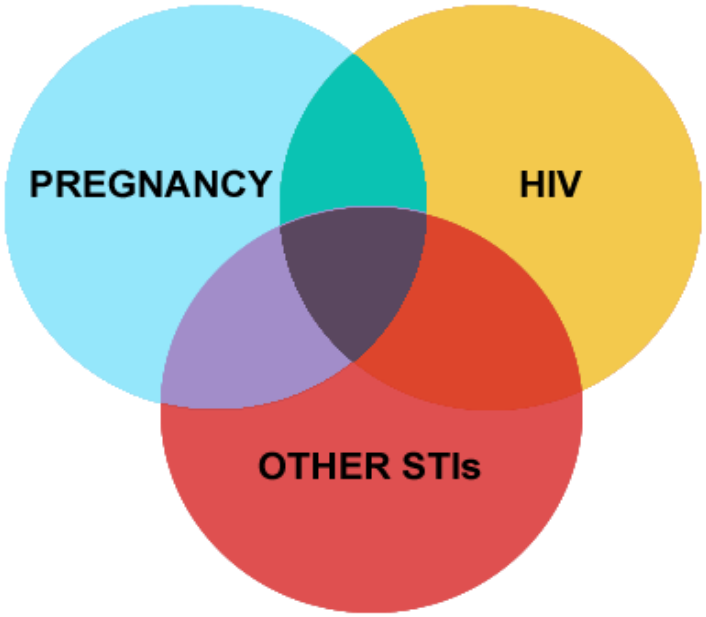

MULTIPURPOSE PREVENTION TECHNOLOGIES FOR REPRODUCTIVE HEALTH

Advancing the Scientific and Product Development Agenda

Report of a "Think Tank"
Washington, DC, USA
5 May 2011

USAID FROM THE AMERICAN PEOPLE
AVAC Global Advocacy for HIV Prevention
CAMI COALITION ADVANCING MULTIPURPOSE INNOVATIONS
MARY WOHLFORD FOUNDATION

The **Mission** of the Initiative for Multipurpose Prevention Technologies (IMPT) is to raise awareness about and support for the development of multipurpose prevention technologies (MPTs) that can simultaneously address multiple sexual and reproductive health (SRH) needs, specifically unintended pregnancy; sexually transmitted infections (STIs), including HIV; and other reproductive tract infections.

The **Vision** of the IMPT is that those MPTs with highest impact potential are advanced with maximum efficiency and speed, through an integrated development program comprising pre-clinical investigation, translational research, clinical testing, regulatory approval, scale-up, public readiness, and product evaluation. Toward realization of that vision, the IMPT aims to:

- Mobilize financial, scientific, and political resources to support all phases of MPT development
- Motivate synergy and cooperation across scientific disciplines that will help facilitate the sorts of collaborations that can expedite product development and implementation
- Build a cross-sectoral advocacy strategy and cadre of champions for these technologies.

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An electronic version of this document is available at www.cami-health.org. Other organizations that support the Initiative can post this document on their websites as well. For questions or comments, please contact: cami@cami-health.org.

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Purpose of the "Think Tank"

On May 5, 2011, the US Agency for International Development (USAID), Coalition Advancing Multipurpose Innovations (CAMI), and Global Advocacy for HIV Prevention (AVAC) convened a small group of scientists with expertise in contraception, HIV and STI prevention, vaccines, and devices to discuss and recommend practical strategies for accelerating the development of multipurpose prevention technologies (MPTs) for simultaneous protection against unintended pregnancy, HIV, and other sexually-transmitted infections (STIs).

Meeting Objectives

1. Review some of the ideal characteristics of MPTs for different target populations identified as most likely to benefit from such products.
2. Consider the pipeline of relevant technologies, advise on the steps required for their advancement, and identify further research needs and obstacles.

Define a clear agenda for MPT research and development (R&D) that would provide both the scientific rationale for their accelerated development as well as concrete information for developers, scientists, funders and advocates as to how they could support and further MPT R&D.

Core Definitions

- **Multipurpose prevention technologies** are understood for the purposes of this initiative as strategies that propose at least two health indications (unintended pregnancy; HIV/other STI; RTI). MPTs may include available methodologies; capitalize on emerging technologies or development of new strategies, therapeutic products, vaccines, or devices; and/or drug-delivery systems with potential for enhancing the safety, activity, and potential uptake of these products.
- A **Target Product Profile (TPP)** is both a description of how a proposed candidate product addresses critical attributes, and a proposed framework for its development.

Participant Representation

- Participating USG agencies (besides USAID) included: the FDA Center for Drug Evaluation and Research; and several branches of NIH: the NICHD Contraception and Reproductive Health Branch; the NIAID Division of AIDS and Division of Microbiology and Infectious Diseases; and the National Cancer Institute.
- Participating businesses, foundations, universities and organizations (besides AVAC and CAMI) included: the Association of Reproductive Health Professionals; Dartmouth Medical School; the Bill & Melinda Gates Foundation; Gilead Sciences; the Guttmacher Institute; the Kenya Medical Research Institute; Magee Women's Hospital/University of Pittsburgh; Medsa Ltd.; Mapp Biopharmaceutical; Osel Inc.; the Public Health Institute; and USAID implementing partners CONRAD, FHI360, IPM, PATH, and the Population Council.

Summary of Key Points from the Presentations and Discussions

Introduction

- MPTs are promising in their potential to enable women to simultaneously address multiple reproductive health risks and needs.

- The Initiative for Multipurpose Prevention Technologies (IMPT) is housed at CAMI, which serves as the convener of multidisciplinary meetings and provider of MPT outreach, education, and resource mobilization.
- A framework for MPT development priorities must be devised that weighs candidate products according to avertable risk and highest impact across a range of criteria.
- MPT development cannot be donor-driven for extended periods of time, and must take into account market potential to attract the private sector.

MPT microbicides and devices in the clinical pipeline

A number of promising drugs, dosage forms, devices, and platform technologies already exist as the basis for new MPTs. Issues offering particular challenges to such development are:

- Intravaginal dissolution time of films and tablets
- Tissue concentrations and duration of protection after administration
- Influence of endogenous and exogenous hormones and concurrent vaginal infections on HIV acquisition
- The focus of MPT research and development must be on product candidates that are realistically achievable, and promise high impact and utility in identified target populations.
- Prioritizing is crucial to identify requirements for additional knowledge, mobilize existing expertise, and facilitate productive and coordinated relationships among pertinent research efforts.

Multipurpose vaccines

- The vaccine field has long been using multipurpose vaccines that combine several agents for multiple indications.
- Work on new vaccines is in various stages of research, from basic (e.g., chlamydia, gonorrhea, herpes, syphilis), to advanced (e.g., second-generation HPV vaccines).
- Understanding of mucosal immunity, response measures, and immune tolerance or potentiation remains essential research for all vaccine development.
- Vaccine delivery is evolving, and new techniques are improving the stabilization of existing vaccines and increased shelf life.
- Most multipurpose vaccines were first licensed for a primary indication in a developed country and then expanded to include multiple indications, combinations, and licensure in other countries.
- Vaccines could be a promising option for MPTs since they offer various delivery options, devices and formulations.
- Preclinical candidates for a MPT vaccine could include antivirals against HIV, HPV, or HSV; vaccines against bacterial infections; and contraceptive vaccines.
- In assessing the feasibility of multipurpose vaccines, one needs to consider the needs of end-users, availability of providers and manufacturers, health system infrastructures, and ideal ages for delivery within the spectrum of other vaccines.
- MPT reproductive health vaccines would combine different drugs that have a separate regulatory pathway for each compound. Thus, trial designs would be extremely challenging and require prolonged commitment of time and resources.
- Use of a vaccine platform for delivery of microbicides or combining a future vaccine (e.g., HIV, HPV) with a microbicide to improve overall efficacy merits consideration.
- Rollout of the HPV vaccine in the United States has shown that coverage and user acceptance are low despite an outstanding safety record and level of efficacy.

- The time line for development of combination MPT vaccines for reproductive health is likely to extend further into the future than is the case for other MPT approaches.

MPTs in the preclinical pipeline

- Developing MPTs requires an expansion of the classic pipeline concept to incorporate the three different pipelines for prevention of pregnancy, HIV, and other STIs and RTIs.
- There is now a range of options that merit exploration as MPTs, each in a different stage of development, each with limitations and/or confounding variables that require attention.
- Some microbicide candidates not shown to be effective against HIV but with demonstrated activity against other STIs or RTIs might still merit further exploration as MPT components.
- Single compounds with multiple indications face a complex regulatory pathway. Similarly, a product combining multiple compounds for different indications will be required to demonstrate safety and effectiveness for all drug components and the delivery system itself independently.
- Combining compounds with different pharmacological characteristics is challenging, since they may require different carrier systems to each be released properly.
- Microbicides to prevent HIV transmission are positioned to dominate near–term MPT options, but the MPT pipeline needs to include research beyond anti-HIV microbicides and established contraceptive hormones delivered by vaginal rings.

Rationale for advancing MPTs in the preclinical pipeline

- Preclinical evaluations need to be designed that follow the critical pathway for IND studies set forth by the FDA and other pertinent regulatory authorities.
- Target Product Profiles provide a strategic development process tool based on science, indications, impact potential, and desired product characteristics.
- Establishing “best practices” algorithms for decision-making will help to identify unsuitable product candidates at the earliest possible time point.
- Decisions on product candidates will have to evaluate the relative advantages, novelty, versatility, cost, manufacturing and licensing requirements of new product candidates.
- Even a robust preclinical pipeline will generate only a few candidates suitable for advancement into clinical stages of development, making preclinical research on many compounds essential to the viability and success of the MPT field.
- The development of new STI components suitable for the MPT pipeline could attract new funders whose primary focus is on developed-country markets.

Determining and advancing promising MPT leads

- A robust MPT framework is needed to:
    - Identify target populations across regional, cultural, and socioeconomic backgrounds.
    - Characterize the products best suited to fit their respective needs.
    - Define desired indications, prioritize available drug candidates, and identify research gaps.
- Emerging priority indications for MPTs are pregnancy prevention and HIV prevention. Current stages of development make a combination of antiretrovirals (e.g., tenofovir, dapivirine, or MIV-150) with a contraceptive such as levonorgestrel the most immediately feasible option.
- Gaps in knowledge regarding the effects of hormones on the vaginal mucosa, as well as on differences in female and male metabolism of these combined drugs, will be an obstacle in proceeding with the most feasible option. These gaps must therefore be addressed as basic and translational research to develop parameters for clinical testing of such products.

- Globally, non-HIV STIs are a serious threat to reproductive health and must be an equal driver of the MPT development pipeline. The current focus for MPT vaccines should be on the non-HIV STI indications.
- From a regulatory perspective, the most efficient approach for MPT development is to build on the foundation of already-approved products.
- Advancement of candidates with commercial viability will be critical. Early involvement of private-sector business strategists to evaluate candidates in the MPT pipeline could be very helpful in ensuring eventual product success and sustainability.

