The Case for Multipurpose Prevention Technologies

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Bureau for Global Health

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Dakar, Senegal
The challenge: **how to address the primary sexual and reproductive health needs of all women?**

1. Healthy timing & spacing of intended pregnancies

2. Safe birth for mother and child

3. Protection against HIV, other STIs & RTIs (HPV, HSV, GC, CT, BV)
1. Healthy timing & spacing of intended pregnancies

Percent of unmet need is highest in SSA (64%)
- But the absolute number with unmet need is highest in S/W Asia (88 million women, or 41% of all unmet need)

Unmet need of 215 million women in these countries translates annually to:
- 53 million unintended pregnancies
- 25 million abortions

Source: AGI 2004; Guttmacher “Adding it Up” report, 2009
2. Safe birth for mother and child

- Each year, 450,000 women in developing countries die from complications related to pregnancy and childbirth.
- An additional 15 to 20 million women suffer debilitating consequences of pregnancy.

- Annually, 4 million newborns die in the first four weeks of life, accounting for 40 percent of all deaths among children under the age of five.

Source: USAID MNCH fact sheet, 2010
3. Protection against HIV, other STIs & RTIs

- Use of a vaginal microbicide like tenofovir gel could prevent 1,323,000 new HIV infections in South Africa alone over the next 20 years.

  Source: Mathematical modeling from CAPRISA 004 results presentation, Int’l AIDS Conference, 2010

- New vaccines against HPV infection could ultimately prevent ~500,000 new cases of cervical cancer every year in resource-poor settings.

The solution: focus on those countries in SSA and S. Asia with the greatest SRH needs

- **24 priority countries**: represent 1.4 billion population; 4.3 TFR, 24% MCPR
- **23 additional assisted countries**: represent 515 million; 2.8 TFR, 48% MCPR
- **21 graduate countries**: represent 926 million; 2.1 TFR, 64% MCPR
- No significant FP/RH assistance historically

**Note:** The 24 priority countries encompass more than half of the 215 million women with a current unmet need for family planning.
Aim: develop multipurpose prevention options that...

- Prevent unintended pregnancy
- Protect against HIV, other STIs & RTIs
- Provide additional health benefits

Our Ultimate Goal:
An expanded range of
- **Effective**
- **Acceptable**
- **Accessible**
prevention options for women that address their sexual and reproductive health concerns as they change over time.
We want and need your input!

Please respond to a 2-minute survey on MPTs:

https://www.surveymonkey.com/s/MPTsDec1English

https://www.surveymonkey.com/s/MPTsDec1Francaise

THANK YOU!  -- MERCI!
MPTs in Clinical Development for Use in Low Resource Settings

2011 International Conference on Family Planning
Dakar, Senegal

Jill Schwartz, MD; CONRAD
Tom Zydowsky, PhD; Population Council
MPTs to be Described:

**Dr. Jill Schwartz; CONRAD**
- SILCS diaphragm + tenofovir (TFV) gel
- TFV+LNG intravaginal ring

**Dr. Tom Zydowsky; Population Council**
- MZL vaginal gel
- MZL intravaginal ring
SILCS: NOT your Mother’s Diaphragm
Advantages of SILCS

- Single size negates need for clinical pelvic exam and fit assessment, thus reducing obstacles to access
- 6-mo typical use pregnancy rate comparable to standard fitted diaphragm when used with a contraceptive gel (10.4%)
- 5-yr shelf life simplifies logistics of supply and provision
- Potential as a delivery device for a microbicide such as tenofovir (TFV) gel, which was shown to be 39% effective in preventing HIV, and 51% in preventing HSV-2

Thus SILCS+TFV gel would be a "barrier device + drug" MPT for prevention of pregnancy, HIV and HSV-2
TFV + Levonorgestrel (LNG)
Intravaginal Ring (IVR)

**TFV + Levonorgestrel (LNG)**

**Intravaginal Ring (IVR)**

**LNG 10-20 µg/day**
LNG is a safe, effective and affordable hormonal contraceptive

**TFV 10 mg/day**

- Combination polyurethane IVR designed for continuous use (sustained release) for up to 90 days
- Clinical studies to begin in 2012
The Population Council’s MPT Development Plan

To develop and deliver safe and effective MPTs that prevent HIV, other STIs, and unintended pregnancy

Guiding principles:

✓ Improve safety and efficacy of current pipeline
✓ Diversify delivery and/or dosing options
✓ Create products that are acceptable, affordable and scalable
MZL Combination Topical Gel

Combines the anti-retroviral MIV-150 with Zinc Acetate and the hormonal contraceptive LNG (MZL)
- Carrageenan-based
- Coitally-dependent
- Appropriate for intermittent or emergency contraception
- Effective protection for ~24 hours

Scientific rationale:
- MZ carrageenan gel protects macaques against SHIV-RT infection
- Zinc-containing carrageenan gels block HSV-2 infection in mice
- LNG carrageenan gel raises LNG serum levels, disrupting ovulation

