Technical Meeting on Hormonal Contraception (HC) in MPTs

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IMPT for Reproductive Health

The **Initiative for Multipurpose Prevention Technologies (IMPT)** is a product neutral, global collaboration that advances the development of MPTs to address the interlinked risks of unintended pregnancy and sexually transmitted infections (STIs), including HIV. Comprised of members from across disciplines and more than 15 countries, the IMPT is the central body that researchers, product developers, funders, policymakers, and advocates rely on for objective technical guidance and strategic planning related to MPTs.

Multipurpose prevention technologies (MPTs) are an innovative class of products that deliver varied combinations of HIV prevention, other STI prevention, and contraception and will improve the lives of women and families worldwide. The vision for **MPTs** is an array 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.

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The Initiative for Multipurpose Prevention Technologies (IMPT) is a project of CAMI Health, an organization dedicated to women's reproductive health and empowerment. CAMI Health is housed at the Public Health Institute (PHI).

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Background

In 2015, the IMPT Secretariat conducted a survey among MPT experts to identify the most urgent research gaps for field-wide follow up, during which work on hormonal contraception (HC) in MPTs was identified as a priority. Through two stakeholder meetings held with the Contraceptive Clinical Trials Network (CCTN) and a prioritization survey specifically on HC-related issues, the IMPT has identified many challenges critical to advancing work on combining HC and antiretroviral drugs (ARVs) in MPTs and issued recommendations around next steps in this field of research. These challenges focused on four areas: HC and HIV susceptibility; dosing of HC in combination with an ARV; topical effects and drug-drug-interactions (DDIs); and biological and social-behavioral aspects of MPT development.

Meeting Objectives

With support from the United States Agency for International Development (USAID), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), and the Bill & Melinda Gates Foundation, the IMPT organized this one-day technical meeting that brought together experts and supporters of the CCTN, MPT developers, and other stakeholders to plan the next steps in operationalizing the recommendations from previous HC in MPTs meetings. Specific meeting objectives included:

1. Review and update previously identified **research priorities** for the field, key considerations for these priorities including: their importance for progress, urgency, and feasibility.

2. Identify and prioritize **data and knowledge gaps** that are relevant to HC in MPTs for further investigation.

3. Outline potential **challenges and strategies** to address the identified priorities and ensure maximum impact of contraceptive MPTs.

This meeting was held in conjunction with an IMPT Clinical Trial Evaluation Workshop for MPTs, the report from which is available on the IMPT website.

Main Research Gaps

Through presentations and discussions, the meeting participants identified several key research gaps related to HC in MPTs. Many of these issues were also discussed and prioritized for action during the subsequent IMPT Clinical Trial Evaluation Workshop for MPTs.

1. Target Population and User Preferences

- The target population of adolescent girls and young women (AGYW) with high HIV incidence, generally those aged 15-24, has the greatest potential for impact of a contraceptive/HIV prevention MPT. It is important to characterize this target population more specifically in different geographical contexts.

- Market assessment tools and design thinking approaches that engage end users are needed to identify and assess desirable product characteristics, user practices, acceptable side effects, and acceptable bleeding patterns in different priority user groups. It is important to draw on experience and knowledge from related fields, including microbicide and oral pre-exposure prophylaxis (PrEP) research as well as contraceptive introduction, to understand the dynamics of product use, including low adherence in some clinical studies. User perspectives from these and other areas should be incorporated into the MPT drug development process at an early stage.

- Effective messaging is and will remain important in ensuring uptake and use of MPTs, and to enhance provider and end-user comfort with these new and unfamiliar technologies. The contraceptive component of MPTs could increase the overall appeal of the product to end users and help to minimize the stigma often associated with HIV prevention.

2. Selecting Active Pharmaceutical Ingredients (APIs)

- A number of possible combinations for contraceptive/HIV prevention MPTs were reviewed and discussed, along with some of the implications for commercialization, including regulatory review and manufacturing.

- Although the use of HC for MPTs was given priority, both hormonal and non-hormonal approaches should be explored as possible components for MPTs.

    - <u>Hormonal Contraceptives (HCs)</u>:

        - Levonorgestrel (LNG) is the current contraceptive component of the HC/ARV IVRs being developed by the International Partnership for Microbicides and CONRAD. Given some of the limitations of LNG (see below), many experts have recommended that the field also explore other progestins, such as etonogestrel, nesterone, or desogestrel.

- One challenge associated with combining HC and ARVs is that for oral pills and vaginal rings, a monthly pause is typically built into HC use to allow for breakthrough bleeding and to decrease intermittent spotting (i.e., cyclical use), while HIV prevention using currently available ARVs would likely need to be uninterrupted to ensure continuous protection. Considering this discrepancy, acceptable regimens for cyclical or continuous HC use in MPTs need to be determined among different possible options, such as continuous use for 28 days, use for 21 days with a regular seven-day pause (i.e., 21/7), or shortening the pause to four or even two days (i.e., 24/4 or 26/2) to allow for withdrawal bleeding while keeping the vulnerability window for HIV infection as short as possible because of low ARV drug levels. Here, "acceptable" refers to: (1) maintaining protective ARV levels for HIV prevention during non-use term, and (2) ensuring acceptability among end users in target populations.