Meeting Outcomes and Next Steps

The consensus from the Think Tank was that the development of safe and effective MPTs is clearly feasible, although scientifically challenging. The participants agreed to form two task groups to develop specific TPPs for MPTs, with a focus on the following:

1. Combination products for the prevention of unintended pregnancy, HIV and other STIs
2. Multipurpose vaccines

The task groups will work over the next several months, with the goal of presenting and discussing their respective TPPs at the International MPT Symposium, 3-4 November, 2011 in Washington, DC, USA.

ABBREVIATIONS

API	Active pharmaceutical ingredient
ART	Antiretroviral therapy
ARV	Antiretroviral (drug)
AVAC	Global Advocacy for HIV Prevention
BV	Bacterial vaginosis
CAMI	Coalition Advancing Multipurpose Innovations
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBAS	Cervical Barrier Advancement Society
CMC	Chemistry, manufacturing, and controls
DMPA	Depot medroxyprogesterone acetate
DPT	Diphtheria/tetanus/pertussis vaccine
EU	European Union
FDA	(US) Food and Drug Administration
GC/CT	Gonorrhoea/chlamydia
GRAS	Generally recognized as safe
HC	Hormonal contraception
HCG	Human chorionic gonadotropin
HIV	Human immune deficiency virus
HPV	Human papillomavirus
HSV	Herpes simplex virus
IDE	Investigational device exemption
IND	Investigational new drug
IMPT	Initiative for Multipurpose Prevention Technologies
IPM	International Partnership for Microbicides
IUD	Intrauterine device
IVR	Intravaginal ring
LNG	Levonorgestrel
MMR	Measles/mumps/rubella
MMR	Maternal mortality ratio
MPT	Multipurpose Prevention Technologies
MRI	Magnetic resonance imaging
MSM	Men who have sex with men
MTN	Microbicide Trials Network
NDA	New drug application
NGO	Non-governmental organization
NHP	Non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRTI	Nucleoside reverse transcriptase inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PK/PD	Pharmacokinetics/ pharmacodynamics
PrEP	Pre-exposure prophylaxis
RH	Reproductive health
RTI	Reproductive tract infection
RVI	Rabbit vaginal irritation
R & D	Research and development
SIV	Simian immune deficiency virus
STI	Sexually transmitted infection
SRH	Sexual and reproductive health
TFR	Total fertility rate
TFV	Tenofovir
TPP	Target Product Profile
USAID	US Agency for International Development
UTI	Urinary tract infection
VLP	Virus-like particles
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WHO	World Health Organization

MULTIPURPOSE PREVENTION TECHNOLOGIES FOR REPRODUCTIVE HEALTH: ADVANCING THE SCIENTIFIC AND PRODUCT DEVELOPMENT AGENDA

REPORT OF A "THINK TANK", 5 MAY 2011, WASHINGTON, DC, USA

"Think Tank" Purpose

On May 5, 2011, the US Agency for International Development (USAID), the Coalition Advancing Multipurpose Innovations (CAMI), and AVAC (Global Advocacy for HIV Prevention) convened a small group of scientists with expertise in contraception, HIV and STI prevention, vaccines, and a variety of product delivery systems to discuss and recommend practical strategies for accelerating the development of multipurpose prevention technologies (MPTs) for simultaneous protection against unintended pregnancy, HIV, and other sexually-transmitted or reproductive tract infections (STIs/RTIs).

Objectives

The meeting objectives were to:

- Review the ideal characteristics of MPTs for target populations identified as most likely to benefit from such products.
- Consider the pipeline of relevant technologies, advise on the steps required for their advancement, and identify further research needs and obstacles.
- Define a clear agenda for MPT R&D that can provide the scientific rationale for their accelerated development and concrete information for developers, scientists, funders, and advocates as to how they could support and further the advancement of these technologies.

Core Definitions

The key concepts that guide this initiative are the following:

- **Multipurpose Prevention Technologies (MPTs)** are understood for the purposes of this initiative as products designed to prevent at least two of the following health indications: unintended pregnancy, HIV, other STIs, and/or RTIs. MPT development may include available or emerging methodologies and new strategies, therapeutic products, vaccines, devices, and/or drug-delivery systems with potential for enhancing MTP safety, activity, and uptake.
- A **Target Product Profile** both describes those attributes of a candidate product that are considered critical and serves as a framework for its development pathway.

SETTING THE STAGE

The Initiative for Multipurpose Prevention Technologies: Origins and Status

Bethany Young Holt, CAMI

The concept underpinning multipurpose prevention technologies for sexual and reproductive health is not new. The notion of convenient, easy-to-use products that would enable women to simultaneously address the multiple health risks associated with unintended pregnancy and sexually transmitted infections was the initial driver of the development of topical microbicides over 20 years ago. Lessons learned over those years -- about microbicides, HIV and its co-infections, and antiretrovirals -- together with a pipeline that can begin to produce a range of products responsive to different user needs and preferences, suggest that developing multipurpose prevention technologies is now a realistic goal.

As a critical first step, in 2009 an International Symposium was held in Berkeley, California, that convened 150 multidisciplinary participants from 11 countries, with expertise in product development, engineering, behavioral science, clinical care, and advocacy to address the opportunities and challenges of advancing the development of MPTs. A decision was made to form the Initiative for Multipurpose Prevention Technologies (IMPT) and house it in an entity that would permit it to function as a non-aligned convener with no proprietary conflicts of interest. CAMI -- a project of the Public Health Institute (PHI)[1] -- was chosen as responsive to those criteria. Since then, as the IMPT secretariat, CAMI has been expanding its network of support globally and domestically to nongovernmental organizations, academic research centers, government agencies, funding entities, product developers, scientists, and advocates.

USAID is a key funder of the Initiative, which has also received support from the Mary Wohlford Foundation; AVAC, which contributed travel support for the Think Tank; and the NIH Office of AIDS Research, which is supporting international participation in the November 2011 MPT Symposium. With PHI administrative support, creative mobilization of consultant support, and active advisory groups, the Initiative continues to convert a relatively small total budget into the launch of a number of activities that are proving critical to:

- Outreach, awareness-raising, education, resource mobilization
    - 2009 Symposium, 2011 Symposium
    - Engagement of colleagues in Australia, China, India, Kenya, South Africa, the UK, Zimbabwe
    - Outreach to US executive and legislative offices and nongovernmental organizations that have stimulated interest and resulted in legislative language calling for support for MPTs
- Framing and supporting advancement of the MPT R&D agenda
    - The Think Tank, MPT Pipeline & Environmental Scan (www.cami-health.org)
    - Collaboration with Population Council's USAID-funded Regulatory Road Map Project
- Messaging:
    - Collaboration with PATH's USAID-funded Message Development Project

[1] The Public Health Institute (PHI, with offices in Oakland, California, and Washington, DC, is an independent, non-profit organization dedicated to promoting health, well-being, and quality of life for people throughout California, across the nation, and around the world.

Priorities going forward will include:

- Support for and coordination of novel approaches to multi-disciplinary collaboration around MPTs
- Expanded global and US support for MPTs
- Expanded scientific engagement in MPT research and development.

Ideal Characteristics of MPTs: What to Consider

Judy Manning, USAID

USAID's global health program focuses on developing countries whose public health indicators show substantial potential for improvement. In the area of reproductive health, many developing countries have high total fertility rates (TFR) and, in several regions of the world, there is a striking overlap between high TFR and high HIV prevalence. Those two indicators also fuel high maternal mortality rates (MMR) and high under-5 mortality rates. These regions must be USAID's areas of focus.

The scenarios for women's reproductive health risks change over the course of their lives. Pregnancy prevention, for example, dominates for most of a woman's 30+ years of fertility, while the perceived risks of HIV or other sexually transmitted infections (STIs) wax and wane as sexual partners and activity change. Despite the obvious biological, behavioral, and physiological linkages among all aspects of women's reproductive health, researchers in the fields of prevention of pregnancy, HIV, and other STIs often operate in silos within their respective organizations. A primary objective of the MPT Initiative is to bridge those silos and facilitate the interdisciplinary research that will address all reproductive health risks as necessarily integrated.

When identifying possible MPT target populations, certain criteria must be considered: gender and age, geography (high vs. low resource settings), demographics (teens, women with one or multiple partners), and perceived primary risks (unintended pregnancy, HIV, STIs, and RTIs). Preferred mode of protection and the required frequency and duration of method use are important additional considerations. Women's needs and desired product characteristics will vary by target population and the MPTs being developed must address that variability. Segmenting target populations thus becomes useful for defining priorities, focus and, ultimately, product design and development.

After identifying different target populations, research and development priorities can be sorted into possible target product profiles according to such criteria as the following *(see Figure 1)*:

- Target indications (unintended pregnancy, HIV, STIs, or RTIs)
- Product components (single drug/device/biologic for multiple indications, or various combinations of drug/device/biologic for separate indications)
- Product characteristics (effectiveness, side effect profile, additional health benefits, reversibility, resistance)
- Delivery (mode, dosing schedule, required user action)
- Product availability (over the counter or requiring prescription)
- Storage requirements (e.g., USAID requires 3-years minimum in high temperature conditions)
- Pricing.

FIGURE 1. ALTERNATIVE TPP SEGMENTATIONS: *WHAT WILL BE THE MAIN DRIVER OF CONSISTENT USE?*

Primary TPP segmentation options	Segments	Rationale
Geography	• High-resource settings (HRS) • Low-resource settings (LRS)	• How important is this distinction -- will some MPTs be more successful in HRS, and others in LRS?
Perceived Primary Risk(s)	• Pregnancy • HIV • Other STIs • RTIs	✓ Complex segments; multiple unmet need segments within each that change over sexual / reproductive lifetime ✓ Need multiple TPPs that address primary risks via different delivery modes and for different durations ✓ Predominant need for MPT for pregnancy + HIV
Delivery Mode	• Vaginal gel, tablet, ring, cervical barrier, oral pill, injectable, implant, vaccine	• Delivery mode and product components will effect TPP, but neither alone will drive women's decisions o Delivery mode captured within the TPP as a specific criteria o Product components reflected in delivery, side effects
Product Components	• Single drug, biologic or device • Drug + drug or biologic • Device + drug or biologic	
Usage / Duration	• Pericoital • Coitally-independent	✓ Key factor driving unmet need and women decision-making ✓ Technologies addressing segments more easily compared ✓ Satisfying TPPs would provide options of varying coverage

Such criteria can be used to construct a framework for decision-making that can be applied to evaluate products in development. For example, technologies will be needed that can be applied around the time of intercourse, while others will be coitally-independent. In this prioritization process, not all criteria will weigh equally, but all should be carefully considered. Dedicated working groups could take the lead in furthering such a process of product definition and developing milestones and "Go/No-Go" decision criteria for desired and minimally acceptable qualities of prospective technologies. The resulting priorities and recommendations from such working groups could, in turn, guide donors concerned with setting their own funding priorities for MPT investments.