Thus, MZL carrageenan gel will likely prevent HIV, HSV-2, and conception
MZL Combination Vaginal Ring

Combines MIV-150 + Zinc Acetate + LNG in an intravaginal ring (IVR)

- EVA or polyurethane ring platform
- Coitally-independent
- Safe for sustained use
- Continuous protection for >1 month

Scientific Rationale:

- MIV-150 IVR provides significant protection in macaques from SHIV-RT
- Zinc acetate IVR releases zinc
- LNG IVR releases LNG
- MZL IVR will likely release all three APIs

Thus, MZL IVR would be expected to prevent HIV, HSV-2, and conception
Conclusion: first-generation MPTs

- The combinations of drugs and devices presented today could simultaneously prevent pregnancy, HIV and HSV-2

- Diversifying delivery and dosing options is key to expanding acceptability and use:
  - **SILCS+TFV gel** could meet the needs of women who want a non-hormonal contraceptive method that they control, especially for intermittent sex
  - The **MZL gel** could meet the needs of women who want a pericoital method that lasts up to 24 hrs
  - The **combination IVRs** (TFV+LNG, and MZL) could meet the needs of women who want a highly effective method that they don’t have to think about, and that provides continuous protection for 1-3 months

- By expanding the range of safe, effective and acceptable prevention options for women, we can help meet their sexual and reproductive health concerns as they change over time
Pathway from Product Development to Introduction:
A Focus on Regulatory Processes

MARTHA BRADY, M.S.
SENIOR ASSOCIATE, POPULATION COUNCIL

DAKAR, SENEGAL
DECEMBER 1, 2011
Who are the Regulators?
Key Regulatory Agencies

- EMA (European Medicines Agency)
- SRA (Stringent Regulatory Authority)
- NRA (National Regulatory Authority)
- US FDA (United States Food and Drug Administration)
- MHRA (Medicines and Healthcare products Regulatory Agency)
Combination Products

• A product comprised of two or more regulated components—any combination of a drug, device, and biological product—produced as a single entity.*

• Intended to address single indication.

*(Code of Fed Reg. 21 CFR 3.2 )

Multipurpose Prevention Products

(FDA has not published a definition)

• A single agent intended to address more than one indication.

• A combination product intended to address more than one indication.
What Goes Where at USFDA?
Designation and Division

- **Drugs**
  - CDER (Center for Drug Evaluation and Research)

- **Biologics**
  - CBER (Center for Biologic Evaluation and Research)

- **Device and radioactive therapy**
  - CDRH (Center for Devices and Radiological Health)

- **Combination products***
  - OCP (Office of Combination Products)

*In cases where the primary mode of action is not obvious or easily determined
## Application of Key Guidance Documents to MPTs

<table>
<thead>
<tr>
<th>Source of Guidance</th>
<th>Includes info on “combination products”?</th>
<th>Refers to both therapeutic and prevention products?</th>
<th>Includes info about multi-indication?</th>
<th>RH-related mentioned?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - CDER</td>
<td>YES</td>
<td>Therapeutic only</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>2 - OCP</td>
<td>YES</td>
<td>Therapeutic only</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>3 - EMA</td>
<td>YES</td>
<td><strong>Both</strong>: however prevention is only mentioned in dosage proposal</td>
<td><strong>YES, but only for “two closely related diseases such as hyperglycemia &amp; hypertension….”</strong></td>
<td>NO</td>
</tr>
</tbody>
</table>
Regulatory Challenges for MPTs

- MPTs do not fit into discrete category of drug, device, or biologics, though they may involve any or all of these.
- Applicability of existing guidance is unclear.
- Knowledge about safety and/or efficacy of one of the MPT components may be inadequate.
- Marketing, product positioning, labeling issues
Advancing the MPT Agenda: Challenge and Opportunity

The Challenge: Complexity in product development requires innovative approaches to trial designs, and guidance on regulatory requirements for development and licensure.

The Opportunity: Combination and/or multi-indication products represent cutting-edge science, a promising area for health improvements, possibly larger markets, and potentially cost-savings.
Multipurpose Prevention Technology Introduction: Planning for Success

Elizabeth Tolley
Behavioral & Social Science Research/FHI360
Session Outline

Aim is to highlight how geography, culture, health infrastructure and behavior may impact acceptability and use of MPTs:

1. Adolescent woman in Dar es Salaam, Tanzania
2. Young married couple in Pune, India
3. Female sex worker in Cotonou, Benin
Trends in HIV Prevalence

