

# MULTIPURPOSE PREVENTION TECHNOLOGIES

TECHNOLOGY LANDSCAPE AND POTENTIAL FOR LOW- AND MIDDLE-INCOME COUNTRIES



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# FOREWORD

Innovation is essential to better meet sexual and reproductive health (SRH) needs and preferences for all, especially key populations such as adolescent girls and young women (AGYW). Global health agendas, including for HIV and other STIs, are prioritizing people-centered services, community-tailored responses, solutions that overcome stigma, and integrated approaches that address complementary needs. Emerging multipurpose prevention technologies (MPTs) have the potential to be transformational by preventing multiple causes of mortality and morbidity at once, both in on-demand and long-acting formulations. These tools can be woman-initiated and have potential to be game-changers for the most at-risk populations.

Despite progress in recent years, the Sustainable Development Goal of ensuring universal access to SRH services, including family planning and HIV & STI prevention, diagnosis, and treatment services by 2030, will not be met without the development and introduction of novel solutions. In 2020, there were 1.5 million new HIV infections, a disproportionate burden of which was borne by vulnerable populations such as AGYW in Sub-Saharan Africa. In addition, there were 374 million new cases of curable sexually transmitted infections (STIs) globally. And, still today, over 200 million women of reproductive age in low- and middle-income countries (L/MICs) have an unmet need for contraception.

Further progress against HIV, STIs, and unintended pregnancy is only possible by taking the opportunity to address these overlapping global health challenges in a coordinated way and removing the silos to care. The rich pipeline of MPTs demonstrates the opportunity for change on the horizon; however, development of novel products alone is insufficient to reach target populations and achieve health impact. Preferences from targeted communities need to inform the design, introduction, and scale-up of MPTs from the early stages of development to ensure that end-user needs will be met, and products will be fit-for-purpose in priority settings, such as L/MICs. In addition to ensuring acceptability, market barriers will also need to be addressed to ensure that novel products are accessible and affordable through a broad supply base and an effective roll out strategy. These proactive considerations and timely interventions can enable the smooth introduction and rapid adoption of MPTs, therefore maximizing their ability to save and improve lives.

Empowering women to choose if and when they have children and enabling vulnerable populations to prevent morbidity and mortality caused by STIs and HIV is fundamental to human rights and gender equality. By improving sexual and reproductive health outcomes, MPTs also have the power to improve women's ability to pursue and attain their educational and economic goals, contributing to the advancement of their families and communities more broadly. The MPT Landscape Review highlights the potential of innovative tools to accelerate progress across these domains and outlines critical gaps that need to be addressed for this potential to be realized.

# ABBREVIATIONS AND ACRONYMS

AGYW	Adolescent Girls and Young Women
AMA	African Medicines Agency
API	Active Pharmaceutical Ingredient
ARV	Antiretroviral Drug
BV	Bacterial Vaginosis
CAB-LA	Long-Acting Injectable Cabotegravir
CADO	Conference on Antiretroviral Drug Optimization
CHAI	Clinton Health Access Initiative
CIFF	Children's Investment Fund Foundation
DPP	Dual Prevention Pill
EE	Ethinyl estradiol
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDI	Fast Dissolving Insert
FTC	Emtricitabine
GNP+	Global Network of People Living with HIV
HCP	Health Care Provider
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSV	Herpes Simplex Virus
IMPT	Initiative for Multipurpose Prevention Technologies
IND	Investigational New Drug
IPM	International Partnership for Microbicides
ISFI	In-Situ Forming Implant
ISL	Islatravir
IUD	Intrauterine Device
IVR	Intravaginal Ring
KII	Key Informant Interview
LAI	Long-Acting Injectable
L/MIC	Low- and Middle-Income Countries
mAB	Monoclonal Antibodies
MAP	Microarray Patch
MPP	Medicines Patent Pool
MPT	Multipurpose Prevention Technology
MSM	Men Who Have Sex With Men
MTCT	Mother-to-child transmission
MTN	Microbicide Trials Network
NGO	Non-governmental Organization
NIH	US National Institutes of Health
OTC	Over the Counter
PADO	Paediatric Antiretroviral Drug Optimization
PrEP	Pre-Exposure Prophylaxis
R&D	Research and Development
SRH	Sexual and Reproductive Health
STI	Sexually Transmitted Infection
TAF	Tenofovir alafenamide
TRIO	Tablets, Ring, Injections as Options Study
UNFPA	UN Population Fund
USAID	United States Agency for International Development
WCG	WomanCare Global
WHO	World Health Organization

# EXECUTIVE SUMMARY

An array of MPTs are in development for the prevention of two or more adverse SRH outcomes: unintended pregnancies, human immunodeficiency virus (HIV) and/or other sexually transmitted infections (STIs). External and internal condoms (also referred to as male and female condoms, respectively) are currently the only approved method that provide simultaneous protection against these interlinked SRH risks. New and more diverse types of MPTs can revolutionize the health of AGYW and other priority populations by better meeting their preferences and providing prevention for multiple indications. Globally, there is a prevailing preference for MPTs over single indication products across populations and geographies, with as many as 96% of women surveyed in parts of sub-Saharan Africa indicating their preference for MPTs. Preferences for specific product attributes, such as delivery form and duration of protection, vary widely across settings and populations. As such, it is important to advance a robust pipeline of MPTs to enable end-users to choose the method that best suits their needs.

Key benefits of MPTs perceived by end-users include the potential for a reduction in clinic visits and alleviation of the stigma associated with HIV and sexual activity. Moreover, the need for more streamlined approaches to SRH product and service delivery has been underscored by barriers posed by the COVID-19 pandemic. The promise of MPTs can be transformative and improve SRH outcomes globally if emerging products are accessible, affordable, and fit-for-purpose to meet the needs of diverse populations in a range of contexts, especially L/MICs where they have potential to be most impactful [1].

To realize this potential, end-user preferences must be considered from the early stages of development. For example, attributes for which users indicate the greatest preference include being discreet, long-acting, and easy to store and transport [2], [3]. MPT R&D is leveraging recent progress in single-indication products, such as contraceptives and HIV pre-exposure prophylaxis (PrEP), yet MPT development remains scientifically and logistically complex and the majority of products are in early stages of development. As such, this is a critical time to engage communities and plan for timely interventions that can advance the pipeline and accelerate access [4].

Most MPTs are being developed by academic researchers and small biotechnology companies. The resources critical for transitioning promising preclinical product candidates and formulations into clinical evaluation remain limited despite intensified collaborations and investments between government and private sectors. As such, only the products with the highest potential impact should be prioritized to move forward to introduction. A coordinated and well-funded response to the gaps and next steps outlined in this report can optimize use of technical capacities, enhance collaboration, leverage additional resources, support prioritization according to needs in L/MICs, and add rigor to the development process required to advance the most promising products.

This review provides an overview of the landscape of MPT product candidates currently in development, acknowledging that the field is dynamic, and the array of product candidates will change over time. It builds on data gathered annually by the IMPT, as well as other publicly available literature and resources for MPT candidates. **Section 4**



includes a summary of all topical delivery types currently in development (vaginal rings, vaginal and rectal gels, fast dissolving inserts, enemas, and vaginal films), followed by systemic delivery types currently in development (oral pills, long-acting injectables, implants, and microarray patches).

Considerations from end-user studies relevant to MPTs are summarized in **Section 5**, with a focus on L/MICs. Numerous end-user studies of biomedical HIV prevention product preferences, based primarily on theoretical product use and conducted in sub-Saharan Africa and the United States, have confirmed that women would **prefer an MPT over single-indication products**. As noted in Section 5, this preference for multipurpose products seems to outweigh preference for a particular delivery type.

Finally, **Section 6** of the report provides a summary of the pathway to MPT introduction and scalability in L/MICs. Building upon critical insights from key experts in product development, introduction, regulatory, and marketing as well as end-users' perspectives, considerations and recommendations for MPTs in L/MICs are outlined with an emphasis on areas where supporting agencies can strategically help advance the MPT field.