The development of MPTs offers a global opportunity to substantially improve reproductive health, maternal health, and child survival, and reduce the transmission of HIV and other STIs. By expanding the range of such prevention options for women, MPTs offer new ways by which women can address their changing reproductive health needs and risks.

DISCUSSION

- Because of their mechanisms of action and formulation, the first microbicide candidates had to be administered pericoitally within 8 hours of sexual intercourse in order to achieve efficacy. A 24-hour window of effectiveness would be far more desirable for an MPT, which would then be effectively coitally-independent and correspondingly more convenient, acceptable, and likely to be consistently used.
- Distinctions among target populations in different settings can be useful, but there are significant differences in particular user needs even within a specific geographical setting that may add complexity to decision-making but still must be taken into account. Different target circumstances

such as clustered sexual activity, high multiplicity and concurrency of partners, and nonconsensual sex also require consideration. Finally, the MPT development agenda must take into account technologies that are suitable for men and adolescents of both sexes.

- While the goal of product efficacy is to be as high as possible, definitions of what would be "minimally acceptable" and "optimally desired" efficacy are moving targets that may differ by product type, available alternatives, and risk. Risk, in turn, varies epidemiologically by partnership type and phase, and by individual circumstances and needs. For example, optimally desired efficacy for pregnancy prevention methods must be almost 100% to be acceptable and widely adopted; in contrast, lower efficacy targets for prevention of curable genital infections or even prevention of still incurable HIV may be both acceptable to individuals and sufficient from the perspective of their prospective public health impact.
- Although the product development framework may assign highest priority to avertable risk and highest impact, user preferences such as pleasure, enhancement of the sexual experience, and partner communication also merit being taken into account.
- Some MPTs may present characteristics which in themselves are desirable or acceptable but which in combination present real dilemmas. For example, the monthly removal of a MPT vaginal ring in order to initiate withdrawal bleeding may be desirable or even essential for a contraceptive device, but could prove problematic for continuous HIV prevention.
- The pharmaceutical industry uses the term "Target Product Profile/TPP" to refer specifically to the dossiers assembled by product sponsors for communications with the FDA. The term is used in the MPT context more broadly, since it both describes those attributes of a candidate product which is considered critical and serves as framework for its development pathway.
- Experience with other public health technologies makes it clear that the development of MPTs for reproductive health cannot be donor-driven for extended periods of time. MPT product prioritization and decision-making must contemplate market potential in developed countries that could offset the costs of these products for developing countries. The more attractive MPTs are to the private sector, the more likely it is that they will find a sustainable and large-scale market.

KEY POINTS

Multipurpose Prevention Technologies (MPTs) are promising in their potential to enable women to simultaneously address multiple reproductive health risks and needs associated with unintended pregnancy; sexually transmitted infections, including HIV; and other reproductive tract infections.

The Initiative for Multipurpose Prevention Technologies is housed at CAMI, which furthers the IMPT mission as the primary convener of multidisciplinary stakeholders and provider of MPT outreach, education, and resource mobilization; maintains and communicates the findings of the MPT Environmental Scan, and is a key collaborator in message development and identification of regulatory pathways for multipurpose prevention technologies.

A framework for MPT development priorities must be devised that weighs candidate products according to avertable risk and highest impact, assessing criteria such as target populations, primary indications, product components, minimally acceptable safety and effectiveness, user acceptability, delivery mode, product availability, storage requirements, and pricing.

MPT development cannot be donor-driven for extended periods of time. Product development must take into account the prospect that market potential is most likely to attract the private sector and thereby ensure sustained and large-scale method availability.

MULTIPURPOSE MICROBICIDES & DEVICES IN THE CLINICAL PIPELINE

Drugs and Dosage Forms

Alan Stone, MEDSA Ltd.

A case can be made that the primary indications for multipurpose prevention technologies for sexual and reproductive health should be combinations that address prevention of both HIV and unintended pregnancy. Secondary indications for MPTs would be combinations incorporating protection against other viral, bacterial, protozoan, and fungal RTIs. In either case, effectiveness and safety will be paramount. Aesthetic qualities, convenience, affordability, and sustainability of supply will be additionally crucial since they will affect, perhaps govern, product acceptability and consistent use. The product, its formulation, and means of delivering it must also accommodate the needs and preferences of a range of users. Experience with a number of compound classes and delivery systems, together with what is in the clinical and preclinical segments of the potential "MPT pipeline", are the foundation for MPT research and development. The major classes of current interest follow.

Semi-solid gels. Substantial work over the past two decades with microbicides formulated as semi-solid gels confirmed their versatility in delivering a wide range of active pharmaceutical ingredients (APIs) and excipients, as well as their potential for delivery by a variety of pre-filled or re-useable plastic applicators, capsules, sponges, and barrier devices. Gels were also found to have lubricant qualities that proved desirable even in "dry sex" settings.[2] Since the costs of plastic applicators and pre-filling them remain high, inexpensive, user-filled, disposable cardboard applicators that would also reduce problems of storage and disposal are in development at PATH.

Vaginal tablets and suppositories have lower manufacturing costs than gel-filled applicators and can be packaged in small bulk blister packs, which improve portability, reduce domestic storage concerns, and lower shipping and warehousing costs. Mass production of this product category on regional and even global scale is facilitated by the ubiquity of tablet-manufacturing plants. More studies will be required for better understanding of tablet dissolution, distribution, and retention in the variable vaginal environment and quantities of liquid in the vagina, which depend in turn on menstrual cycle phase, level of sexual arousal, use of other products (such as contraceptive hormones), and user age**.**

Vaginal films are inexpensive to manufacture and to distribute and have minimal disposal issues. They are not, however, without challenges, which include a limited maximum capacity for drug content and the propensity for some messiness and stickiness during handling and insertion.

Intravaginal rings (IVRs) loaded with one or more active pharmaceutical ingredients (APIs) can remain *in situ* for weeks or months and, through sustained release of drug, provide long-term protection. Several rings are in use for contraception and relief of menopausal symptoms. APIs may be impregnated throughout the ring (matrix rings) or contained within defined pods/chambers (reservoir rings). Challenges for this technology include drug release, limited polymer sources and suitable manufacturing facilities, and possible issues related to long-term drug exposure.

Contraceptive implants and subcutaneous injection. After a somewhat difficult start, contraceptive implants -- flexible tubes containing drugs such as progestogen and inserted under the skin of the upper arm by a trained professional -- have proved to be a convenient and effective means of family planning. They are effective for up to three years, and normal fertility returns after their removal. Implants are also being explored as a potential delivery mechanism for anti-infectives, as is subcutaneous injection; a long-acting formulation of the ARV rilpivirine (TMC278 LA) is being tested by the International Partnership for Microbicides for HIV prevention, which suggests a possibility that this delivery strategy might lend itself to long-term multi-purpose protection.

[2] Tillman SN. Dry sex and implications for topical microbicide development. Microbicide Quarterly, April-June 2008.6(2):8-12.

Oral pre-exposure chemoprophylaxis (PrEP), using ARV-containing tablets, depends upon the drug reaching and maintaining inhibitory drug concentrations in target tissues. The recently reported iPrEX trial of oral PrEP (Truvada®) in men who have sex with men (MSM) showed a significant level of protection from HIV infection, [3] though a trial of the same product in women (FemPrEP) was unsuccessful, for reasons that are still unclear. [4] Potential toxicity problems with long-term regular use of oral PrEP, possibilities for emergence of drug-resistant viral strains, maintenance of adherence, sustainability, and cost are just some of the concerns associated with this HIV prevention strategy.

Topical ARV applications. Several products in this category, which is dominated by HIV nucleoside reverse transcriptase inhibitors (NRTIs/NNRTIs), are in clinical trials or late-stage preclinical status:

- ***1% tenofovir gel (***NRTI), successfully tested in a Phase 2b trial (CAPRISA 004) that showed a 39% reduction in HIV transmission and a 50% reduction in herpes simplex virus-2 (HSV-2) infections compared to placebo.[5] A confirmatory trial of 1% tenofovir gel led by a South African consortium ("FACTS") is scheduled for launch in summer 2011.
- ***1% tenofovir gel compared to oral tablets*** containing tenofovir or Truvada® in the Phase 2B Microbicide Trials Network (MTN) VOICE trial, which is testing daily dosing of both formulations against placebo in 5,000 African women, to ascertain the efficacy and safety of both formulations and determine which approach women may prefer.
- ***Dapivirine ring*** Dapivirine (TMC-120, an NNRTI) will be tested by the MTN in the first-ever Phase 3 trial of a vaginal ring, to evaluate its safety, effectiveness, and acceptability in monthly use, as well as in a parallel Phase 2 study conducted by the International Partnership for Microbicides (IPM). Other combinations of dapivirine, maraviroc, and tenofovir are in the IPM portfolio but all are intended for HIV prevention only.

At the moment, tenofovir gel is relevant for only a single indication (HIV) but the fact that the CAPRISA 004 results showed significant activity against both HIV and HSV-2 suggests that tenofovir might be in itself multifunctional and could lend itself to an MPT combination with such other drugs as the contraceptive levonorgestrel.

Polyanions as a class fell out of favor due to trial failures. However, a just-completed Phase 2 trial of **VivaGel (SPL7013)**, a sulphonated nanoscale dendrimer developed by Starpharma, showed efficacy in treatment of bacterial vaginosis (BV); a BV prevention trial is planned for late 2011 and the product has been licensed to Durex as a condom coating. Laboratory evidence of activity against HIV, HSV-2, and human papillomavirus (HPV) has been emerging from preclinical testing and consideration is being given to the product's potential as a platform for combination strategies.[6]

Bacterial therapeutics (for example, the probiotic LACTIN-V containing lactobacilli strains), are believed effective against BV and urinary tract infections (UTIs) through maintenance of a healthy vaginal microbiota, and are being studied in Phase 2 trials by Osel, Inc. The company is moving forward with preclinical research on a genetically modified lactobacilli strain secreting cyanovirin-N, a potent HIV-1

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[3] Grant RM, Lama JR, Anderson PL, et al. Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with Men. N Eng J Med 2010; 363:2587-2599.

[4] Results from two trials (Partners PrEP and TDF2), announced as this report was in final preparation, showed that taking an oral ARV tablet containing either tenofovir or Truvada® once daily significantly reduced risk of HIV infection in uninfected heterosexual men and women (Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med July 2011; Centers for Disease Control and Prevention. CDC trial and another major study find PrEP can reduce risk of HIV infection among heterosexuals. Press release, 13 July 2011.)

[5] Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science 2010; 329:1168-1174.

[6] Telwatte S, Moore K, Johnson A, et al. Virucidal activity of the dendrimer microbicide SPL7013 against HIV-1. Antiviral Res, 4 Apr 2011; Tyssen D, Henderson SA, Johnson A, et al. Structure activity relationship of dendrimer microbicides with dual action antiviral activity. PLoS One (2010) 5: 2 Sept 2010.

inhibitor.[7] Challenges for this technology will be to ensure propagation and survival of probiotic organisms in diverse vaginal environments, and concerns in the general public about genetically modified organisms.

