Meeting Report

IMPT Scientific Advisory Working Group (SAWG)
Sub-Working Group on Sexually Transmitted Infections (STIs)
19 February 2014

- UNINTENDED PREGNANCY
- HIV
- MPTs
- OTHER STIs
The Initiative for Multipurpose Prevention Technologies (IMPT) is a global collaborative partnership to advance the development and introduction of products that simultaneously address multiple sexual and reproductive health needs, namely unintended pregnancy and sexually transmitted infections (STIs), including HIV. Established in 2009, the IMPT has engaged product developers, scientific researchers, health care providers, funders and community-based advocates in Africa, China, India, the United States and Western Europe behind this common agenda. The IMPT Secretariat is housed at CAMI Health, a project of the Public Health Institute, Oakland, CA, USA.

Multipurpose prevention technologies (MPTs) for reproductive health are products that combine protection against unintended pregnancy and STIs, including HIV. The vision for MPTs is a suite of accessible products that are woman-initiated, efficient and easy to use. Safe and effective MPTs that are also acceptable, affordable, and made widely available would greatly improve health and save resources across the globe.

This report was prepared by Elizabeth McGrory (Consultant to CAMI Health), in collaboration with Bethany Young Holt (CAMI Health).

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For questions or comments, please contact: cami@cami-health.org.
Background

This report summarizes the discussions and next steps from the meeting of the IMPT SAWG sub-working group on STIs. The meeting, held on February 19, 2014 in Washington, D.C., had three main goals: 1) review the STI Product Prioritization process and outcomes to date; 2) confirm the priorities and goals for the STI sub-working group; and 3) outline the operating processes for the group. The group also worked to identify and prioritize next steps, including expanding the range of expertise and perspectives involved. The review of the STI Product Prioritization process is captured in that table, while this summary focuses on other aspects of the discussions.

Product Leads/Active Pharmaceutical Ingredients (APIs)

Limited interest from HIV and family planning communities and donors, as well as few known current product leads for Multipurpose Prevention Technologies (MPTs) addressing STI indications other than HIV or HSV-2, present a significant challenge for moving this category of prevention products forward. Given the limited number and range of product leads to work with, basic research remains a priority.

Creative approaches are needed to identify potential APIs, and several were discussed.

• It is important to first differentiate between bacterial and viral STIs.

• There may be companies with potential leads left “on the shelf” because they were not commercially viable. Most product development focuses on treatment rather than prevention, so exploring this area should start with companies that work on STI treatment. Antibiotics used to treat bacterial STIs are not likely to be appropriate for prevention due to concerns about resistance.

• What limited interest big Pharma has shown in STI treatment is for viral STIs (GlaxoSmithKline [GSK]). The group agreed to follow up on whether topical acyclovir has been evaluated by GSK for herpes treatment as prevention, and whether there are data on using acyclovir for prevention in people who are HSV negative.

• While there is now a reasonably good pipeline of potential products to prevent HSV-2, leads for all the other STIs fall much further behind. Developing or identifying APIs for other STIs is a priority.

• Similar to the broader IMPT initiative, the STI sub-working group recognizes that topical on-demand use of hormones for contraception presents serious challenges and should not be considered as the key contraceptive option for MPTs with STI indications.

• Barrier methods could be explored, particularly to prevent gonorrhea and chlamydia.

• It may be worthwhile to reconsider Buffergel by re-examining the data from the contraceptive trial where it was delivered with a diaphragm (Duet).

• The California Family Health Council suggested re-examining several products that were not effective for contraception, but may be effective against chlamydia.
• Recombinant proteins face a number of challenges including cost and relatively high risk of development. However, given the paucity of potential APIs for many STIs, this class should be examined again in light of their suitability for STIs.

• The sub-group began to consider how best to categorize a product that would prevent bacterial vaginosis (BV) and whether it could be considered an MPT. Given that BV plays such a large role in potentiating other STIs, some felt that a product to prevent BV could be categorized as an MPT while others felt it should be categorized separately. It would be useful to continue this debate and to articulate the important role that reducing the burden of BV could play in reducing the risk of STI acquisition.