### MPT technical landscape

- **Nearly half of the products currently in the pipeline are rings** but, importantly, there is a growing number of MPT product candidates providing systemic drug delivery, such as injections or implants.
- The MPT field is expanding with the inclusion of **diverse Active Pharmaceutical Ingredients** (APIs), in addition to the typical combination of hormonal contraceptives and antiretroviral drugs. New molecules are being investigated, including biologics (monoclonal antibodies) and non-hormonal contraceptives.
- The number of product candidates with **non-HIV STI indications is also expanding**. Several of these products offer prevention of other viral STIs such as HSV-2, or bacterial STIs such as chlamydia and gonorrhea, in combination with HIV prevention or contraception.
- While the focus of MPT R&D to date has primarily been on **cisgender AGYW practicing vaginal intercourse**, some MPTs that address combined risks for HIV and other STIs **hold promise for those who practice receptive anal intercourse**, including men who have sex with men (MSM).
- A key technical challenge for MPT development is **combining or co-formulating APIs for different indications** that can be delivered for the same duration, safely and effectively. Complexities include competing metabolic pathways, differing drug release patterns in devices used to combine APIs with different hydrophobic and hydrophilic chemical properties, and API compatibility with the polymers used in drug delivery devices.
- Most pre-clinical MPT candidates are developed by academic researchers and small biotechnology companies, mostly supported by the U.S. government (United States Agency for International Development (USAID) and National Institutes of Health (NIH)).

- Progression from the pre-clinical stage through phase 1-3 clinical evaluation is a challenge, and **many pre-clinical products never reach clinical development**. While some of this loss is due to attrition, the development of many innovative and **promising product candidates by academic laboratories and smaller companies often stalls** due to **insufficient financial resources**, and training and regulatory expertise, resulting in major losses to drug development efforts.

### End-user considerations

- Incorporating **end-user research early** and throughout the R&D has become increasingly recognized as a critical part of the product development process to optimize and align products with end-user preferences and needs.
- Numerous end-user studies of biomedical HIV prevention product preferences, based primarily on theoretical product use and conducted in sub-Saharan Africa and the United States, have confirmed that women would **prefer an MPT over single-indication products**. This preference for multipurpose products seems to outweigh preference for a particular delivery type. Further research is warranted.
- While user preferences vary and are dependent on many factors, among women in sub-Saharan Africa, there is generally a **preference for discreet and familiar provider-administered long-acting products** (i.e., injectables and implants), over less familiar user-controlled or on-demand delivery forms of MPTs. For novel user-controlled methods, end-users prefer to have initial training by health care providers before managing self-administration and a built-in feedback mechanism to increase confidence that the product is working correctly.

### Pathway to introduction and scalability of MPTs in L/MICs

- Large-scale **manufacturing capabilities and intellectual property status** will impact the complexity of each MPT product's regulatory pathway, manufacturability, availability, cost, and feasibility, key to ensuring uptake and a pathway to scale in L/MICs.
- **Implementation research and demonstration studies** should inform international and national recommendations, as well as practicalities for improved access and use for the end-users.
- Visibility on future uptake, including key elements for selection and **procurement by L/MICs and funders regarding emerging MPT products, would be required to timely inform development as well as plans for production at scale**.
- Careful and efficient planning, from end to end, is warranted to ensure that products that eventually prove safety and efficacy are quickly timely introduced in countries and brought to scale. **Learnings from introduction of long-acting contraception, and current introduction of emerging options in long-acting PrEP, and ongoing efforts to integrate HIV and family planning services would support such strategic planning**.

## Key gaps and next steps

The following key gaps and next steps identified through this review merit further exploration by a range of MPT stakeholders and funders to advance the MPT field:

### (1) Critical research and interventions required to inform product development and investment

- Prioritize **integration of community and end-user perspectives**, especially from L/MICs and key populations, into MPT R&D and introduction strategies.
- Assist MPT researchers/developers (academic labs and start-ups) to **identify and access MPT-relevant active pharmaceutical ingredients (APIs)** from medicinal chemists and pharmaceutical companies.
- Engage with MPT researchers/developers on **favorable terms related to licensing and intellectual property** that enable global access and adequate supply capacity in L/MICs.
- **Increase industry involvement** in MPT R&D to achieve scalability of products ensuring access is built in in any agreement.
- **Optimize funding to support promising MPT candidates between phase 1 and phase 2** development to inform investment decisions by pharmaceutical companies and other investors.
- Assess the risks and benefits of **co-administering single-indication products vs co-formulating MPTs, including end-user preferences**. As new PrEP products become available in formulations aligned with existing contraceptives (e.g. pills, long-acting injections or implants), these can be implemented as separate products that are co-administered or MPTs that are co-formulated.

### (2) Critical policy and access elements required to accelerate and simplify market entry

- **Early involvement of both communities and commercial partners to inform design, introduction and production at scale** is essential to ensure acceptability, equitable access, and timely market entry for the most impactful products.
- **Ensure access elements (low production cost and selling price, ease of use amongst key populations, capacity for manufacturing, intellectual property sharing, availability at country level)** are included in commercialization and introduction strategies and plans.
- Ensure **adequate benchmark criteria are applied when prioritizing MPT candidates**, such as through the establishment of a target product profile and/or an objective committee that determines prioritization for global development.

### (3) Critical research and actions required to inform successful product introduction

- **Support implementation research and demonstration studies** which could provide important evidence to inform deployment and implementation strategies and guidelines, including co-administered and co-formulated options.
- Include **health care providers** in end-user and implementation science research.
- **Plan early for introduction and future adoption.** MPT awareness raising, civil society engagement, promotion and training for target populations and health care providers are all needed early to help ensure potential end-users start thinking about MPTs well before they reach the market.
- **Simplify accessibility and method delivery**, including through the **self-care approach**. Offering a one-stop shop for multiple prevention needs, some types of MPTs (depending on the delivery system and APIs) have the potential to expand self-care options for end-users.

MPTs present considerable SRH opportunities for addressing multiple indications in at-risk populations, particularly AGYW in regions of the world where risk of HIV, other STIs, and unintended pregnancies remains high. Given limited resources for expansion of MPT product development and complex product profiles, ongoing strategic thinking and coordinated action is necessary between all stakeholders, including high priority communities. A harmonized and well-funded response will ensure that MPT product candidates are not only technically feasible, but also, importantly, are cost-effective and acceptable to end-users globally.

## I. LANDSCAPE OBJECTIVE

The objective of this report is to provide an overview of the current landscape of MPTs, products that simultaneously prevent HIV, other STIs, and/or unintended pregnancy, and assess their relevance and potential challenges for L/MICs. The report aims to support the timely introduction of these innovations and identify challenges, including in research and development (R&D) or related to market entry, which may hamper the adoption and impact of MPTs in L/MICs if not promptly addressed.

The IMPT, a product-neutral global collaboration that advances the field of MPTs, was founded in 2009 by researchers, policymakers, funders, and advocates working across the spectrum of women's global health to help facilitate strategic thinking for MPT development. MPTs currently in development are tracked annually and updated in an online MPT product development pipeline database [5], [6].

Unitaid and the Children's Investment Fund Foundation (CIFF) have identified overlapping interests to further assess the potential of MPTs, leading to a partnership to enrich the design of this landscape.

Unitaid makes a unique and high-impact contribution to the global response in areas including HIV/AIDS, tuberculosis, and malaria in L/MICs. It invests in forward-looking and time-limited investments that are designed to increase access to better, more effective and more affordable health products. Investments typically target market-based interventions such as price reductions, improvements in quality and supply, and the introduction of fit-for purpose, innovative products that are adapted for the people who may benefit from them the most. Through its investments in novel products, Unitaid also aims to accelerate the impact of long-acting technologies in L/MICs, and identifies MPTs as promising tools in its HIV Disease Narrative [7] as well as in its Reproductive, Maternal, Newborn, and Child Health Thematic Narrative [8].