In summary, there is a wide range of promising drugs and dosage forms of relevance to MPTs. The variety of devices and vaccines to deliver these drugs affords many possible combinations. The next most important task is to be selective and focus attention on a handful of potential products that promise high impact, are realistically achievable in a reasonable timeframe, and are assessed as highly useful to the identified target populations.

Drug and Device Combinations

Judy Manning, USAID

In addition to the drugs and dosage forms described above, the present MPT pipeline contains combinations of drugs with devices for single or multiple indications:

The SILCS Diaphragm developed by PATH is a reusable "one size fits most" device that does not require fitting by a health care provider. It is intended for "over-the-counter" provision and the CE Mark -- a mandatory conformance mark on many products placed on the market in the European Economic Area (EEA) -- is expected in 2011, at which time it will be transferred to Kessel Marketing, FRG. US–based clinical trials for contraceptive effectiveness have been completed with efficacy results comparable to the standard diaphragm, and US FDA approval for contraception is expected in 2012.

The SILCS Diaphragm with tenofovir gel, a combination device for prevention of pregnancy, HIV, and HSV-2, is being developed by CONRAD. In March 2011, key stakeholders convened by USAID discussed a potential product development plan for all three indications; further collaboration is anticipated. CONRAD holds the IDE for SILCS and the IND for tenofovir gel for HIV, and the submission for the second indication for HSV-2 is under development.

The Woman's Condom, also developed by PATH, is designed to be easier to insert, use, and remove than current options. The new polyurethane material is more comfortable for both partners, tiny bioadhesive pads ensure stability during use, and the device will ultimately be less expensive. The EU CE Mark was received in December 2010. US clinical trials to assess contraceptive effectiveness as a surrogate for HIV prevention are under way, and FDA approval is expected in 2013. The design of the Woman's Condom makes it possible to include any microbicide in a film formulation in the fast-dissolving insertion capsule and deliver it to the upper vagina and cervix.

Intravaginal rings (IVR) offer potential as delivery devices for a variety of drugs. Three combination rings for multiple indications are being developed by three different nonprofit entities:

- ***IVR with MIV-150, zinc acetate, carrageenan gel, and levonorgestrel (LNG).*** The Population Council is expecting FDA approval for a 1-year vaginal ring for the single indication of contraception. Building on that, the Council is working on a vaginal ring that would combine a highly effective hormonal contraceptive, levonorgestrel (LNG); a potent NNRTI, MIV-150; plus zinc and carrageenan. Recent research on MIV-150+zinc+carrageenan in non-human primates (NHP) and murine models demonstrated protective efficacy against HIV and HSV-2.[8] Further development is contingent on funding.
- ***LNG/tenofovir IVR.*** CONRAD is developing a 3-month vaginal ring that releases LNG and tenofovir for protection against pregnancy, HIV, and HSV-2. USAID is supporting a Phase 1 clinical study for dose-finding, safety, and pharmacokinetics and pharmacodynamics (PK/PD), to be followed by a Phase 2 contraceptive effectiveness study.

[7] Lagenaur LA, Xu Q, Lee PP, et al. A live microbicide shows efficacy in a repeated low dose challenge model. JAIDS Journal of Acquired Immune Deficiency Syndromes April 2011:56; 64.

[8] Kenney J, Aravantinou M, Singer R, et al. (2011). An antiretroviral/zinc combination gel provides 24 hours of complete protection against vaginal SHIV Infection in macaques. PLoS ONE 6(1):e15835. DOI: 10.1371/ journal. pone.0015835; Fernandez Romero J. (2011) Unpublished data.

- ***Tenofovir/acyclovir IVR.*** CONRAD is seeking funds to support further development of this potential MPT.

DISCUSSION

This discussion session addressed some critical gaps in what is an expanding but still insufficient body of knowledge that will be critical for MPT development, priority emphases for future research, and potential obstacles. Its premise and primary conclusion was that to advance the MPT initiative efficiently and effectively, it will be essential to prioritize needs for additional knowledge, identify existing expertise and relevant research efforts, and coordinate such information effectively. Consensus on a priority task list is more likely to encourage potential funders to step away from their usual networks and funding preferences and be willing to dedicate resources to fill well-defined gaps in the MPT pipeline and knowledge base.

Intravaginal Dissolution of Films & Tablets

Vaginal films could become a viable alternative to vaginal gels, given their potential for longer duration of activity in the vaginal environment and possibly greater acceptability to users due to their discreet product packaging. If produced at large quantities, the cost of production for films is comparable to the production costs of vaginal gels. A number of issues pertaining to films such as dissolution time and the relationships between dissolution and cervicovaginal fluid volumes in the vagina are being resolved, so that newer-generation films are now positioned for further preclinical and clinical testing. Although amounts of vaginal fluid do vary throughout the menstrual cycle, peaking during ovulation, production is high enough at any time during the cycle to allow complete dissolution of vaginal films; studies of safety, distribution, and PK/PD of new quick-dissolve vaginal films in human and monkey tissue models are under way.[9]

Issues remain, however. One limitation of vaginal films may be the boundaries of maximal drug load. In contrast, vaginal tablets can accommodate significant drug loads; in fact, CONRAD studies of vaginal tablets have found complete dissolution within 30 minutes.[10]

Vaginal Tissue Concentrations after Administration

Magnetic resonance imaging (MRI) has been used to assess the spread of administered gel in the vaginal cavity;[11] repeat experiments with films and, possibly, tablets are planned. Recent data show that while a drug may migrate well within the vagina, speed of drug spread may depend on the composition of a particular drug. The fact that the CAPRISA 004 study of tenofovir gel showed a 39% reduction in HIV transmission offers an example of how much vaginal spread and tissue concentration are sufficient for protection. Small gaps in coverage of vaginal surface by gel may not significantly affect the level of protection that is afforded by a highly soluble and diffusible drug.

Preliminary data from studies done on the dapivirine IVR confirm that even the small amounts of dapivirine released per day achieved high tissue concentrations, both in the immediate proximity of the ring at the cervix and at the vaginal introitus; there are less data on the concentration levels throughout the vagina.[12] If rings can deliver sufficient drug concentrations, tablets, with their higher drug load and significant initial burst effect of high drug release, may perform similarly. However, coverage by any administered drug within the vaginal cavity is also highly dependent on physical and sexual activity, so that it cannot be assumed that results of *in vitro* studies will adequately mimic *in vivo* situations. Clearly, emerging evidence about vaginal drug dissolution and spread will have to be incorporated and reflected in strategies for MPT pipeline development and prioritization.

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[9] Sassi AB, Cost MR, Cole AL, et al. Formulation development of retrocyclin 1 analog RC-101 as an anti-HIV vaginal microbicide product. Antimicrob. Agents Chemother. 2011 May; 55(5): 2282-9. Epub 2011 Feb 14.

[10] CONRAD. Preliminary data; unpublished.

[11] Lai BE, Geonnotti AR, Desoto MG, et al. Semi-solid gels function as physical barriers to human immunodeficiency virus transport *in vitro*. Antiviral Res. 2010 Nov; 88(2):143-51. Epub 2010 Aug 13.

[12] Romano J, Variano B, Coplan P, et al. Safety and availability of dapivirine (TMC120) delivered from an intravaginal ring. AIDS Res Hum Retro. 2009 May; 25(5):483-8.

Duration of Protection after Administration

Another important consideration for MPT development is duration of activity of the administered drug, since that will determine whether it will be coitally -- dependent or coitally -- independent. For example, rabbit studies found that BufferGel®'s activity had diminished 45 minutes post- administration, disappearing entirely after one hour; in contrast, recent Population Council studies of MIV-150 found that it provided 24 hours of protection in monkeys. Some women may prefer intermittent drug use with application just before intercourse; others may favor regimens with regular daily administration or continuous intravaginal release.

This implies a need for a range of dosing regimens, from fast-acting, short-lasting compounds for pericoital application, to compounds that can keep concentrations sufficiently high for longer time periods. It also means that future studies will have to incorporate outcome measures that include vaginal and plasma sampling at multiple time points after drug application. This will be challenging, since synchronization of clinical study visits within narrowly-defined time sampling windows has its limits. This process becomes more complicated when different compounds intended for use in MPTs have different pharmacodynamics.

Influence of Hormones on HIV Protection

This is a large issue with extensive implications, from the laboratory through clinical testing and in the populations ultimately using these products. For instance, trial participants are often required to use effective contraception and may already be doing so, particularly in areas with large family planning efforts, for example southern Africa. In CAPRISA 004, about 75% of participants were using injectable Depo-Provera (DMPA) and 25% were using oral contraceptives.

Both administered contraceptive hormones and endogenous hormonal changes throughout the menstrual cycle may interact with concurrently administered ARTs, leading to possible variation in vaginal and tissue ART concentrations. A further complication is that different hormonal contraceptives (e.g., estrogen+progestin vs. progestin alone) may impact HIV acquisition differently. Research on these possible associations (all observational) has not yet produced results that can be considered definitive. The largest study specifically designed to evaluate such associations was the HC-HIV study by Morrison et al.[13] Recent re-analysis of those study data found that use of progestin-only injectable DMPA -- but not use of combined oral contraceptives -- was associated with increased risk of HIV acquisition compared to no use of hormonal contraceptives at all.[14] An earlier study by CONRAD investigated the impact of DMPA on human vaginal and cervical epithelium after data in primates had suggested that DMPA caused thinning of the vaginal epithelium; however, the effect of DMPA in women was found to be less pronounced.[15]

However, contraceptives that are applied topically in the vagina rather than injected or taken orally may produce different effects on the vaginal epithelium. There are other intervening variables as well, such as the influence of semen (which is alkaline) on a healthy vaginal environment, which typically has an acidic low pH. Another critical variable is the impact of concurrent vaginal infections. For instance, women with bacterial vaginosis or herpes will have an impaired vaginal microflora that is more vulnerable to HIV infection. None of these variables and their effects has been sufficiently explored and some are quite challenging.

[13] Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. AIDS 2007; 21:85-95.

[14] Morrison CS, Chen PL, Kwok C, et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. AIDS 2010; 24:1778-1781.

[15] Mauck CK, Callahan MM, Baker J, et al. The effect of one injection of Depo-Provera on the human vaginal epithelium and cervical ectopy. Contraception 1999 Jul; 60(1):15-24.

KEY POINTS

A number of **promising drugs, dosage forms, devices, and platform technologies already exist** as the basis for new MPTs.

Issues offering particular challenge to such development are:

- **Intravaginal dissolution** of films and tablets
  - These must dissolve rapidly, even in what may be small amounts of vaginal fluid.
- **Tissue concentrations and duration of protection after administration**
  - To optimize protection, concentrations of administered drug must reach sufficiently high and sustained levels in the relevant vaginal and rectal compartments (ideally maintained for24 hours following a single dose).
- **Influence of hormones and concurrent vaginal infections on HIV protection**
  - The possible effects of contraceptive hormones (regardless of mode of administration), endogenous hormonal changes during the menstrual cycle, and concurrent vaginal infections, on the vaginal epithelium and vaginal microbiota, HIV acquisition, and concurrently administered ARTs.