• Nearly all the product leads and APIs are from U.S.-based research groups or companies, and active outreach is needed to identify possible product leads in other settings: Europe, Brazil, India, China, or elsewhere. The group mapped out an approach to do so, including identifying key informants, and possibly diversifying membership in the STI sub-group (see below).

• Given the limited number and range of product leads to work with, basic research remains a priority.

**Product presentations and formulation**

Several considerations were raised related to product presentations and formulation for MPTs for STIs.

**Rings**

• Rings need to be examined for how well they can deliver API targeting different STI pathogens. Rings are more likely to work to prevent chlamydia and Nesseria gonorrhoea which infect at the cervix, and are less likely to effectively prevent HSV-2.

• A clear research gap is an animal model for vaginal rings for HSV-2. Rings have been evaluated in pigtailed macaques for HIV, which is also the animal model for chlamydia. While guinea pigs are currently the model for HSV, there may be a need for a non-human primate model for HSV.

• A priority is to evaluate ring delivery for APIs targeting STIs that are at high risk for transmission in the cervical area (e.g. Nesseria gonorrhoea and chlamydia for which target cells are in the endocervix). However, at this time there are no candidate APIs to put in the rings targeting these STIs.

• Several candidate MPT rings incorporating contraception rely on levonorgestrel (Lng) although it is unclear how well rings can deliver Lng. The MPT field needs a careful analysis and demonstration of what types of rings of different design and materials can successfully deliver Lng, but also other potential hormonal contraceptives.

• Several of the rings under development as MPTs are quite complex in design and production. Costing and feasibility need to be carefully analyzed and used to inform product prioritization.

• MPT rings, including those targeting STIs, need clear plans for clinical development and licensure that specify a regulatory strategy (see below).
Film

In general, films are seen as a very promising approach to delivering MPTs for STI.

- One of the advantages offered by new films for MPTs is that 2 separate films can be cast with different APIs and then combined. This means that co-formulation options may be easier to address than with gels.

- Acceptability and market data are needed for film.

Bioadhesive polymers

Research in bioadhesive polymers is promising and important to move forward, especially for STI MPTs.

- One example, a novel bioadhesive polymer, is a two-drug carrier that delivers the API to the mucosal surface and could function with any combination of drugs. The components are kept separate until combined when applied. Because the APIs remain separate, they are much more stable until they are combined when applied.

- Testing to date has shown that the bioadhesive polymer coats well and forms a film. It may have less leakage than with gel formulations, so it may be more acceptable to users.

Regulatory Considerations

Echoing the broader IMPT effort, there is ongoing concern about regulatory pathways for some of the product leads containing multiple APIs, especially those where none of the APIs are already licensed. Not all the product leads have a clear clinical development plan that addresses two or more indications (such as pregnancy, HIV, and HSV-2) and it will be important to ascertain how each product will be moved forward. A number of specific questions and issues related to the clinical development plan should be addressed as part of the product prioritization.

- How will the different indications be prioritized? Will the APIs be studied for efficacy in sequence? Could the different trials be done to study efficacy at the same time? Would these studies be done in different populations?

- Relying on bioequivalence between a gel and a ring, film, or other drug delivery approach may be a high-risk strategy. Drugs may need to be distributed to the site of infection and that distribution may be quite different for gels, rings, films, etc. For example, a ring lodged against the cervix would likely need a strong, sustained release rate to make the API available at the site of herpes infection. Even if the biodynamics are similar, the group thought that the FDA’s concern would likely center around dosing and drug availability at the site of infection.

Cost

- Several of the rings under development utilize experimental and sometimes complex structures and production processes. Developers and funders need to ensure that the feasibility and cost of manufacturing different rings is a central component of a product’s development plan from the start.
The cost, complexity, and feasibility of ring production and cost must be considered at an early stage as a key factor in priority setting.

- STI MPT products may find a substantial market in the United States and Europe, meaning that “affordability” and willingness to pay may differ from products aimed mainly at developing country users (like those targeting HIV and unintended pregnancy prevention).

