Note: ABL conducted the nonhuman primate study with Cabotegravir provided by ViiV Healthcare.
Questions