The focus of MPT research and development must be on product candidates that promise high impact, are realistically achievable within a reasonable time frame, and are evaluated as highly useful to the identified target populations.

Prioritizing is crucial: It is essential to prioritize requirements for additional knowledge, identify and mobilize existing expertise, facilitate productive relationships among pertinent research efforts, and coordinate research efforts.

MULTIPURPOSE VACCINES

Existing Vaccines with Multiple or Expanded Indications

Kevin Whaley, Mapp Biopharmaceutical

Vaccines combining multiple agents for multiple indications have been used for decades. Existing vaccines use either attenuated live/killed bacteria or viruses, or contain a purified or recombinant subunit. Among the commercially available multipurpose vaccines is the MMR vaccine for measles, mumps, and rubella -- a mixture of three live attenuated viruses that is usually given in childhood and does not require later booster doses. The classic DPT combined vaccine for diphtheria, tetanus, and pertussis has been available and widely used for 60 years. Newer versions like pentavalent (DTaP, Hib, IPV) and hexavalent (DTaP, HBV, Hib, IPV) vaccines are available in many countries and have acceptable response rates and safety profiles.[16] When available, combination vaccines are often preferred because they enhance parental and provider satisfaction, improve schedule compliance by decreasing the number of injections, and may be more cost-effective. Possible disadvantages include potential for increased or decreased antibody response to individual antigens that may be associated with combination vaccines compared to monovalent vaccines, and constraints to availability since all manufacturers may not have access to all antigens.

Because their overall advantages outweigh their disadvantages, the vaccine field has long been developing and using vaccines that combine several agents for multiple indications. It is both possible and necessary to learn from those experiences and exploit the many intersections among vaccines, devices, and microbicides that might serve to accelerate development of multipurpose prevention technologies for reproductive health.

Considerations for Combination Vaccines: Now and in the Future

Carolyn Deal, NIAID

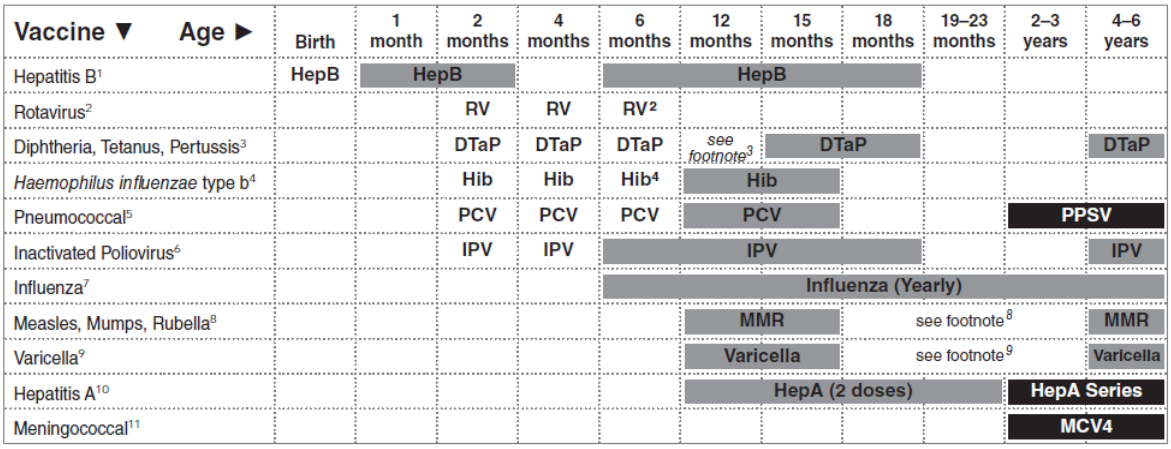
The National Institutes of Health and National Institute of Allergy and Infection Disease (NIAID) have spent substantial resources on research and development of vaccines, now approximately US$1.2 billion per year. The goals of the NIAID Vaccine Research and Development Program are the identification of new vaccine candidates for diseases for which there are no vaccines, and improvement in the safety and efficacy of those that exist. The program supports development of novel vaccine approaches and strategies; innovative technologies and delivery methods' stabilization techniques and adjuvants; and, in addition, conducts research related to vaccine safety.

Many new vaccines have been licensed since 1994, among them a number of combination vaccines, such as: the Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; Hepatitis A Vaccine, Inactivated; Hepatitis B Vaccine, Recombinant; Human Papillomavirus (HPV) Quadrivalent (Types 6,11,16,18), Recombinant; and Poliovirus Vaccine, Inactivated. Many of these new vaccines were initially developed by academic institutions with substantial NIH support and several were first licensed for a single primary indication and later evaluated and licensed as combination vaccines.

[16] Plotkin SA, Liese J, Madhi SA, et al. ADTaP-IPV/PRP-T vaccine (Pentaxim): a review of 16 years of clinical experience. Exp Rev Vaccines 2011 July 12 (Epub ahead of print); Skibinski DAG, Baudner BC, Singh M, et al. Combination vaccines. J Global Infect Dis 2011;3:63-72; Diaz-Mitoma F, Halperin SA, Tapiero B, et al. Satety and immunogenicity of three different formulations of a liquid hexavalent diphtheria-tetanus-acellular pertussis-inactivated poliovirus-Haemophilus influenzae b conjugate-hepatitis B vaccine at 2, 4, 6, and 12-14 months of age. Vaccine 2011;29: 1324-31.

FIGURE 2. RECOMMENDED IMMUNIZATION SCHEDULE FOR PERSONS AGED 0-6 YEARS, US 2011

(US Department of Health and Human Services/Centers for Disease Control and Prevention)



New and modified vaccines pass through the customary phases of research and development. Currently at NIH, a number of new vaccines are in different stages of that sequence: basic research focused on chlamydia infection, gonorrhea, herpes and syphilis; target identification and preclinical development focused on second-generation HSV vaccines; and vaccines for hepatitis B and C as well as for HSV are in clinical development. Once FDA licensure has been obtained, efforts turn to manufacturing and post-licensure evaluation.

Vaccine developers must consider the best and the most feasible delivery time points for vaccines. The Advisory Committee on Immunization Practices (ACIP) recommends immunization schedules for the pediatric, adolescent, and adult age groups *(Figure 2)*. Most vaccines are delivered during childhood, and immunization rates for young children are quite good, but challenges arise in older childhood and adolescence. The immunization schedule during adolescence is evolving and a number of vaccines are now recommended in that age range, including a booster dose for acellular pertussis, tetanus, and diphtheria (DPT) and the meningococcal vaccine. This opens a new window of opportunity to establish a vaccine visit during adolescence. Currently the new HPV vaccine is recommended for routine use in women and adolescent girls but although it is scheduled to be delivered to 11-12 year olds, initial vaccine coverage has been modest. The vaccine has also been licensed for men and boys, since research showed preventive efficacy against genital warts and anal cancer. Ongoing work is evaluating the potential for herd immunity and decreased risk of cervical cancer in the female partners of immunized men.

In recent years, there has been considerable evolution in product delivery. For cutaneously-administered vaccines, coated microneedles -- devices that penetrate the upper epidermal layers and dissolve to deliver the vaccine antigens -- are in preclinical development. Research efforts are being dedicated to delivery of mucosal vaccines as edible products and to spray injectors for oral and nasal administration. There has also been progress in stabilizing existing vaccines and increasing shelf life using new techniques such as nanoparticles, protein-coated microcrystals, and excipient-enhanced lyophilization.

Vaccines could be a promising option for multipurpose prevention in reproductive health. They offer numerous potential systemic and mucosal delivery options and a variety of delivery devices and formulations, and have attracted broad interest from both industry and academia. Among the remaining challenges is the persistent, though evolving, need to understand the mechanisms of mucosal immunity, develop better response measures, arrive at a clear definition of some clinical endpoints, and answer questions around immune tolerance or potentiation.

MPT vaccine candidates or components could include antivirals against HIV, HSV, or HPV; vaccines against bacterial infections such as the four major curable STDs (chlamydia, gonorrhea, syphilis,

trichomoniasis); or even contraceptive vaccines targeting human chorionic gonadotropin (HCG) or sperm. Even vaccines against malaria or tuberculosis might be future MPT components.

The role of the NIH in partnership with academia, global organizations, industry, non-profits, and other government agencies is to support acquisition of fundamental knowledge for new or improved vaccine approaches, share risks and costs in the early development stages of novel vaccines of public health importance, and assist in development of vaccines lacking a broad commercial market.

MPT-related Research at the National Cancer Institute

John Schiller, NCI

The commercially available HPV vaccines are generally safe and have a high degree of efficacy (~100%) against incident infection and pre-malignant cervical neoplasia by vaccine-targeted types. Based on safety and immunogenicity in clinical studies, the HPV L1 VLP vaccines appear compatible with co-administration (on different injection sites) with the hepatitis B, meningococcal, DPT, and polio vaccines.

Despite an outstanding efficacy record, comprehensive HPV vaccine coverage remains problematic. The vaccine is expensive -- about US$120 per dose in the United States -- and prohibitively expensive in low-resource countries, where 85% of the world's cervical cancer cases occur. Impact on those cases will remain modest unless the vaccine reaches girls in those countries who, as women, are unlikely to be adequately screened for HPV infection. In the United States, where HPV vaccine coverage in 13-to-17-year-old girls reaches just 44% for the first dose, only 27% receive all three doses. In contrast, coverage in school-based programs in the UK reaches 80%.

Work has already begun on next-generation HPV preventive vaccines. Merck has launched a Phase 3 trial of a nonavalent L1 VLP that adds protection against six more HPV types (31,33,45,52,58), bringing the total types protected to nine. Other approaches in preclinical development include an L1 recombinant measles vaccine, a widely-distributed pediatric vaccine by Zydus-Cardila, and an L2 minor capsid protein vaccine by Sanofi-Pasteur/Shantha that might induce broad cross-type protection with a monovalent polypeptide vaccine made in *E. coli*.[17]

Therapeutic HPV vaccines are also being explored. Strategies being pursued include genetic immunization of the female genital tract with HPV pseudovirions. The rationale behind this approach is that while the mucosa of the female genital tract is an important entry site of infection, the female genital tract is generally considered a poor site for inducing immune responses. Thus there is little evidence so far for effective intravaginal vaccination and attempts to generate genital tract immunity have centered on vaccination at remote sites (e.g., intranasal or intramuscular) and subsequent trafficking to the vaginal mucosa. However, studies, largely unpublished to date, suggest that the female genital tract can also be a potent inductive site when the antigen is expressed transiently in "wounded" keratinocytes.[18] HPV-based gene delivery to the genital tract has been found to induce a strong and durable intraepithelial CD8 T-cell response in the female genital epithelium and was more effective than vaccination at a distant mucosal site. It may be that the most effective strategy will be some combination of systemic priming followed by a local vaginal booster vaccination. Potential applications of these new findings could be a therapeutic vaccination of already existing HPV-induced cervicovaginal intraepithelial neoplasia or prophylactic vaccination for HSV or HIV.