2010: A global view of HIV infection

33.3 million people [31.4–35.3 million] living with HIV, 2009

Source: UNAIDS
... and contraceptive use

<table>
<thead>
<tr>
<th></th>
<th>Tanzania DHS 2010</th>
<th>India NHFS 2006</th>
<th>Benin DHS 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Women married</td>
<td>48</td>
<td>75</td>
<td>69</td>
</tr>
<tr>
<td>Mean total fertility rate/woman</td>
<td>5.4</td>
<td>2.7</td>
<td>5.7</td>
</tr>
<tr>
<td>% Current modern contraceptive use:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condoms</td>
<td>23.6</td>
<td>48.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Oral pills or injectable contraception</td>
<td>4.2</td>
<td>5.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Female Sterilization</td>
<td>13.6</td>
<td>3.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Other</td>
<td>2.5</td>
<td>37.3</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>2.7</td>
<td>1.2</td>
</tr>
<tr>
<td>% with at least one STI/RTI in last 12 months</td>
<td>2.9</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>HIV prevalence (All women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women 15-19</td>
<td>6</td>
<td>0.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Women 20-24</td>
<td>1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>% 15-24 with 2+ partners in last 12 months</td>
<td>6</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>% aged 15-24 tested for HIV in last 12 months</td>
<td>24</td>
<td>3</td>
<td>16</td>
</tr>
</tbody>
</table>
Aziza is a 15 year old student. Her 1\textsuperscript{st} sexual experience was at age 13. Since then, she’s had 5 different partners – she broke up with the last one – and aborted the pregnancy, after she found out he had sex with his friend’s girlfriend.

On being an adult, she says: \textit{I am vulnerable to pregnancy, so I have to be very careful. Even AIDS, but mostly ... there is a risk of pregnancy and not AIDS. Because getting AIDS – even a child can get that.}

She adds, \textit{I have never used any method. And I even don’t need. I remember my aunt who has now become very thin – you can not believe it! She used the syringe; I don’t know if it is family planning.}

Aziza feels she and other girls could be ready to use a microbicide gel, because most girls these days have a tendency of having unprotected sex. However, she feels it is better to use oral pills because even if (my sister) finds me and asks ‘Sister, you are taking pills – are you sick? Yes I don’t feel well and am taking these medicines, these Panadol, so as at least I may feel better.
Multiple Risks, Barriers to Access and Use

- High risk for unplanned pregnancy, abortion, and STIs/HIV
- Relatively low use of contraception and disease prevention methods
  - Need to show “faithfulness” to partner prevents condom use
  - Fear of side effects prevents modern contraceptive use
- Low access to health services
  - VCT visit more common than other doctor’s visits
- Some preference for pill formulation
Married since 17, Manju is now 29 and has 2 daughters. Her husband is HIV+.

Thinking about microbicides, she says: *I feel that people in my situation that is if the husband has HIV and the wife does not have, then it will be beneficial to them.*

*if the woman has not done the operation and if she does not want to be pregnant she will prefer the one that prevents both HIV and pregnancy. And if a woman wants a child, she would want to use the one that prevents HIV but she can still become pregnant. So it depends from woman to woman.*

*I will have some tension. Actually..... I will come to know everything about this product, how to use it etc... doctors will tell everything about that.*

*But still, I will have some tension. When the copper-T was not well know, we heard that women have problems using it... but even then, women were not afraid to put it in, ... though they have some fear in their minds, they also have some daring...*
Facilitating Protection

- Low perception of risk for HIV
- RTI/STI symptoms fairly common, but not always treated
- Contraceptive use accepted, but temporary methods less commonly used
- Husband’s/family’s approval important
- Health care access relatively high, especially related to pregnancy
- Vaginal ring – contraceptive or non-contraceptive, with RTI and/or HIV protection
Case 3: Ayoola, a FSW in Cotonou

In her early 30s, Ayoola lives and works in a brothel in Cotonou. Her family lives in the north of the country; she sees them occasionally and takes them gifts.

I’m happy to have used the gel because earlier, in the past, I used to get infections often. But ever since I started using the gel, I no longer got infections. For example, after two sex acts I would notice I had abdominal pains ... But when I started using the gel, after two months, all those problems had disappeared. That’s why I liked the gel.

With her clients, using both condoms and gel is the best.

But my lover, with him, I can say that I started to use the gel, but he didn’t like it because he was worried that I would prostitute myself....
Enhancing Protection

- High perceived risk for HIV/STIs and pregnancy
- High use of condoms (particularly with clients)
- Non-condom contraceptive use low, in part due to low access to contraceptive methods
- Access to STI/VCT clinics
- Adherence to prevention methods challenged by daily routine
- Daily gel with condoms provide increased protection
Implications

• Despite risky sexual practices, women’s (and men’s) risk perceptions may remain low
• PrEP messages should be compatible with local concepts of “faithfulness” and “trust”
• Different geographic and cultural contexts will require different strategies
  – Among sex workers or other groups with identifiable risk, combination prevention messages may be needed that include continued condom use
  – In contexts with high stigma and low risk perception, thoughtful consideration of appropriate channels and linkages are needed
References for Case Studies


2. Tolley: 5 R01 MH086160-02 - Adolescents Women And Microbicide Trials: Assessing The Opportunities And Challenges Of Participation.

3. Tolley, Elizabeth; Eng, Eugenia; Kohli, Rewa; Bentley, Margaret; Mehendale, Sanjay; Bunce, Arwen; Severy, Lawrence. “Examining the context of microbicide acceptability among married women and men in India.” Culture, Health & Sexuality, July-August 2006;8 (4):351-369.