CIFF is the world's largest philanthropy that focuses specifically on improving children's lives, including work in the areas of maternal and child health, adolescent sexual health, and increasing opportunities for girls and young women. Core to achieving CIFF's goals of ending unwanted pregnancy and HIV infection is ensuring that girls and women have access to a basket of product choices that meet their diverse sexual and reproductive health needs. CIFF supports new product innovation and market entry where products address under-served needs or preferences and where they enable women to exercise autonomy over their sexual and reproductive health.

## 2. METHODOLOGY

This review focuses on MPT product candidates that are in all stages of preclinical and clinical development. The search strategy included three principal avenues: product developer surveys, a desk review, and key informant interviews.

**The product developer surveys** consisted of 18 questions about each MPT candidate, four of which were supplemental questions added specifically to align with this landscape assessment and vetted by United and CIFF to be included as part of the IMPT's annual MPT product development pipeline update process. The research team surveyed 18 product developer organizations, representing the products in the MPT pipeline as of July 2021. 83% of the product developer organizations surveyed responded (n=15). 87% of respondents (n=13) included information about the supplemental questions, in addition to the standard questions. All responses were compiled and reviewed to reflect the most up to date information in this review, particularly the technology landscape (section 4).

**The desk review** consisted of reviewing MPT technologies in all stages of development – both those already in the MPT Product Development Database [6] and those identified through a supplementary literature review for the purpose of this report to ensure all new or emerging MPT candidates are reflected. A desk review was also conducted on available end-user research for MPT candidates, technical and regulatory considerations and challenges, and market considerations for MPTs, including product introduction and rollout considerations. The keywords for the search included: multipurpose prevention technology, multi-purpose prevention, dual prevention, dual method, HIV, contraception, STI, microbicide. The search included a review of the following databases with peer-reviewed publications, publicly funded research, and ongoing registered clinical trials: PubMed, National Institutes of Health (NIH) RePorter, and ClinicalTrials.gov, as well as other online resources. Lastly, recent conference abstracts for 2020-2021 were included in the search from the following conferences and annual meetings: IAS (International AIDS Society), HIV R4P (HIV Research for Prevention), and CROI (Conference for Retroviral and Opportunistic Infections).

**The key informant interviews (KIIs)** consisted of identifying and conducting qualitative interviews with technical experts in the areas critical for this assessment. A total of 28 key informants participated through 24 interviews, representing a vast array of HIV and STI prevention and contraception expertise. They included product developers, regulatory experts, program implementers, civil society leaders, policy makers, and donors/supporting agencies, among others. Some of the key informants aligned with multiple stakeholder categories. Respondents brought L/MIC perspectives from sub-Saharan Africa, Latin America, and the Asia Pacific Region. A list of the key informants that participated in this review is available in Appendix A. To facilitate this process, the research team developed a pre-KII self-administered form and a KII interview guide. These tools were used to explore key informant input on missing/outdated research in the product developer surveys and desk review and other additional details on new or ongoing MPT R&D, as well as insights around priority MPT approaches and indications, key gaps and challenges, and recommendations for the field. Following the interviews, the research team aggregated and reviewed the interview notes to identify key themes. Key themes and KII insights are reported on in section 6 of this report (Pathway to introduction and scalability of MPTs in L/MICs).

### 3. PUBLIC HEALTH CHALLENGES IN THE PREVENTION OF HIV, OTHER STIS AND UNINTENDED PREGNANCY

Women, including AGYW in L/MICs, experience a range of SRH challenges. The HIV and STI syndemic and the unmet need for modern contraceptive methods continue to pose significant health risks for AGYW [9]. The number of new HIV infections globally per year – 1.5 million – showed limited decrease from 2018 to 2020 [10]. Women and girls are at a heightened risk of HIV in many regions of the world in sub-Saharan Africa where they accounted for 63% of all new infections in 2020 [11], [12]. Globally, HIV remains a leading cause of death for women of reproductive age. The risk of HIV acquisition and transmission through mother-to-child transmission (MTCT) and among pregnant and breastfeeding women are significant contributors to the HIV epidemic [13].

Rates of other STIs, such as gonorrhoea, chlamydia, syphilis, and herpes simplex virus (HSV) are rising and compounding the risk of HIV acquisition [14], [15]. These STIs are major causes of genital inflammation and have a negative impact on the female genital mucosa, which is an important biological and physical barrier that forms the first line of defense against invading microorganisms such as HIV, and are thus implicated in increased risk of HIV acquisition and transmission. Many STIs, particularly non-ulcerative infections, are often missed due to poor sensitivity and may remain asymptomatic and untreated for long periods of time [16]. Untreated STIs can also cause severe reproductive health complications in women, including stillbirth, preterm delivery, infertility, and cancer, among others. Another challenge is antibiotic resistance. *Neisseria gonorrhoeae*, for example, is increasingly resistant to standard antibiotic drug therapies [17], further underscoring the need for expanded prevention options.

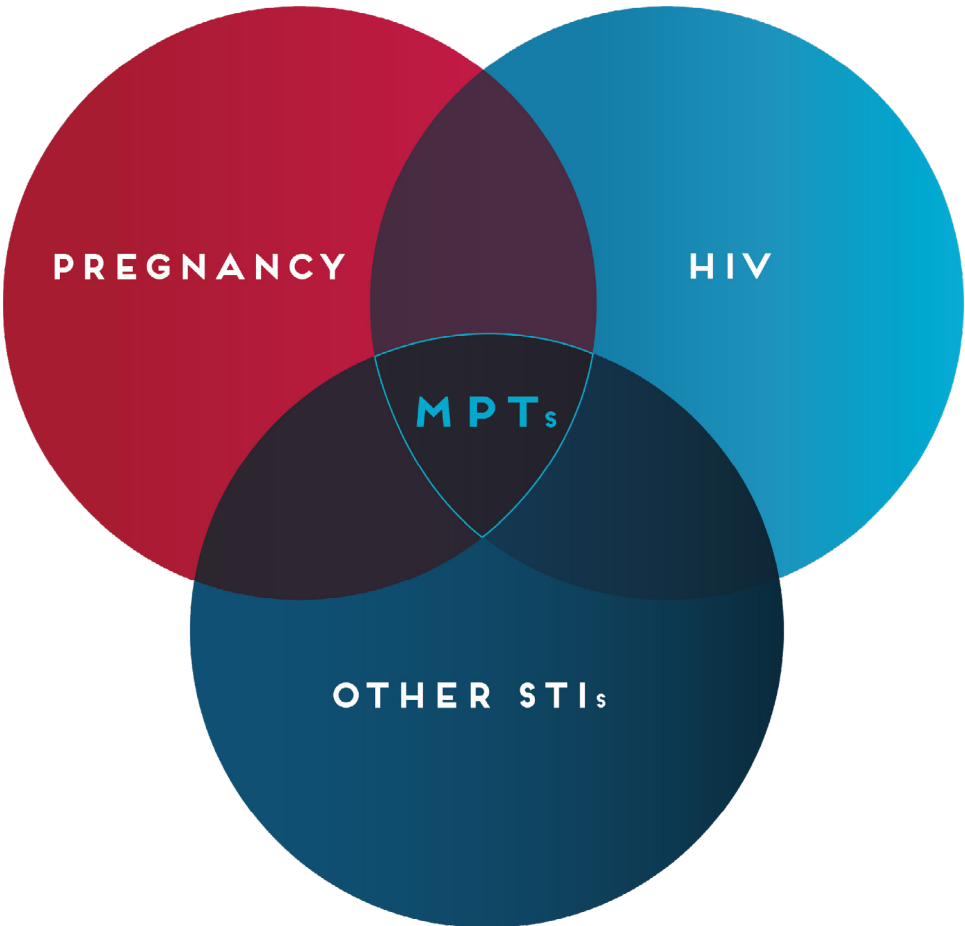
Concurrently, out of 923 million women of reproductive age in L/MICs who want to avoid having a pregnancy, an estimated 218 million have an unmet need for contraception—that is, they want to avoid a pregnancy but are not using a modern method [18]. Unmet need amongst women living with HIV is reported to be even greater with data from a number of high prevalence settings. 817 women die each day from preventable causes related to pregnancy or childbirth [15]. Sub-Saharan Africa also has the highest proportion of women worldwide who have an unmet need for contraception [19]. In sub-Saharan Africa, young women aged 15-24 years are twice as likely to be living with HIV and other STIs than men [19]. The correlates of risk for unintended pregnancy, HIV and other STIs among women is complex and extend beyond traditional, individual risk factors to underlying structural factors.