- The unpredictable bleeding patterns associated with progestin-only contraception may be mitigated by combining use of progestins with estrogen such as ethinylestradiol or estradiol. However, these combinations may lead to more side effects such as deep-vein thrombosis (DVT), and represent a more complicated formulation challenge.

  - Non-hormonal contraceptives:

    - Given the potential challenges associated with HC in MPTs, some of which are described above, it would be useful to explore the technical feasibility, as well as the acceptability and potential demand, for non-hormonal contraceptive approaches that could be incorporated into MPTs. These could include, for example, a copper intrauterine device (IUD) capable of ARV delivery, or new spermicides. However, the feasibility and timelines of such options could present potential challenges.

- Additional ARVs that are suitable for use in MPTs, which could be used either systemically or locally, need to be identified. Especially urgent is the need for access to highly potent ARVs (e.g., tenofovir alafenamide, or TAF), or ARVs with long *in vivo* half-life for long-acting MPTs and MPTs that have a "forgiveness" potential for periods of non-use.

- Regulatory complexities increase with the number of APIs combined in a single co-formulated product.

- Drug release and manufacturing complexities increase when APIs of different chemical properties (e.g., hydrophobic/hydrophilic) are combined in a single product.

3. Selecting a Target Dose for HC

- Identifying the appropriate dose of hormonal contraceptives in MPTs will require balancing the required high level of efficacy while using the lowest possible dose of hormones to minimize unacceptable side effects.

- Identifying the target dose of HC in MPTs is complicated by the fact that the threshold, or transition zone, for HC blood serum levels needed for contraceptive efficacy is still undetermined for many HCs.

- Dosing of HC is further complicated by emerging data suggesting that women with a higher body mass index (BMI) may require higher dose levels of HC than contained in current standard medications.

- HC delivered systemically or topically may have different mechanisms of action (MoA) and consequently, different target dose levels are needed for each drug delivery pathway. While systemic HCs generally prevent pregnancies through hormone levels that are high enough to completely suppress ovulation, vaginally administered lower-dose HCs are known to work without achieving ovulation suppression. However, details about how local MoAs effectively prevent pregnancy using IUDs and intravaginal rings (IVRs) remain unclear and are important to characterize (e.g., changes in endometrium and cervical mucus creating unfavorable conditions for implantation).

4. Pharmacokinetics (PK) and Drug-Drug Interactions (DDIs)

- Shared metabolic pathways for concurrently administered APIs may lead to DDIs and consequently accelerate or prolong the elimination of drugs from the user's system. This can result in systemic drug levels that are either too low to be effective or high enough to be toxic.

- There is still much to learn about how, what, where, and when to measure for reliable PK and DDI data when combining ARVs and HCs. Issues and questions that emerged include:

    - Should measurements be based on samples of plasma, cervicovaginal fluid, cervical or endometrial tissue, or cervical mucus?

    - How can variability in sampling be implemented to ensure valid measures? For example, the time point of sample collection during the menstrual cycle leads to different results for hormone levels.

    - Markers for contraceptive efficacy are still based on methods that have been used for decades, mainly whether pregnancy occurred. New, validated surrogate markers for contraceptive efficacy are needed to measure:

- Changes in cervical mucus, including mucus quality, sperm penetration, and concentration of HC delivered to the cervix.

- Inhibition of ovulation, including the concentration of HC in serum, serum progesterone levels, and whether oocyte maturation is disrupted.

- Alteration of the endometrium to prevent implantation of a fertilized egg, facilitated by changes in histology and immunohistochemistry.

- To avoid redundant and expensive PK measurements in clinical studies, preclinical animal and *in vitro* studies for vaginal PK need to be developed for various HCs and correlated with *in vivo* human performance.

5. Susceptibility to HIV Acquisition

The influence of HC on women's susceptibility to HIV acquisition is the topic of much debate in the global public health arena. It has potentially significant implications for MPTs, which seek to protect women from HIV and pregnancy using HC and ARVs. ECHO, a large, open-label clinical trial, is underway to examine the effects of three different highly active reversible contraceptives (i.e., DMPA injectable, Jadelle LNG-containing implant, and Copper T IUD) on HIV acquisition. It will be critical to continue research on HIV risk to determine:

- How progestins affect susceptibility to vaginal HIV acquisition.

    - Recent findings suggest that the cervicocvaginal microbiome is more complex and new measurements beyond standard STI testing and inflammatory profiles need to be included in future research.