**Implications of Limited Data**

- Work on STI MPTs, and STIs overall, is hampered by the lack of data on STI prevalence and incidence in most of the world. It is difficult to generate interest or make an investment case without robust data on the burden of disease.

- WHO is updating its figures on STIs worldwide for the first time in a decade, and it is telling that these figures are not based on surveillance data, but also rely on literature reviews and extrapolation from specific studies where data is limited. Resource-poor settings where HIV and unintended pregnancies are high often lack adequate data on STIs.

- Unlike HIV and unintended pregnancy incidence, STIs are a global problem. Advocacy for strengthening surveillance on STIs should therefore be a clear priority for the Initiative. Messaging should reinforce that the absence of data should not be construed as an absence of STIs, but rather that the data that are available are “the tip of the iceberg” and suggest a massive and world-wide problem.

- Institutionally, there remains less interest and understanding of STIs among key global health agencies in comparison to their interest in HIV or family planning. This has been a result of the siloed approach for both HIV and reproductive health issues, which has left STIs other than HIV not addressed by one group or the other.

- It is important to underscore that successes with HIV programs will be dimmed over the long-term if other STIs are not addressed.

**Diversifying the STI Sub-group and database of product leads**

Recognizing that both the product database and the composition of the sub-group is primarily U.S.-based, the meeting participants discussed and identified several strategies for drawing in a more diverse set of expertise and perspectives, as well as some specific next steps.

- The main priority is to draw in individuals with a clear understanding of the field, including potential product leads and the implications of incomplete data. Recognizing that it can be difficult to engage people to work on an ongoing basis, some people will be asked for technical input on specific issues on a one time or ad hoc basis.
  
  - Over the next three months, identify key people who can help identify possible product leads, especially in China, India, South America (Brazil), Japan, Australia, and Europe.
• Carolyn Deal (NIAID) can send out an email to initiate contact, and Jon Glock (NIAID) can help coordinate input on products. Identify others to follow up through email or phone contact.

• Manjula LUSTI-Narasimhan (WHO) will follow up with the WHO STI Expert Working Group which has a meeting scheduled end-August 2014 in Geneva. A list of possible STI experts will be shared with the IMPT.

• Once these leads have been added to the existing database, identify experts to advise on the need for different products and product types from a public health perspective.

• Reach out to professional associations for other experts and/or sources for product leads, including: PAHO and IUSTI (which sponsors the ISSTDR) internationally, and ASTDA and ASHA in the US.

**Communications and Advocacy**

• Communications and advocacy are critical to bring attention to a number of pressing public health concerns related to STIs: the urgent need to strengthen surveillance on STIs, the potential for STIs to undermine progress on combatting HIV, the threat of drug-resistant gonorrhea, and so forth.

• The IMPT should develop a “one pager” summarizing key issues related to MPTs focused on STIs. Bethany Young Holt (CAMI Health) suggested that the communications and advocacy group could possibly take this on and that such a document could provide an opportunity to highlight the potential for MPTs in the United States and Europe as well as global needs.

• The IMPT will also follow up with the communications and advocacy group to encourage the group to build STIs into its broader messaging work.

• Manjula LUSTI-Narasimhan noted that the BJOG: An International Journal on Obstetrics and Gynaecology supplement on MPTs does not yet include anything specific on STIs. The group brainstormed possible authors who could be invited to submit a commentary. Carolyn Deal and Jon Glock would be logical candidates, but cannot author a commentary without clearance from NIH, which has a long lead time. Other ideas include: Jeanne Marrazzo (University of Washington), Brad Stoner (Washington University in St. Louis), or possibly the president of the IUSTI.

• Craig Cohen (UCSF) has spoken with Manjula LUSTI-Narasimhan, Bethany Young Holt, Anke Hemmerling (UCSF/ CAMI Health), and Joe Romano (NWJ Group/ CAMI Health) about putting together a panel on MPTs with an STI focus at the Brisbane ISSTDR meeting in 2015. This meeting is a good opportunity to reach out to STI experts. Regional IUSTI meetings are another good setting for advocacy and generating new ideas and participants.