As awareness of the need to address these interlinked risks has increased, the need for new technologies that combine protection against unintended pregnancy, HIV and other STIs is a growing research priority [20]. Addressing these interlinked risks also aligns with the goals of the World Health Organization (WHO)-led initiative for the elimination of maternal-to-child transmission of HIV and syphilis as a public health priority [13].

These data underscore the need for innovative prevention products that can simultaneously address multiple, overlapping health risks (Figure 1). MPTs are being designed to deliver multifaceted reproductive health prevention, largely focused on contraception and prevention of HIV and/or other STIs. Building on over 60 years of contraceptive research and several decades of HIV prevention research, the MPT field formally emerged over a decade ago to address the intrinsic links between unintended pregnancy, HIV and other STIs by developing single products with multiple indications. While the focus of MPT research today, and this report, is on cisgender women, some dosage forms of MPTs that address combined risks for HIV and other STIs hold promise for those who practice receptive anal intercourse, including MSM.

For MPTs to successfully meet the public health opportunities and challenges outlined here, they must not only be technically feasible but also, importantly, acceptable to end-users and cost-effective. The following sections of this report explore MPT progress to date and opportunities to strategically address gaps to ensure the most promising MPT candidates reach the hands of end-users.

**FIGURE 1.** Multipurpose Prevention Technologies





## 4. MULTIPURPOSE PREVENTION TECHNOLOGY PIPELINE LANDSCAPE

### Highlights from the MPT Pipeline Landscape Assessment

- **Nearly half of the products currently in the pipeline are vaginal rings** but, importantly, there is a growing number of MPT product candidates providing systemic drug delivery, such as injections or implants.
- The MPT field is expanding with the inclusion of **diverse** APIs, in addition to the typical combination of hormonal contraceptives and antiretroviral drugs. New molecules are being investigated, including biologics (monoclonal antibodies) and non-hormonal contraceptives.
- The number of product candidates with **non-HIV STI indications is also expanding**. Several of these products offer prevention of other viral STIs such as HSV-2, or bacterial STIs such as chlamydia and gonorrhea, in combination with HIV prevention or contraception.
- While the focus of MPT R&D to date has primarily been on **cisgender AGYW practicing vaginal intercourse**, some MPTs that address combined risks for HIV and other STIs **hold promise for those who practice receptive anal intercourse**, including MSM.
- A key technical challenge for MPT development is **combining or co-formulating APIs for different indications** that can be delivered for the same duration, safely and effectively. Complexities include competing metabolic pathways, differing drug release patterns in devices used to combine APIs with different hydrophobic and hydrophilic chemical properties, and API compatibility with the polymers used in drug delivery devices.
- Most preclinical MPT candidates are developed by academic researchers and small biotechnology companies, mostly supported by the U.S. government USAID and NIH.
- Progression from the preclinical stage through phase 1-3 clinical evaluation is a challenge, and **many preclinical products never reach clinical development**. While some of this loss is due to attrition, the development of many innovative and **promising product candidates by academic laboratories and smaller companies often stalls** due to **insufficient financial resources** and training and regulatory expertise, resulting in major losses to drug development efforts.

## 4.1 Product development efforts and technology status: Introduction

The IMPT, along with a number of other organizations (e.g., funders/investors, advocates, etc.) have kept track of the active development of MPT products and technologies. The IMPT's MPT Product Development Database [6] is updated annually and on a rolling basis and reviewed for accuracy in a product-neutral manner. As of September 2021, over two dozen MPTs are in active development. Figure 2 below provides a top line summary of the MPT products currently in the pipeline.

FIGURE 2. Status of MPTs in the Pipeline (N=26)\*

Indications		Preclinical	Phase 1	Phase 2	Phase 3	Pre-market approval
HIV + Pregnancy	T					
	S					
HIV + STIs						
HIV + STIs + Pregnancy						
STIs + Pregnancy						

\*adapted from MPT Product Development Database (mpts101.org)

### Legend:

Topical (T)	
Intravaginal Rings	
Gels (Vaginal + Rectal)	
Films (Vaginal)	
Fast-Dissolving Inserts (Vaginal)	
Enemas	
Systemic (S)	
Implants	
Injectables	
Microarray Patches	
Oral Pills	

The majority of the products currently in the pipeline are funded by the public and philanthropic sectors (see more on MPT R&D funding in section 6).

The current MPT candidates include an expanded set of indications, several of which hold promise to fill the gap for biomedical prevention products targeting non-HIV STIs. Most of these products are in very early-stage development (preclinical or limited early clinical).

Another common element is that many of these products are intended to be female-initiated, with eleven (almost half of all products in development) configured as intravaginal rings (IVRs) – also referred to as vaginal rings or rings. Importantly, there is a growing number of MPT products with systemic long-acting administration.

Another important trend in MPT development is the expansion of API types used to address the increasing number of indications. The field originated primarily from hormonal contraceptive drugs and antiretroviral drugs (ARVs), since preventing HIV and unintended pregnancy was considered the initial fieldwide priority. This had the advantage of using drugs that were well-established (separately) for contraception and HIV treatment or prevention (e.g., regulatory approval, safety and efficacy data from patient use, API manufacturing methods and capacity in place, etc.). As summarized in the sections below, today a number of alternative APIs are being investigated for use in MPTs, including biologics (monoclonal antibodies) and non-hormonal contraceptives. For more information on APIs for potential MPTs, please refer to the following: *The Future of ARV-Based Prevention and More* [145] and *Compounds with Potential Activity to Prevent or Treat HIV and Other Sexually Transmitted Infections: A Landscape Review* [113].

Different products and health sectors define ‘long-acting’ as different lengths of time. For the purpose of this report, ‘long-acting’ products are defined as sustained/extended release products that allows for a long duration of intended effect. For example, at least a month for injectables and other devices such as implants, patches or rings. ‘Short-acting’ products are anything with a shorter target duration. In alignment with this definition, the target durations for 26 products in the pipeline are included in the product summary tables below. These are anticipated durations and subject to change, as many MPT candidates are still in early stages of development. For this reason, numerous product candidates also list a range of time for the target duration while, for others, it is unspecified.

What follows is an outline of the product candidates currently in the MPT pipeline with active funding, organized by delivery type. The first section (4.2) includes all topical delivery types currently in development: intravaginal rings, vaginal and rectal gels, fast dissolving inserts, enemas, and vaginal films. The second section (4.3) includes all systemic delivery types currently in development: oral pills, long-acting injectables, implants, and microarray patches. The sub-sections for each specific delivery type include a summary of the specific products in the pipeline that leverage that technology. The product summaries contain publicly available information, including that in IMPT’s public-facing MPT Product Development Database [6], as well as in-depth explanations of the technology form, API combinations, dosage information including target duration when available, cold-chain requirements (if any), clinical trial and target population plans (if available), among others. Subsequent sections of this report review end-user acceptability study findings relevant to MPTs, consider pathways for MPT product introduction, and provide insights from experts on the applications of MPTs in L/MICs.