    - Although in anatomical close proximity, the endometrium and endocervix are different tissues and may consequently differ in their immune composition, drug absorption capacities, and tissue response to progestins.

6. Developing a Regulatory Pathway to Meet FDA Requirements

- Given the complexity of developing, testing, licensing, manufacturing, and marketing new products, the most efficient and quickest approach to delivering MPTs would be to co-package products for HIV prevention and contraception that have already been approved. Regulatory processes will be longer and less certain for products that contain co-formulations of approved APIs or approved and experimental APIs.

- The MPT field as a whole, including individual developers and investigators, needs to remain disciplined in identifying and prioritizing data gaps for each product (e.g., safety, efficacy, and toxicity). This will ensure that resources are focused on research that is critical to meeting

regulatory requirements, rather than research that pursues answers to questions with scientific merit but no immediate contribution to advancing a product along the regulatory pathway.

7. Manufacturing and Commercialization

The manufacturing and commercialization potential of products must be key factors in determining which products advance and attract from a limited quantity of available resources. It is important to assess cost of goods, cost effectiveness, and feasibility of scaled-up production early on in MPT development. MPTs will likely need to have commercial potential to attract commercialization partners. This may include cross-subsidization, whereby profits in European and American markets can support reduced priced products in lower-resource settings. This topic was explored in more depth at the Clinical Trial Evaluation Workshop for MPTs, and more details can be found in the relevant meeting report.

Next Steps

Although much of the meeting was spent outlining priority research gaps, there was some discussion around actionable next steps for these gaps, which carried over into the IMPT Clinical Trial Evaluation Workshop for MPTs. These next steps include:

- Commission analyses, including demand and impact modelling, to characterize the **priority target populations** for contraceptive/HIV prevention MPTs. These analyses should draw on epidemiological information; existing research and experience with contraception, PrEP for AGYW, microbicide clinical trials, and microbicide market introduction; and other relevant areas.

- Examine **microbicide and PrEP research among priority target populations, prior experience with introduction of new contraceptives**, and other related work for insights that can be applied to MPT product development through design thinking and other approaches. This review should be conducted by a small expert group or commission.

- Encourage supporting agencies funding contraceptive, ARV, and MPT research to **create new or expand existing funding mechanisms** to specifically call for HC other than LNG-only approaches and for highly effective ARVs suitable for topical use or long acting devices.

- Urge existing networks of contraceptive researchers, such as the CCTN, to **include selected research questions** on systemic/local HC target dose levels for normal weight and obese women, as well as on topical MoA characterization into their ongoing work.

- Leverage resources of existing contraceptive, HIV, and microbicide research networks to support these specific issues by **nesting sample collection and analysis into existing larger clinical studies**.

- Integrate preclinical work developing PK models into the scope of responsive research in existing funding mechanisms and related RFAs.

- Develop, in partnership with MPT developers, a **specific regulatory strategy** for each of the MPTs in development, including target product profiles, necessary toxicity studies, and clinical development plans with clear timelines, milestones, and go/no-go decisions.

Conclusion

Time and resources are limited for developing and bringing effective MPTs to women in need. While it is important to maintain a robust and diverse product development pipeline for early-stage MPT candidates, the field needs to focus on ensuring that the best product candidates are tested in the costly and limited opportunities that exist for clinical trials. This process requires the ongoing collaboration of funders, developers, behavioral scientists, market assessment professionals, and manufacturing experts. These stakeholders must continue to engage in an objective evaluation of research opportunities, challenges, and gaps in order to agree on research priorities for the MPT field.

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List of Acronyms & Abbreviations

AGYW – Adolescent Girls and Young Women
API – Active Pharmaceutical Ingredient
ARV – Antiretroviral
CCTN – Contraceptive Clinical Trials Network
DDI – Drug-Drug-Interaction
DMPA – Depot Medroxyprogesterone Acetate
DVT – Deep-Vein Thrombosis
FDA – U.S. Food and Drug Administration
HC – Hormonal Contraceptives / Hormonal Contraception
HIV – Human Immunodeficiency Virus
IMPT – Initiative for Multipurpose Prevention Technologies
IPM – International Partnership for Microbicides
IUD – Intrauterine Device
IVR – Intravaginal Ring
LNG – Levonorgestrel
MoA – Mechanisms of Action
MPTs – Multipurpose Prevention Technologies
NIAID – National Institutes of Health – National Institute of Allergy and Infectious Diseases
NICHD – *Eunice Kennedy Shriver* National Institute for Child Health & Human Development
NIH OAR – National Institutes of Health – Office of AIDS Research
PK – Pharmacokinetics
PrEP – Pre-Exposure Prophylaxis
STI – Sexually Transmitted Infection
TAF – Tenofovir Alafenamide
USAID – United States Agency for International Development

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