Yet despite promising leads to new HPV vaccines, HPV microbicides could still fill an important gap in HPV protection. Studies indicate that, in contrast to other STIs, condoms afford at best limited protection against sexual HPV transmission, at least under normal patterns of use. This means that a topically applied HPV inhibitor could function as an adjunct to HPV vaccination, especially if it were inexpensive and had broad spectrum activity. A potential candidate for such a role is carrageenan, an exceptionally potent inhibitor of oncogenic HPVs. The compound was investigated in a gel formulation in Phase 3 trials as a topical

[17] Schiller JT, Lowy DR. Vaccines to prevent Infections by oncoviruses. Ann Rev Microbiology (Oct 2010); 64:23-41.

[18] Kines RC, Thompson CD, Lowy DR, Schiller JT, Day PM. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. PNAS 1 Dec 2009; 106(48); 20458-20463.

microbicide against HIV but, while found to be safe, it showed no anti-HIV efficacy, perhaps at least in part because overall compliance was poor.[19]. The first clinical trials investigating efficacy of carrageenan against HPV are in planning stages at Albert Einstein College of Medicine in New York City and McGill University in Montreal.

DISCUSSION

This discussion focused on lessons learned from prior vaccine research and specific challenges of relevance for the development of MPT vaccines.

- Minimally acceptable efficacies for STI vaccines must be rather high, on the order of 80-100%. Most vaccine trials use 70-80% efficacy assumptions for their sample size calculations. However, in determining acceptable efficacy levels, a population effect such as herd immunity can also be taken into account, so that in the case of fatal diseases such as HIV, especially in high-risk settings, a lower level of efficacy may be found acceptable.
- The fact that modern vaccines are safe could -- and should -- be better communicated to the public, since vaccine misinformation and confusion have compromised more than one immunization initiative. For instance, the fact that a child's immune system is more challenged by the common cold than vaccine administration is not well known. Another poorly appreciated fact has to do with optimum age(s) for vaccination. Because of the immaturity of the immune system, immune response in children under age 2 is limited; vaccine trials indicate that older children have better immune responses than adults so that adolescence is an ideal time window for immunization.
- Attempts to develop contraceptive vaccines were pursued over 20 years ago but encountered heavy political backlash. The immunocontraception approach used at the time was based on antibodies against the "pregnancy hormone" HCG, which had the advantage of non-interference with other hormone levels. However, the irreversibility of the process and general safety concerns doomed those efforts. Still, it might be worth revisiting HCG antibodies as a possible MPT strategy component for women wishing to complete childbearing but still sexually active.
- The February 2011 Population Council-led meeting regarding a regulatory road map for MPT development emphasized the centrality of the regulatory aspects of MPTs and the challenges of combination trial design. The development trajectory of the HPV vaccine is instructive here. The HPV vaccine was first licensed by the FDA for only the most rigorous endpoint, prevention of cervical dysplasia; then, as more safety and efficacy data emerged, for genital warts; and now, again with new data, for anal cancer prevention.
- MPT vaccines combining different drugs and/or antigens with different indications will face additional challenges. Typically, combinations of different antigens can be tested as a single product; each antigen need not be tested separately. MPT vaccines, which would combine different drugs rather than different antigens, will require a separate regulatory pathway for each compound. This would also apply to compounds with multiple indications. Trial designs of combination products using multiple compounds for different indications would be extremely challenging and demand a high commitment of time and resources.
- Two lessons from vaccine research have to do with developing a market and, correspondingly, eliciting industry involvement. Lesson number one is to seek licensure for developed countries first, since successful marketing, cost reductions, and development of global manufacturing capacities make later introduction of the vaccine in developing countries more feasible. As this has proved to be a viable business model, the pharmaceutical industry is increasingly using expired vaccine patents from developed countries and adapting them for developing country markets. The second lesson comes from US domestic market experience. The Vaccine Compensation Injury Program

[19] Skoler-Karpoff S, Ramjee G, Ahmed K, et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomized, double-blind, double-blind, placebo-controlled trial. Lancet. 6 Dec 2008. Vol 372 Issue 9654:1977-1987.

(VCIP) requires that a portion of the proceeds of every vaccine sold be forwarded to the VCIP. Established to protect companies from liability in cases of rare adverse events, the fund has helped motivate industry involvement in vaccine research.

KEY POINTS

The vaccine field has long been using **multipurpose vaccines** that combine several agents for multiple indications.

Work on new vaccines is in various stages: basic research is focused on chlamydia, gonorrhea, herpes, syphilis, and second-generation HPV vaccines. Hepatitis B and C vaccines and first-generation HSV vaccines are already in clinical phases of development.

Understanding of mucosal immunity, response measures, and immune tolerance or potentiation continues to evolve and remains essential research for all vaccine development.

Vaccine delivery is evolving toward dip-coated micro-needles and mucosal vaccines for oral and nasal administration. New techniques are improving the stabilization of existing vaccines and increased shelf life.

Most **multipurpose vaccines** were first licensed for a primary indication in a developed country and then expanded to include multiple indications, combinations, and licensure in other countries.

Vaccines could be a promising option for MPTs since they offer various delivery options, devices and formulations.

Preclinical candidates for a MPT vaccine could include antivirals against HIV, HPV, or HSV, and/or vaccines against bacterial infections such as chlamydia, gonorrhea, syphilis, or trichomoniasis, and contraceptive vaccines against HCG or spermatozoa.

Aspects to be considered in **assessing the feasibility of multipurpose vaccines** include: needs of end-users, availability of providers and manufacturers, national public health system infrastructures, and ideal ages for delivery within the spectrum of other vaccines.

MPT reproductive health vaccines would **combine different drugs that have separate regulatory pathway** for each compound. Trial designs for testing vaccines with multiple compounds for different indications would be extremely challenging and require prolonged commitment of time and resources.

The potential for **using a vaccine platform for delivery of microbicides** or combining a future vaccine (e.g., HIV, HPV) with a microbicide to improve overall efficacy merits consideration.

Experiences with rollout of the HPV vaccine in the United States have found that coverage and user acceptance are low despite an outstanding safety record and level of efficacy.

The **time line for development** of combination MPT vaccines for reproductive health is likely to extend further into the future than is the case for other MPT approaches.

MPTS IN THE PRECLINICAL PIPELINE

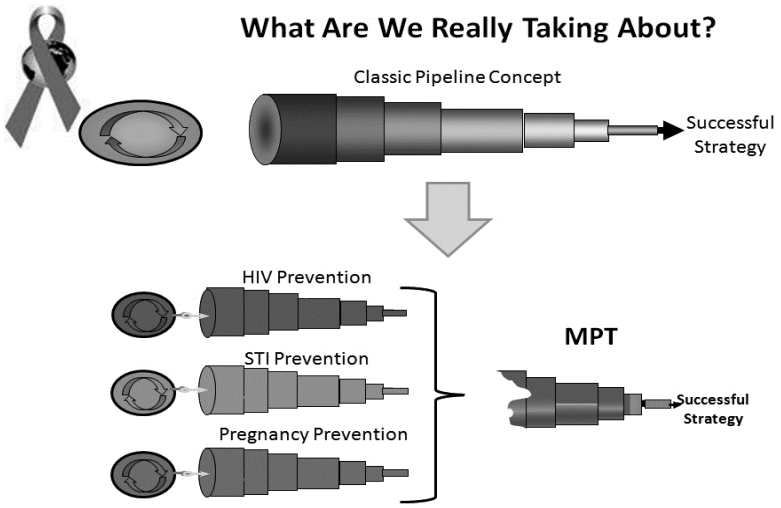
Overview of the Preclinical MPT & Microbicide Pipeline

Jim Turpin, NIAID

Developing multipurpose prevention products demands an expansion of the classic pipeline concept. A pipeline can be defined as a set of iterative development efforts to advance a drug product through discovery and preclinical/clinical testing to licensure. Because of regulatory differences in product development for prevention of pregnancy, HIV, and other sexually transmitted infections, pipelines to support development of MPT strategies will need to fuse the salient features of each type of prevention strategy. These unique multicomponent pipelines must then be capable of addressing preclinical, clinical, and regulatory requirements for all indications of the MPT under development.

Each prevention pipeline is unique, with its own development pathway and focus. The pregnancy prevention pipeline is dominated by hormonal contraception, which has a longstanding, excellent safety and efficacy record coupled with high user motivation. The STI prevention pipeline must accommodate development of prevention for a wide range of sexually transmitted organisms and is dominated by strategies, apart from the HPV vaccine, designed to prevent, treat or cure STI infections. The HIV prevention pipeline, which for the purposes of this discussion will focus on potential microbicides as MPTs, is advancing both antiretrovirals (ARVs) and non-ARV strategies *(Figure 3).*

FIGURE 3



The MPT pipeline is fusion of existing iterative development efforts

DHHS/NIH/NIAID/DAIDS

A legacy of early microbicide development was a focus on compounds with multiple indications, and many candidates that advanced to clinical testing had potential STI or pregnancy prevention indications. Among those were BufferGel®, Carraguard, and PRO 2000 -- which, while they failed to prevent HIV infection, might still be useful as components of first-generation MPTs against other STIs such as chlamydia, gonorrhea, HPV, and HSV. Other microbicide multi-target candidates still active in the pipeline are VivaGel® (SPL7013), which in laboratory studies shows activity against HIV, HSV-2, and HPV, as well as contraceptive activity in animal models; and glycerol monolaurate (GML), which shows activity *in vitro* against HIV and STIs. Finally, there is 1% tenofovir vaginal gel which, in the CAPRISA 004 trial, showed unexpected and significant level activity against HSV and provided proof-of-concept that a single drug product can, in itself, be an MPT.

The combination of hormonal contraceptives and microbicides offers a good starting point for an MPT pipeline and both are often considered the best first options for MPT development and are discussed earlier in this report. Although prevention of pregnancy and HIV infection has been identified as "low-hanging MPT fruit", there are nevertheless some large and critical issues, such as biochemical and biophysical compatibility of the agents and delivery systems, to be overcome before a pregnancy/HIV MPT is a reality. Water-soluble tenofovir can be incorporated into silicone or EVA IVRs that readily release less water-soluble contraceptive hormones; however, unlike the hormones, tenofovir's release is limited. There is also the question of off-target effects that might alter pharmacokinetics and/or the innate defense mechanisms that naturally control HIV and STI acquisition and disease progression. Finally, the regulatory requirements governing the advancement of candidates for prevention of pregnancy may be incompatible with those for an ARV microbicide, thus requiring unique solutions to meet regulatory requirements for licensure.