## 4.2 Topical MPT product candidates

This category of MPT products follows in the path of early-stage microbicide products for HIV prevention. What has been learned from these early microbicide on-demand product development efforts in terms of advantages and challenges, end-user preferences and partner perceptions on the use of such products can largely be applied to MPT products of the same type. A great deal of data from end-user research on these types of products is available (see section 5).

With the exception of rings, the majority of the topical product candidates are short-acting. To the extent possible, the delivery types that currently have the most advanced stage products are presented first (rings, vaginal and rectal gels, enemas, fast dissolving inserts, and vaginal films), acknowledging this may change over time. Table 1 (rings) and Tables 2-5 (other topicals) include a top line summary of the topical MPT products described in this section.

### 4.2.1 Vaginal Rings

**TABLE 1.** Intravaginal Rings (IVR) in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
Copper Intravaginal Ring (Cu-IVR)	copper	HSV-2, Zika Virus, Pregnancy	Early Preclinical	N/A
dapivirine/irivirine + pritelivir + levonorgestrel 3D Printed IVR	dapivirine, levonorgestrel, pritelivir	HIV, HSV-2, Pregnancy	Early Preclinical	1 month
islatravir (EFdA) + etonogestrel/ethinyl estradiol 3D Printed IVR	etonogestrel, ethinyl, estradiol, islatravir	HIV, Pregnancy	Early Preclinical	90 days
90-day Pod-type etonogestrel/ethinyl estradiol/Q-Griffithsin (EQQ) IVR	etonogestrel, ethinyl, estradiol, Q-Griffithsin	HIV, Pregnancy	Early Preclinical	90 days
Novel mAb contraceptive + tenofovir disoproxil fumarate IVR	monoclonal antibodies, tenofovir disoproxil fumarate	HIV, Pregnancy	Early Preclinical	28 days and 90 days
dolutegravir + rilpivirine + acyclovir + ethinyl estradiol + etonogestrel IVR	acyclovir, dolutegravir, etonogestrel, ethinyl, estradiol, rilpivirine	HIV, HSV-2, Pregnancy	Advanced Preclinical	30-90 days
Human contraceptive antibody + VRC01+N6 IVR	human contraceptive antibody, VRC01+N6	HIV, Pregnancy	Advanced Preclinical	1 month
mAb 2C7 + tenofovir disoproxil fumarate IVR	monoclonal antibodies, tenofovir disoproxil fumarate	Gonorrhea, HIV	Advanced Preclinical	1 month
dapivirine + levonorgestrel IVR	dapivirine, levonorgestrel	HIV, Pregnancy	Phase 1 Clinical Trial	90 days
tenofovir IVR	tenofovir	HIV, HSV-2	Phase 2 Clinical Trial	90 days
tenofovir + levonorgestrel IVR	tenofovir, levonorgestrel	HIV, HSV-2, Pregnancy	Phase 2 Clinical Trial	90 days

There are multiple types of rings that differ in terms of configuration, drug compatibility and mechanism of drug release, polymer systems involved, and manufacturing processes. Most rings in development include HIV prevention as one of the indications, with the lead combination being HIV prevention and contraception. There are eleven rings in the database which are described below. Some of the different ring technologies for MPTs are described in Figure 3. Additional structural details on different types of rings can be seen in Krovi et al [21].

**FIGURE 3.** Examples of Ring Designs

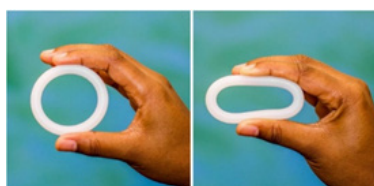
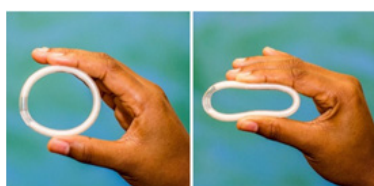


Image source: MTN. (2018). MTN 036 In-depth interview topic guide: Ring Comparison Tool [Photograph]. [https://www.mtnstopshiv.org/sites/default/files/mtn\\_036\\_idiguide\\_v1.1\\_19feb18.pdf](https://www.mtnstopshiv.org/sites/default/files/mtn_036_idiguide_v1.1_19feb18.pdf)

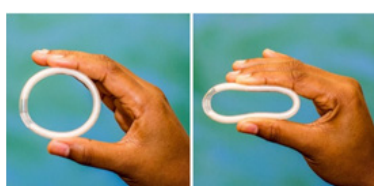
**Silicone matrix ring:** APIs are incorporated directly into the silicone matrix, rather than inside tubes, as noted in the segmented, dual reservoir ring below. This type of ring is perhaps the simplest from design and manufacturing perspectives and is consistent with the hormone replacement type ring products already on the market. However, this simplistic design could also provide challenges for delivery for multiple drugs that differ in terms of physical-chemical properties.

Controlling stability and desired release kinetics of different drugs with this design could be difficult to achieve, depending on the specific drugs and the desired release kinetics, and the potential need to avoid drug-drug interactions in the device. **[Example iii.]**



**Segmented, dual reservoir ring:** This design involves hollow, polyurethane tubes of two types to accommodate different release rates for drugs that differ in terms of physical and chemical properties. Release rates can also be altered per drug based on length of the specific drug segment and thickness of the tubing wall. Although this

design strategy can likely accommodate independently regulated release kinetics of different drugs in the device, the manufacturing element of this approach could provide challenges and increased costs, relative to the matrix type ring (see above). **[Example i. and ii.]**



**Pod ring:** This technology has been reported to deliver multiple drugs targeting independent indications with a unique ring design [22], including antibody delivery [23], [24]. The pod ring typically involves a solid silicone ring produced by injection molding, which subsequently is modified through the generation of small “pods” in the

ring. In an independent process, a tablet-like formulation of the API is produced and packed into the pods. Once this material is packed into the pod, a thin coating is applied to the entire surface of the ring, serving as a release regulating sealant over the pods. Thus, release of individual APIs is controlled by the number of pods, the amount of drug packed into a pod, the surface size of each packed pod in the ring, and the type and amount of final sealant in the ring surface. The opening of the pods can have different diameters to achieve different release rates. Some pods can include the same drugs if such delivery levels are needed, or if a longer duration of delivery is required. **[Example iv. and v.]**

### **i. Tenofovir + levonorgestrel IVR (CONRAD, USA)**

CONRAD first published their initial MPT ring development efforts in 2014, which focused on prevention of unintended pregnancy and HIV prevention, through vaginal delivery of two different API [25]. Levonorgestrel is a synthetic progesterone with a long-established history in contraceptive products, either in combination with an estrogen as an oral contraceptive [26], as a single API in a Plan B type emergency oral contraceptive, in subdermal implants (e.g., Norplant®) [27], in an API delivered via an intrauterine system (IUS) [28], and in contraceptive rings [29]. Other progesterone-delivering rings have also been developed with or without co-delivery of an estrogen for contraception (e.g., NuvaRing®, Merck & Company; Progering®, Laboratorios Andrómaco SA, Santiago, Chile, respectively).

In the case of the CONRAD rings, contraception relies exclusively on the delivery of levonorgestrel into the vagina. The HIV prevention indication is addressed via vaginal delivery of the HIV treatment drug, tenofovir, which has been shown to prevent HIV infection with daily oral administration [30]. Tenofovir is a nucleoside analog that functions as an inhibitor of HIV reverse transcriptase (a non-nucleoside reverse transcriptase). The use tenofovir topically in the CONRAD ring is further supported by the results obtained from the phase 2 trial with tenofovir vaginal gel, which was applied at the time of sexual intercourse (before and after sex) and demonstrated partial protection from HIV infection in South Africa. Interestingly, in the analysis of a subset of women in the same study, the tenofovir gel demonstrated a significant reduction in incidence of herpes simplex virus 2 (HSV-2), consistent with earlier non-clinical evaluations of tenofovir against HSV-2. In fact, the prevention effect on HSV-2 was more pronounced than it was on HIV incidence [31].