**Other Key Issues**

• IMPT and the field of MPTs and microbicides will continue to grapple with how best to use market data to build go/no go decisions into product prioritization. The STI sub-group may need to consider different factors given the potentially different market dynamics for these products (see above).
• Big Pharma has demonstrated interest in a vaccine for HSV and for chlamydia prevention. It would be useful to explore potential market interest in some of the large companies for these and other indications.

• There is a need for ongoing discussion and debate to map out clinical trial designs for MPTs, including those for STIs. While trial designs will likely need to be determined on a product by product basis, it may be timely to develop a fact sheet or other material on trial design to begin engaging regulators, communities, and others in shaping and understanding these how clinical evaluation of MPTs will proceed.

• There is currently no good animal model for gonorrhea, so testing moves from the laboratory right to humans.

**Summary of Priority Gaps**

• Lack of reliable data on STI prevalence and incidence hampers work in this area, and advocacy for strengthening surveillance on STIs is a clear priority. Advocacy can reinforce the potential for STIs to undermine progress on combatting HIV and the threat posed by resistant gonorrhea.

• The current pipeline includes tenofovir gel that targets HSV-2, but developing or identifying active compounds for preventing other STIs is a priority.

• Basic research to supplement the limited number and range of product leads.

• Product leads and APIs are largely from U.S. researchers and companies, and active outreach is needed to identify potential leads and APIs in Europe, Brazil, India, China, and elsewhere.

• An animal model for vaginal rings for HSV-2. Rings have been evaluated in pigtailed macaques for HIV, which is also the animal model for chlamydia. While guinea pigs are currently the model for HSV, there may be a need for a non-human primate model for HSV.

• An animal model is also needed for gonorrhea to prioritize which candidate products to move to clinical testing.

• While rings have potential against STIs that mainly target transmission in the cervical area, there are no candidate APIs targeting these STIs to put in the rings.

• Clear evidence and demonstration that rings of different design and materials can successfully deliver levonogestrel.

• Costing and feasibility analyses for different ring designs to inform product prioritization.

• Clear clinical development plans and regulatory strategies for products under development, including the degree to which the FDA will accept bioequivalence data from gels to rings.

• Market assessments for different indications and presentations in the U.S. and Europe to inform product prioritization and cost considerations.
• Acceptability and market data for film.

**Action items**

• Include key conclusions and priority gaps related to MPTs for STIs in broader IMPT scientific agenda currently being updated.

• Expand product database:
  
  • Over the next three months, identify key people who can help identify possible product leads, especially in China, India, South America (Brazil), Japan, Australia, and Europe.

  • Carolyn can send out an email to initiate contact, and Jon can help coordinate input on products. Identify others to follow up through email or phone contact.

  • Once these leads have been added to the existing database, identify experts to advise on the feasibility and need for different products and product types from a public health perspective.

  • Reach out to professional associations for other experts and/or sources for product leads, including: PAHO and IUSTI (which sponsors the ISSTDR) internationally, and ASTDA and ASHA in the US.

  • Reconvene and review towards end of the year.

  • Manjula will follow up with the WHO STI Expert Working Group which has a meeting scheduled end-August 2014 in Geneva. A list of possible STI experts will be shared with the IMPT.

  • Working with the communications and advocacy group, IMPT to develop a “one pager” summarizing key issues related to MPTs focused on STIs. Consider highlighting the potential for MPTs in the U.S. and Europe as well as global needs.

• Encourage communications and advocacy groups to build STIs into its broader messaging work.

• Follow up with potential authors (Jeanne Marrazzo, Brad Stoner, president of the IUSTI) to write a commentary on STIs for BJOG supplement.

• Manjula follow up on putting together a panel on MPTs with an STI focus at the Brisbane ISSTDR meeting.

• Explore regional IUSTI meetings for advocacy and generating new ideas and participants.

• Follow up on whether topical acyclovir has been evaluated by GSK for herpes treatment as prevention, and whether there are data on using acyclovir for prevention in people who are HSV negative.