In summary, microbicides and contraceptive hormones delivered via an IVR are positioned to dominate as near-future options -- "low hanging fruit" -- for MPT development. However, caution is advisable. Emphasis on ARV-based anti-HIV microbicides and hormonal prevention of pregnancy could lead to a very limited first generation of MPT options: ARV and hormones delivered by vaginal rings. It is therefore critical to continue developing other MPT strategies and invest in research to identify new candidates and MPT approaches that are safe and efficacious with regulatory pathways that will facilitate their development.

DISCUSSION

This discussion revisited the implications for MPTs of combining hormonal contraceptive components with microbicides; considered the regulatory challenges for combination products; began to outline what a future MPT pipeline might look like, using current microbicide candidates as a starting point; and began to focus on pipeline management challenges.

- CONRAD had chosen levonorgestrel (LNG)[20] to combine with tenofovir for an intravaginal ring because LNG has a long and extensive safety record in multiple formulations and delivery systems. While LNG can modify the menstrual cycle and trigger intermenstrual bleeding, it might be unlikely to do so at the very low-dose daily release rates of a ring. While both LNG and tenofovir are increasingly well understood, the consequences of their combination are not and therefore will have to be carefully considered. Simultaneous systemic absorption of LNG or, for that matter, any hormone, and tenofovir might affect the pharmacokinetics of each or even both components; impact on renal function is just one case in point.
- Another complication that has emerged in this work and may apply to all device combinations has to do with compatibility -- or lack of compatibility -- between a given device and the compounds it is meant to deliver. Ring materials may limit the choice of loadable compounds; for example, while the EVA[21] ring is very suitable for hydrophobic ARTs like dapivirine or maraviroc, it has so far been resistant to loading with tenofovir, which is highly hydrophilic. This same dissonance may emerge in attempts to combine compounds with different pharmacological characteristics, since each may require a different delivery system for optimized release.
- Current USFDA regulatory requirements stipulate that a product combining multiple compounds for different indications must demonstrate safety and effectiveness for all components independently, with exceptions accorded to components "generally regarded as safe (GRAS)". For instance, while LNG is already licensed as a pill, additional Phase 3 trials will still be necessary for LNG-releasing intravaginal rings. That said, experience indicates that it is still easier to add a new component to an existing licensed product; an apt example might be the addition of tenofovir to an existing LNG-releasing intrauterine device (IUD) or NuvaRing.[22] In all cases, since every new entity requires a

[20] Levonorgestrel (LNG) is a second-generation synthetic progestogen used in many contraceptive pill formulations, emergency contraception, intrauterine systems (IUDs), and contraceptive implants.

[21] EVA--eethylene vinyl acetate--is a clear, soft, flexible, odor-free polymer used in biomedical engineering applications and as a drug delivery device.

[22] NuvaRing is a flexible 2"-diameter ring about 2" in diameter inserted vaginally once a month, that releases a continuous low dose of combined hormones to prevent pregnancy.

new Investigational New Drug (IND) review by the US FDA, well-conceived bridging studies for modified products will be essential.[23]

- The MPT development process will have to maintain several robust, concurrent pipelines, and be diligent about eliminating failing candidates and advancing more promising ones into clinical studies. Pipeline research will build on prior knowledge of pathways and compounds, providing constant feedback to inform necessary changes in strategies and overall pipeline management.

KEY POINTS

Developing MPTs requires an **expansion of the classic pipeline concept** to incorporate the three different pipelines for prevention of pregnancy, HIV, and other STIs and RTIs.

There is now a **range of options** that merit exploration as MPTs, each in a different stage of development, each with limitations and/or confounding variables that require attention:

- Re-engineered **barrier devices**, e.g., diaphragms or condoms, have potential for simultaneously delivering microbicides and providing protection against pregnancy, HIV and other STIs, and RTIs.
- Slow-release **vaginal rings** could combine hormonal contraceptives with microbicides; currently available ring materials are not universally suitable for every compound.
- **Vaginal gels** may have the best track record for formulations that have been tested in clinical trials, but intravaginal rings, tablets, and films are advancing in clinical testing to add to the array of options in the not too distant future.
- Of continued interest are candidate **compounds that are in themselves multipurpose**, having shown activity *in vitro* against multiple targets, e.g., VivaGel®; glycerol monolaurate (GML); and 1% tenofovir gel, the only candidate with data from late-stage clinical testing.

Some microbicide candidates not shown effective against HIV but with **demonstrated activity against other STIs or RTIs** might still merit further exploration as MPT components.

Single compounds with multiple indications face a **complex regulatory pathway**. Similarly, a product combining multiple compounds for different indications will be required to demonstrate safety and effectiveness for all drug components and the delivery system itself independently. **Bridging studies** between existing data and new indications or delivery modes will have to be designed according to regulatory requirements.

Unresolved questions remain regarding mucosal immunity, adequate measurements of immune response, and immune tolerance for different epithelial tissues.

Combining **compounds** with different pharmacological characteristics is challenging, since they **may require different carrier systems** to be released properly. Similarly, combining hormones and antiretrovirals may change the pharmacokinetics of either or both compounds.

Microbicides to prevent HIV transmission are positioned to dominate near–term MPT options, but the **MPT pipeline needs to include research beyond anti-HIV microbicides and established contraceptive hormones** delivered by vaginal rings. Failing candidates need to be eliminated, and the duplication of similar research efforts needs to be avoided. Research derived from prior knowledge of pathways and compounds, failures as well as successes, should be mined systematically for the constant feedback that can inform necessary changes in strategies.

[23] Guidance for Industry Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), December 2010.

RATIONALE FOR ADVANCING MPTS IN THE PRECLINICAL PIPELINE

Preclinical Evaluation of Microbicides and Multipurpose Drug Combinations

Gustavo Doncel, CONRAD

Multiple targets (pregnancy, HIV, HSV, other STIs and RTIs), mechanisms of action (physical or chemical barriers, biologics, immune modulators, vaccines), and dosage forms (condoms, diaphragms, films, gels, rings, tablets) exist for MPTs. The target product profile (TPP) will differ depending on these three sets of variables, so that it is critically important to understand the scientific knowledge underpinning each biomedical intervention type and individual biomedical intervention.

Desired product properties can be used as criteria to guide MPT development. Candidate compounds for MPTs should show no systemic or reproductive toxicity. Clinically relevant doses should be applied repeatedly without signs of toxicity on cervicovaginal epithelial and immune cells, or on the resident microflora. Compounds should have high potency and a wide spectrum *in vitro* and high efficacy *in vivo* (animal models) against target organisms, as well as a high selectivity and therapeutic index. There should be no enhancement of reproductive infections, and products should have good pharmacokinetic and pharmacodynamic (PK/PD) profiles and a high barrier to microbial resistance. Finally, the delivery system or formulation should be stable, easy to manufacture at low cost, and acceptable to users.

The goals of preclinical evaluation of multipurpose microbicides are to produce data to support submission of an Investigational New Drug (IND) application to the USFDA or equivalent authority; complete a TPP that identifies desirable and undesirable compound and formulation characteristics; enable rational selection of candidates; and understand the mechanisms of action of a given compound, especially with respect to its safety and efficacy.[24]

Investigational new drug and new drug application (NDA)-enabling studies for antiretroviral microbicides need to be timed accordingly. Data for chemistry, manufacturing, and controls (CMC), antiviral activity *in vitro*, cytotoxicity, general toxicology (acute and subchronic), genotoxicity, safety pharmacology, rabbit vaginal irritation (RVI), and reproductive toxicology (Segments I & II) need to be collected prior to Phase 1. Antiviral activity (*ex vivo* and *in vivo*), chronic toxicology, and hypersensitivity testing follow prior to Phase 2/3. In the pre-NDA stage, the last Segment (III) of reproductive toxicology and carcinogenicity, plus general toxicity for impurities, must be completed.

Good characterization of API and formulations with respect to their physico-chemical properties, specific activity, cell toxicity, and release of drug should provide a solid foundation for successful preclinical testing of organ toxicity, PK/PD, efficacy, and clinical development of both a safe and effective microbicide and an MPT.

Great effort must be placed on continuously improving and validating the preclinical models of primary relevance for MPT development. These include refined animal models, which can now better characterize epithelial and immunoinflammatory responses to microbicides, and tissue biopsies from the human vaginal tract that can be assessed to measure PK/PD correlations and biomarker concentrations for different dosages of candidate compounds and better define adequate dosing schedules for clinical testing. The timing of product application is critical, since the compound needs to be present in sufficient concentrations at the time of HIV challenge to be effective -- concentrations that must be both high enough to block HIV infection yet low enough to avoid negative effects on the vaginal mucosa.

[24] Doncel GF, Clark MR. Preclinical evaluation of anti-HIV microbicide products: new models and biomarkers. Antiviral Res 2010 Dec: 88 Suppl 1:S10-8. Review.

In summary, both the TPP and testing algorithm must be predicated on the science, the indications of interest, and desired product characteristics. The purpose of preclinical evaluation is to collect necessary data on product properties and mechanism(s) of action for IND review, the critical pathway and associated studies for which are dictated by the FDA. Existing models and endpoints require ongoing improvement and validation in order to enhance understanding of mucosal safety, product pharmacokinetics and efficacy, and optimal clinical dose and dosing schedule with reliable data. Establishing "best practices", selecting algorithms for decision-making and staging progress strategically will, together, make it possible to identify unsuitable product candidates at the earliest possible time point, in accordance with a cardinal rule of innovation "If you're going to fail, fail early."

Critical Decision Points in the Microbicide R&D Pathway

Joe Romano, MTN

The primary task for this Think Tank is to lay the foundation for a clear agenda for the strategic advancement of products that have already reached the clinical stages of development and for preclinical characterization of candidate compounds and delivery systems. Of the many candidates in the preclinical pipeline, only few will be suitable for advancement into clinical stages of development.

A conventional target product profile (TPP) is intended to serve as a strategic development process tool. It is a summary of drug labeling concepts and the specific studies to support those concepts, and includes information on indications and usage, dosages and administration, dosage forms and strengths, storage conditions, shelf life, etc. In the pharmaceutical industry, TPPs are used as tools for communication with the FDA and to suggest an ideal version of product labeling.[25] They are designed to be dynamic and change as knowledge about the properties of the product under development expands.[26] In order to advance the microbicide pipeline, objective, technical "Go" or "No Go" decisions will be necessary at each step along the way, based on the emerging preclinical and clinical data.

Those, however, are not the only considerations of relevance. Product advancement decisions will have to take into account the current, broader development context and be strategic in terms of that broader context, in order that products with the highest potential impact and most efficient development process move forward. As the development context evolves, as it constantly does, and as proofs of concept for ARV microbicides accumulate, it will become necessary to substitute placebo-controlled studies with equivalency trials which, in turn, will affect study designs and resource requirements.