As for the ring formulation, the CONRAD ring is a “segmented,” dual reservoir ring comprised of two tubes made of different types of polyurethanes [25]. Specifically, the tenofovir reservoir urethane tube is made of hydrophilic poly (ether urethanes) and the levonorgestrel reservoir is comprised of simpler polyether urethanes. This MPT configured ring targeting HIV and HSV prevention in women as well as contraception has been evaluated in multiple clinical trials [32], [33], targeting as much as 90 days of use in a phase 2 trial [34].

### **ii. Tenofovir-only IVR (CONRAD, USA)**

CONRAD has also developed a tenofovir-only ring using the same product principles and details outlined in example i., however this does not include a contraception indication. The only API is tenofovir. This ring is still an MPT candidate because it targets HSV and HIV prevention. The dimensions for both rings are the same: overall ring diameter at 55 mm; cross sectional diameter per tube at 5.5 mm. This ring was also evaluated in clinical trials along with the version that included levonorgestrel that were as advanced as far as phase 2.

### **iii. Dapivirine + levonorgestrel IVR (International Partnership for Microbicides (IPM), USA)**

Dapivirine is a non-nucleoside HIV reverse transcriptase inhibitor, which was first formulated in a silicone matrix ring alone as an HIV prevention product for women, originally intended for 1 month of use. This dapivirine-only ring, as a predecessor to the dapivirine+ levonorgestrel MPT ring, was advanced through phase 3 trials and was found to be safe, effective and acceptable [28], [29]. It is now under final stages of local country regulatory review for use in populations in sub-Saharan Africa after being deemed acceptable by the European Medicines Agency (EMA) and has received WHO pre-qualification as well as approval in at least two countries in sub-Saharan Africa.

This is a silicone matrix ring, manufactured via injection molding, where the API is incorporated directly into the silicone matrix, which differs from the filled urethane tube configuration of the tenofovir-only ring. The dimensions of the IPM ring are very similar to those of the CONRAD rings. More recently, the dapivirine ring was shown to be safe in adolescent girls (average age 16 years) in a phase 2a randomized placebo controlled clinical trial [35]. An ongoing multi-site open label phase 2a trial in sub-Saharan Africa (REACH) among AGYW has confirmed ring safety and demonstrated high adherence to the ring during 6 months of use [36], which is relevant for effective product use in AGYW.

The advanced form of the dapivirine ring is a single indication product (HIV prevention). However, IPM, the primary developer of this product, has initiated a meaningful advancement of this product as an MPT by adding delivery of levonorgestrel for a contraception indication to the dapivirine-only version as a next generation product [37], [38]. This is a similar design to the dapivirine-only ring, with necessary modifications to achieve appropriate delivery of the two APIs (dapivirine and levonorgestrel). This next generation MPT product has been engineered to deliver dapivirine for HIV prevention and levonorgestrel for contraception for 90 days and has undergone clinical evaluation in multiple clinical trials by the Microbicide Trial Network (MTN), including: MTN030, MTN036, and MTN044 [39], [40], [41].

#### **iv. mAB 2C7 + tenofovir disoproxil fumarate IVR (MassBiologics; Oak Crest Institute of Science; Planet Biotechnology, Inc; University of Massachusetts, USA)**

This product focuses on the development and use of a novel API, specifically the chimeric monoclonal antibody (mAB) 2C7 for the inhibition of gonorrhea infection, along with tenofovir disoproxil fumarate for the prevention of HIV infection and possibly HSV prevention. Thus, this is an MPT targeting STIs that is relying on a novel MPT ring API—a human immunoglobulin. Tenofovir disoproxil fumarate is a prodrug of tenofovir, an antiretroviral described earlier in products i. and ii. The use of 2C7 is a unique effort attempting to address the fact that multi-drug resistant N. gonorrhea is an expanding global health concern. The mAB 2C7 specifically targets a lipooligosaccharide epitope that is expressed by >95% of N. gonorrhea clinical isolates. Additional details on the mAB 2C7 API, including animal model efficacy data, have been published [42]. This product is in advanced preclinical development.

The unique challenge of this product concept is the delivery of a mAB API from a ring. This is being addressed with a novel ring technology known as the “Pod” ring, which is described in Figure 3 above. The silicone skeleton of this specific ring would have similar dimensions as the silicone matrix rings described earlier, and could accommodate as many as ten different pods.

#### **v. Contraceptive mAB + tenofovir disoproxil fumarate IVR (Oak Crest Institute of Science; University of North Carolina, Chapel Hill, USA)**

This ring delivery technology is also a pod ring, as described in Figure 3 above. Thus, the design and control issues for this ring are the same as those previously described for co-delivery of the 2C7 mAB, however the mAB used in this product is for achieving a contraceptive indication. The tenofovir disoproxil fumarate API is for the same purposes outlined above (iv), namely HIV and HSV prevention. In the case of each of the nucleoside reverse transcriptase inhibitor and non-nucleoside reverse transcriptase inhibitor antiretroviral drug used in the products described earlier, HIV infection is thwarted via inhibition of the enzymatic activity of the HIV reverse transcriptase. Therefore, tenofovir disoproxil fumarate, tenofovir and dapivirine need to be present intracellularly to inhibit the enzyme from achieving intracellular replication and establishing infection. The non-hormonal, mAB contraceptive API relies on a sperm immobilization mechanism of action, which does not involve intracellular activity. It

is a multivalent antibody that inhibits sperm from migrating through vaginal mucous and reaching an egg for fertilization. Thus, this ring technology allows for delivery of very different types of drugs (i.e., chemically/physically divergent) with very different mechanisms of action per indication.

The target duration of delivery for this product is 28-90 days, and it is in early preclinical development.

**vi. Human Contraceptive Antibody + VRC01+N6 IVR (Muccomune, USA)**

A non-hormonal mAB contraceptive MPT ring approach was introduced above [43]. These Human Contraceptive Antibodies (HCA) have been in development and testing for several years and are born out of earlier efforts to create anti-sperm vaccines as a contraceptive. In this product, human contraceptive antibodies are again included to address contraception; however, unlike the ring above (v.), which relies on tenofovir disoproxil fumarate for the HIV prevention indication, the Muccomune ring also uses mABs to address the HIV indication. Specifically, this ring involves two broadly neutralizing antibodies (bNAB): VRC01 and N6, which neutralize HIV virus with slightly different mechanism of action [44]. The strategy is to combine these two broadly neutralizing antibodies to achieve a maximum effect on HIV inhibition. This product is in early-stage preclinical development and technical details on its status are limited.

**vii. Dolutegravir + rilpivirine + acyclovir + ethinyl estradiol + etonogestrel (Auritec Pharmaceuticals, USA)**

This MPT ring targets three different indications: contraception (etonogestrel and ethinyl estradiol, a standard hormonal combination for contraception), HSV-2 (acyclovir, used for herpes simplex virus-2 treatment), dolutegravir (an integrase inhibitor used in combination with other ARV for HIV treatment), and rilpivirine (a non-nucleoside reverse transcriptase inhibitor, similar to dapivirine, and used in combination with cabotegravir- an integrase inhibitor- used in HIV treatment). This product is in advanced preclinical development but there is limited technical information on its status beyond what is available in the IMPT database [45]. Other MPT rings being developed by different groups are relying on similar ring principles (i.e. pod ring design; see products vi. and v. above).



### viii. Other ring candidates in early preclinical development

Additional ring products are also in early-stage development- however, there is minimal information available on the status of product development for each of these candidates beyond what is available in the IMPT database [6]. These include:

- The copper ring in development at the University of California-Davis (USA) targets HSV-2, Zika virus, and contraception;
- Two rings developed at the University of North Carolina-Chapel Hill (USA), which are focused on novel 3D printing technologies for production, one intended to deliver dapivirine, pritelivir, and levonorgestrel for HIV, HSV-2, and contraception; the other delivering islatravir (a novel reverse transcriptase translocator inhibitor) and etonogestrel/ethinyl estradiol for HIV prevention and contraception;
- Lastly, a 90-day pod-type ring is being developed by Population Council and Oak Crest Institute of Science (USA) to deliver the biologic Q-Griffithsin and etonogestrel/ethinyl estradiol for HIV prevention and contraception, respectively [46].

### 4.2.2. Vaginal and Rectal Gels

**TABLE 2.** Gels (Vaginal + Rectal) (n=4) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Gels (Vaginal + Rectal) (n=4)</b>				
VivaGel® Vaginal Gel	SPL7013 (astodimer sodium)	BV, HIV, HPV, HSV-2	Advanced Preclinical	N/A
Yaso-GEL	polyphenylene carboxymethylene	Chlamydia, Gonorrhea, HIV, HPV, HSV-2, Pregnancy	Advanced Preclinical	N/A
MIV-150 and zinc acetate in carrageenan gel (PC-1005)	carrageenan, MIV-150, zinc acetate	HIV, HPV, HSV-2	Phase 2 Clinical Trial	N/A
EVO100 Gel	citric acid, L-lactic acid, potassium bitartrate	Chlamydia, Gonorrhea, Pregnancy	Phase 3 Clinical Trial	N/A



NWHN Staff. (2020). Contraceptive Gel [Photograph]. National Women's Health Network. <https://nwhn.org/phexxi/>



Snuggs, Tania. (2019). Male Contraceptive Gel [Photograph]. Sky News. <https://news.sky.com/story/male-contraceptive-gel-uk-man-among-first-in-world-to-take-part-in-trials-11748858>

In the early days of microbicide development, these gel formulations typically involved detergents, pH lowering and other non-specific antiviral agents (nonoxynol-9, cellulose sulfate, Pro 2000, BufferGel, dendrimers, etc.) solubilized in a stable polymer formulation that was dispensed from a pre-filled vaginal applicator. Although some of these early gels were believed to be potentially MPTs as anti-viral and contraceptives (e.g., nonoxynol-9, cellulose sulfate, C31G and PRO2000 gels), none of these early products were ever shown to be safe and effective and none have been approved for licensure for multiple indications [47], [48]. Tenofovir-based vaginal gel in daily or on-demand dosage were advanced into late stage clinical trials (e.g. CAPRISA 004 phase 2 trial of tenofovir gel, VOICE and FACTS-001) [12], [49], [50]. Although biologically efficacious, development of the tenofovir gel was stopped because lack of

demonstrated protective effect of the gel in the VOICE and FACTS-001 trial [12], [50]. These early gel candidate trials along with the tenofovir gel trials (CAP 004, VOICE and FACTS-001) showed that product adherence was low; gel leakage and partner's negative perceptions were relevant to the failure of these gel candidates in clinical trials.

Current vaginal and rectal gels in development as MPTs include:

- i. **VivaGel (StarPharma, Australia)** is a vaginal gel currently being evaluated for Bacterial Vaginosis (BV), HIV, human papilloma virus (HPV), and HSV-2 prevention in late-stage preclinical studies. This product involves the use of sulfonated dendrimer as the API.
- ii. **EVO100 Gel (Evofem Biosciences Inc., USA)** is a vaginal gel targeting chlamydia, gonorrhea and pregnancy in a phase 3 clinical trial via a low pH regulated formulation mechanism of action achieved via the vaginal delivery of L-Lactic acid, citric acid, and potassium bitrate. This product has initially been approved for contraceptive purposes.
- iii. **PC-1005 (Population Council, USA)** is a vaginal and rectal gel that involves the non-nucleoside reverse transcriptase inhibitor MIV-150 and zinc acetate formulated in a carrageenan gel. The MIV-150 API is a synthetic non-nucleoside reverse transcriptase inhibitor that inhibits HIV reverse transcriptase in a manner similar to dapivirine; zinc acetate is relevant to sustaining an effective immune response, particularly an anti-viral response [51]; carrageenan is a polyanion inhibitor of HIV, and potentially other viral infections. This gel has been evaluated in the non-human primate models as well as in phase 1 clinical trials [52]. In addition to HIV prevention, this vaginal gel product is being evaluated for the potential inhibition of HPV and HSV-2 as well.
- iv. **Yaso-GEL (Yaso Therapeutics, USA)** is a vaginal gel formulation in late preclinical development, and is being evaluated for multiple indications, including gonorrhea, HIV, HPV, HSV-2, and as a contraceptive. The API in this candidate is polyphenylene carboxymethylene. This drug candidate is an anionic mandelic acid condensation polymer [47]. Similar compounds were evaluated for HIV prevention as early era vaginal microbicides.

### 4.2.3. Fast Dissolving Inserts

**TABLE 3.** Fast Dissolving Inserts (Vaginal) (n=3) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Fast Dissolving Inserts (Vaginal) (n=3)</b>				
amphora/Q-Griffithsin Fast-Dissolving Vaginal Insert	citric acid, L-lactic acid, potassium bitartrate, Q-Griffithsin	BV, Chlamydia, Gonorrhea, HIV, Pregnancy	Early Preclinical	N/A
tenofovir alafenamide / elvitegravir Topical Insert	elvitegravir, tenofovir alafenamide	HIV, HSV-2	Phase 1 Clinical Trial	Several hours either before or after exposure
amphora Fast-Dissolving Vaginal Insert (FDI)	citric acid, L-lactic acid, potassium bitartrate	BV, Chlamydia, Gonorrhea, Pregnancy	Early Preclinical	N/A



Microbicide Trials Network. (2019). MTN-039 Backgrounder [Photograph]. CONRAD. <https://www.mtnstopshiv.org/news/mtn-039-backgrounder>

Fast dissolving inserts (FDIs) are another alternative on-demand delivery technology with certain end-user preferences over gels (i.e., no leakage, fast dissolving, reduced risk of partner detection, no applicator needed). This technology has been used for topical application of estrogens to address vaginal health issues frequently associated with menopause. Furthermore, like others discussed earlier here for on demand delivery, has the advantage of minimizing or eliminating systemic delivery, which is an important safety feature for treatments with unopposed estrogen [53]. Thus, it

is an established, topical delivery option for vaginal dosing. Below are brief summaries for Fast dissolving inserts, which could be developed for either vaginal or rectal delivery for prevention of multiple STI including HIV, for MSM or women; or, for STI prevention along with a contraceptive as an MPT for women.

- i. Amphora fast dissolving vaginal insert (FDI) (Evofem Biosciences, Population Council, USA).** This FDI involves basically the same prevention mechanism of action, described above for EVO100 Gel (see product ii. In section 4.2.2 above). The mechanism of action here, as in the gel formulation is the reliance on lower pH for contraception and prevention of chlamydia and gonorrhea infection. Interestingly, the maintenance of a lower pH in the vagina may also inhibit the development of BV as evidenced by studies examining the effects of lactobacillus based probiotic treatments of BV [54]. The formulation difference between a gel and an insert (or suppository) is the hardness of the final formulation with drug, which controls the kinetics of drug release. Polyethylene glycol is a common material used in the production of such inserts. Although the details of the Evofem insert formulation have not been shared with the IMPT, the development of suppositories for the delivery of anti-HIV drugs has been studied [55]. This product is currently in early preclinical development.