Against this background, the critical strategic decision-making process should be guided some fundamental principles:

- Can a candidate product lead to a meaningful improvement in efficacy compared to an available product with proof of concept, either because of broader anti-viral potency or a better adherence potential? Or is the new candidate a "me too" product?
- Can a single product be developed for both vaginal and rectal use, thus expanding effectiveness to new populations (e.g., MSM)?
- Can the candidate product address multiple needs in STI/RTI prevention and contraception?
- Can the candidate product enhance access by optimizing cost, storage, size, discreetness, shipping, associated waste material etc.?
- Is the candidate product amenable to achieving licensure in the era of post-placebo controlled efficacy studies?

[25] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf

[26] In the context of the Think Tank, the TPP was also conceptualized as a list of crucial product parameters and the range of acceptable limits for each parameter, as a tool to advise funders on product support decisions and as guidance to product designers to direct development towards needed product types. In this context a TPP is understood as combining those attributes of a candidate product that are considered critical and a framework for its associated development pathway.

In summary, the primary goal of MPT development is to generate the highest impact products with the greatest degree of efficiency. Thus, decisions about that development process must take place in the context of a defined target product and take into account technical and strategic levels, both of which are highly dynamic, given a market and development environment that is constantly evolving.

Organizing Principles for the Preclinical Development of Multipurpose Vaccines for Sexual and Reproductive Health

Kevin Whaley, MAPP Biopharmaceutical

The pipeline of multipurpose vaccines for sexual and reproductive health (SRH) is presently nonexistent. Although single-purpose vaccines hepatitis B (HBV) and HPV are commercially available, no vaccines that prevent sexual transmission of chlamydia, gonorrhea, HIV, HSV, HIV, trichomonas, or other STIs are on the market. Nor are immunocontraceptives commercially available.

A number of opportunities could make multipurpose SRH vaccines a highly desirable product: (a) improved acceptability due to fewer immunizations; (b) potential for common adjuvants; (c) platform manufacturing that could decrease cost; and (d) new mucosal immunization regimens that could eliminate the necessity for needles and enable self-administration.

Similarly, resolution of some basic scientific challenges could enhance SRH vaccine potential. A major challenge for SRH vaccine development is a poor genital immune response that would prevent transmission of pathogens. The development of new vaccine technologies like gene-based vaccines, virus-like particles (VLPs), or novel adjuvants and delivery systems, driven by the quest to improve safety, tolerability and potency, could be helpful in this regard.

Because SRH vaccines constitute what is almost totally new terrain, the organizing principles for emerging multipurpose vaccines would be determined most effectively by product development teams dedicated to this whole new area of effort, focused on a strategic sequence of organizing principles *(Table 1).* Once a vaccine candidate is conceptualized, an algorithm is available for laying out its development pathway, beginning with preclinical toxicology testing, is available at:

http://www.niaid.nih.gov/topics/HIVAIDS/Research/vaccines/research/pages/preclinicaltoxicology.aspx.

TABLE 1. POTENTIAL ORGANIZING PRINCIPLES FOR MPT/SRH VACCINES
Subsets of pathogens targeted (HSV/HIV/ HPV; chlamydia/gonorrhea, other STI combinations)
Immunogen type (subunit, live, DNA)
Adjuvant (systemic, mucosal)
Manufacturing platform (mammalian, bacteria, yeast, plant)
Prime/boost strategy (systemic, mucosal)
Formulation (liquid, powder, device)
Target costs (per dose, per year)
Access target (physician, pharmacy, self-administered)
Schedule (infant, adolescent, adult)

DISCUSSION

- Experiences with early microbicide safety studies [e.g., nonoxynol-9 (N-9)] and subsequent trials of polyanions make it clear that close attention to allowable safe maximum frequencies for repeated dose applications is critical to forestalling the advancement of products that, while safe for occasional use, may be harmful at higher use frequencies. New diagnostic approaches that can measure safety at the mucosal level will afford the opportunity to discover such product issues in much earlier stages of development. While some products that did not show effectiveness initially -- again, the polyanions stand as an example -- they may warrant re-evaluation for different indications or circumstances, the initial bar for safety and efficacy of any product candidate has to be as high as possible.
- A wide range of product candidates will offer more opportunities for product selection.
- Research is emerging that is relevant to the development of new STI components that would be suitable for both developed and developing country markets, and could rekindle the interest of funders who are typically more concerned about user populations and markets in developed countries where HIV is not the primary public health concern.

KEY POINTS

Preclinical evaluations need to be designed that follow the critical pathway for IND studies set forth by the FDA and other pertinent regulatory authorities and accumulate the data on product properties and mechanism(s) of action that are required for IND review.

Target Product Profiles provide a strategic development process tool and should be evaluated based on science, indications, impact potential, and desired product characteristics.

Establishing "best practices" algorithms for decision-making will help to identify unsuitable product candidates at the earliest possible time point. Objective, technical "Go/No Go" decision points must be observed and acted upon at each step laid out in such algorithms.

Decisions on product candidates will have to be made in what is likely to be a highly dynamic development context; take into account new technical possibilities and strategic considerations; and evaluate the relative advantages, novelty, versatility, cost, and manufacturing and licensing requirements of new product candidates.

No **multipurpose STI or contraceptive vaccine** exists at this time, but would be highly desirable as an uncomplicated, one-time delivery mode that might increase MPT acceptability and access.

The **regulatory pathway for vaccines** is challenging and very different from the regulatory pathway for microbicides and contraceptives.

Even a robust preclinical pipeline will generate only a few candidates suitable for advancement into clinical stages of development, making **preclinical research on many compounds essential** to the viability and success of the MPT field.

The development of new STI components suitable for the MPT pipeline could attract new funders whose primary focus is on **developed-country markets**.

DETERMINING & ADVANCING PROMISING MPT LEADS

SUMMARY DISCUSSION

- The purpose of this final discussion was to consider the day's presentations and conversations and extract those concepts that could be considered the primary drivers of work going forward.
- A robust MPT framework will be required that will identify target populations across regional, cultural, and socio-economic backgrounds, characterize the products best suited to their respective needs, and define the desired indications accordingly. Such characterization will permit prioritization of drug candidates according to their stages of development, suitability for release in particular devices (e.g., gel, rings, films), and possible combination with other drugs. Organizing drug candidates according to such a framework will, correspondingly, organize discussion and determination of priorities, help identify underdeveloped fields, limit duplication of efforts by "siloed" research teams, and assist funders in making decisions about allocation of resources to particular aspects of the MPT development pipeline.
- The emerging priority indications for near-term multipurpose prevention products would seem to be prevention of unintended pregnancy and HIV transmission. From a regulatory perspective, the most efficient, nearer-term approach for MPT development would be to choose the path of least resistance and base the first round of MPT development on already approved products.
- Given their current stage of development and accumulated clinical data, it also appears that the combination of an antiretroviral, e.g., tenofovir, with a contraceptive hormone (HC), e.g., levonorgestrel, would merit development priority. While devices that constantly release tenofovir and contraceptives may be the best option for women who have frequent sexual relations, a combination of TFV gel with a SILCS diaphragm or a spermicidal gel may be suitable for women who have intermittent intercourse.
- Priority research gaps that must be addressed and then taken into account in the design of trials of any candidate MPT that is a combination of an ARVs and an HC are: (1) effects of hormones on the vaginal mucosa and, in the case of both ARVs and HCs, renal function, and (2) differences in female and male metabolism of the drugs being combined.
- Assessment of drug-drug interactions is a normal part of any R& D process and even single-API products must be examined for interactions with other licensed products that occupy the same space and are taken concurrently. New and quite sophisticated tissue and animal models can help predict such effects in preclinical studies, but expanded clinical safety studies including PK/PD measurements will remain essential to assess the effects in humans.
- The CAPRISA 004 trial results provided proof of the concept that 1% tenofovir gel is a viable drug for HIV prevention. Should the ongoing VOICE Phase 3 trial confirm the reductions in HIV and HSV transmission seen in CAPRISA 004, the 1% tenofovir gel will become the new standard for evaluating the efficacy of any comparison product, thereby introducing new complexities into the design of future trials.
- A large proportion of the CAPRISA 004 trial participants were diagnosed with non-HIV STIs and are representative of what is a chronic major problem in a wide range of national and regional settings. These infections constitute serious threats to reproductive, sexual, maternal, and child health and addressing them must be a key driver for the MPT pipeline.
- Pediatric vaccines have a track record of safety and efficacy against multiple indications; the cluster of STIs is amenable to a similar strategy. Independent of multipurpose STI vaccines, immunocontraceptives could be developed to prevent pregnancy when desired by end users.
- While there are highly-effective HPV and HBV vaccines on the market, HSV and HIV candidate vaccines are in clinical development but not yet commercially available. Some emerging STI

vaccines are delivered to the mucosa (e.g. nasal, cervicovaginal) to stimulate antibody and cell-mediated immunity in the reproductive tract and may enhance prevention.

- Multipurpose vaccines that address unmet need in developed, as well as developing countries, will aid in cost recovery.
- Although some MPT vaccines may have extended development timelines, they are potentially powerful technologies for sexual and reproductive health.
- The MPT development pipeline will require prioritization of candidates with the best promise for high efficacy, impact, and demand, which describes the situation in most developing countries. That said, priority attention should be paid to candidates with commercial viability that might serve to cross-subsidize less well-resourced regions. The pharmaceutical industry will be especially interested in products with developed-country market potential and whose track record includes completed proof-of-concept and robust clinical data.
- The involvement of private-sector business strategists to evaluate product candidates at the earliest possible time point in MPT product development could be critical to ensuring successful and sustainable implementation of any new MPT product.

KEY POINTS & FUTURE DIRECTIONS

A **robust MPT framework** is needed to:

- Identify target populations across regional, cultural, and socioeconomic backgrounds
- Characterize the products best suited to fit their respective needs
- Define desired indications, prioritize available drug candidates, and identify research gaps

Emerging priority indications for MPTs are pregnancy prevention and HIV prevention. Current stages of development make a combination of antiretrovirals (tenofovir, dapivirine, or MIV-150) with a contraceptive such as levonorgestrel the most immediately feasible option.

Gaps in knowledge regarding the effects of hormones on the vaginal mucosa, and on differences in female and male metabolism of these combined drugs, will be an obstacle in proceeding with that priority and therefore must be addressed as basic and translational research and parameters for clinical testing of such products.

Globally, non-HIV **STIs are a serious threat to reproductive health** and must be a driver of the MPT development pipeline. The current focus for MPT vaccines should be on the non-HIV STI indications.

From a **regulatory perspective**, the most efficient approach for MPT development is to build on the foundation of already-approved products.

Advancement of candidates with commercial viability will be critical. Early involvement of private-sector business strategists to evaluate candidates in the MPT pipeline could be extremely helpful in ensuring prospects for product success and sustainability.

The Think Tank participants agreed that the development of safe and effective MPTs is clearly feasible, although scientifically challenging. **The participants agreed to form two task groups to develop the MPT product development framework**, to includes specific Target Product Profiles with a focus on the following:

1. Combination products for the prevention of unintended pregnancy, HIV, and other STIs
2. Multipurpose vaccines

The Task Groups are to present and discuss their respective outputs at the International MPT Symposium, 3-4 November 2011 in Washington, DC.

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