- ii. **Amphora/Q-Griffithsin fast dissolving vaginal insert (Evofem Biosciences, Population Council, USA).** This product is in early-stage preclinical development. It is formulated in the same manner as the FDI listed above and involves the Q-Griffithsin API. Details on this specific project are provided in NIH Reporter [56].
- iii. **Tenofovir alafenamide/elvitegravir topical insert (CONRAD, USA).** This insert involves the APIs tenofovir co-formulated with elvitegravir (HIV-1 Integrase enzyme inhibitor) for use vaginally or rectally for HIV prevention along with HSV-2 prevention. It is not contraceptive. The product is formulated as a solid tablet for manual insertion vaginally or rectally. Safety and pharmacokinetics/pharmacodynamics (PK/PD) and safety were evaluated in multiple phase 1 studies [57], [58] involving men and women, with vaginal and rectal exposure. Importantly, a placebo version of this product was also evaluated in the QUATRO study along with other vaginal dosage forms for end user acceptability [59]. The QUATRO study involved end user comparison of on demand vaginal films, gels and inserts, along with a monthly ring. All four options scored similarly in this study. Another end user study comparing three different dosage forms (vaginal insert, suppository, and douche) was also conducted (MTN 035) [60], [61]. Results from the MTN 035 and MTN 039 studies are still pending. Although the CONRAD A18-146 trial was reported on at the HIV R4P conference in 2020, full publication is not yet available.

#### 4.2.4. Enemas

**TABLE 4.** Enemas (Rectal) (n=1) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Enemas (Rectal) (n=1)</b>				
Q-Griffithsin Enema	Q-Griffithsin	Hepatitis, HIV, HSV-2	Phase 1 Clinical Trial	N/A



Wikipedia. (2013). Rectal Bulb Syringe [Photograph]. Wikipedia.  
[https://en.wikipedia.org/wiki/Rectal\\_douching](https://en.wikipedia.org/wiki/Rectal_douching)

Like the gels outlined above, enemas are another on-demand, end-user-controlled product. However, MPT enemas are designed to be delivered rectally, exclusively to provide protection from HIV and other STIs during receptive anal intercourse.

- i. **Q-Griffithsin enema (University of Louisville, USA)** is a rectally administered enema that has undergone a randomized, double-blind Phase 1 safety and pharmacokinetic study. Currently, data review of clinical trial findings is ongoing with results anticipated by the end of 2021. The PREVENT (Griffithsin-based microbicide) program moved from a rectal gel formulation to an enema formulation of Q-Griffithsin since gel formulations were found to be incompatible with condoms and enemas are

considered to be more behaviorally congruent with practices of individuals engaging in receptive anal intercourse. Thus, only the enema formulation was advanced to clinical testing [46].

#### 4.2.5. Vaginal Films

**TABLE 5.** Films (Vaginal) (n=2) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Films (Vaginal) (n=2)</b>				
EFdA-P + progestin Intravaginal Film	4'-ethynyl-2-fluoro-2'-deoxyadenosine prodrug, progestin	HIV, Pregnancy	Early Preclinical	N/A
tenofovir/efavirenz Nanoparticles-in-Film	efavirenz, tenofovir	HIV, HSV-1, HSV-2	Advanced Preclinical	24 hours



Musara, Petina, et al. (2021). Preferences and Acceptability of Vaginal Delivery Forms for HIV Prevention Among Women, Male Partners and Key Informants in South Africa and Zimbabwe: Qualitative Findings [Photograph]. *AIDS and Behavior*. <https://link.springer.com/article/10.1007/s10461-020-02949-4>

Like vaginal gels, vaginal films have been developed for coitally dependent contraception for women [62], [63]. However, there are certain advantages for films over gels as will be discussed further in section 5. From a formulation perspective, films may be easier for co-formulation of multiple API, via layered manufacturing processes. Lastly, production of films via scaled manufacturing processes has been well established and can be achieved via gel casting or hot melt extrusion. Below are summaries for two vaginal films in development as MPTs.

- i. **Tenofovir/efavirenz nanoparticles in vaginal film (Institute for Research & Innovation in Health, University of Porto, Portugal)** is a dual drug vaginal film product in relatively early-stage preclinical development, designed to inhibit HIV, HSV-1 and HSV-2 infection in women. Efavirenz and tenofovir are both anti-HIV drugs, and tenofovir has the advantage of also being anti-HSV as well – providing the MPT capability to this product [64]. This product strategy involves the loading of efavirenz nanoparticles into fast dissolving films, along with tenofovir. This delivery system was evaluated in a mouse model system and demonstrated a log 10 increase in drug distribution with nanoparticles in films relative to free drug doses. Also, film delivered nanoparticles resulted not only in higher levels, but more prolonged as well. The target is 24 hours of inhibitory levels of both drugs in women, which is consistent with the data obtained from the mouse study. The film polymer used for this product is poly (lactic-co-glycolic) acid, which is widely used in drug formulations.

**ii. Islatravir/progestin long-acting intravaginal film (Magee-Women’s Research Institute, USA).** This topical vaginal film MPT candidate product involves the ARV islatravir (also known as EfdA and MK-8591) with progestin, applied vaginally as a bio-adhesive film to prevent HIV infection and provide contraception. It is based on the technology described in more detail in an earlier effort to develop films for co-delivery of dapivirine (a non-nucleoside reverse transcriptase inhibitor) and levonorgestrel for the same two indications [65]. Islatravir had received attention as a strong API candidate for HIV prevention from independent research and development efforts for topical combination delivery and systemic delivery [66], [67], [68]. This technical approach maintains the same advantages for film delivery as noted above, however it has the advantage of a more potent HIV nucleoside reverse transcriptase inhibitor drug. The important formulation observations stemming from this technology development involves the assessment of bio-adhesion, to sustain a longer duration of API delivery. Data from this technology development effort indicated a longer, more sustained drug release with the bio-adhesive film formulation relative to a quick dissolving formulation, which is an advantage for an on-demand product by potentially avoiding the need for repeated dosing. Specifically, this group is moving forward in the delivery of the islatravir prodrug, which has increased permeability relative to the parent drug. The group has further support for the delivery of the EfdA-P and a progestin (levonorgestrel or etonogestrel) for up to one month, even in the context of menses and sexual intercourse [69]. Currently, this product is in relatively early preclinical development.

### 4.3 Systemic MPT product candidates

The following products differ from those described in the previous section (4.2) in that they involve systemic delivery of the drugs targeting the specific indications intended for each MPT product. Although these products have additional development considerations due to the potential safety issues associated with systemic drug delivery, which are less prominent with topical delivery, systemic delivery requires more comprehensive study of pharmacokinetics, safety and toxicity for such products.

To the extent possible, the delivery types that currently have the most advanced stage products are presented first (oral pills, long-acting injectables, implants, and microarray patches), acknowledging this may change over time. Tables 6-9 includes a summary of the products described in this section.

### 4.3.1. Oral pills

**TABLE 6.** Oral Pills (n=1) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Oral Pills (n=1)</b>				
Dual Prevention Pill (DPP) / TELE	emtricitabine (FTC), ethinyl estradiol (EE), levonorgestrel, tenofovir disoproxil fumarate	HIV, Pregnancy	Clinical – Bioequivalence Study (Pre-market approval)	1 per day



Castaneda, Ruben. (2017). 8 Medications That Treat Multiple Conditions [Photograph]. US News. <https://health.usnews.com/wellness/slideshows/8-medications-that-treat-multiple-conditions>

Oral MPTs, or Dual Prevention Pill (DPP) products, can be developed by co-formulation of the drugs already included in the oral PrEP pills (Tenofovir and emtricitabine) along with the API used in oral contraceptives (e.g., levonorgestrel and ethinyl estradiol) into a single, four-drug pill to prevent HIV infection and unintended pregnancy. Friedland, et al from the Population Council recently published a summary development and introduction strategy for a DPP [70]. In this publication, the authors make the case that leveraging the existing market for oral

contraceptive pills and assuming modest conversion from condom users and women with an unmet need for contraception, the dual prevention pill may be the fastest route to take an MPT to market in L/MICs [71].

There is currently one DPP in development as an MPT, as follows:

- i. **Dual Prevention Pill (DPP) / TELE (Viatris, USA)** is a fixed-dose combination tablet of tenofovir disoproxil fumarate / FTC / levonorgestrel / EE indicated for both the prevention of HIV and pregnancy. The product will be supplied as a 28-count blister compliance pack containing 21 tablets of the fixed-dose combination of tenofovir disoproxil fumarate, FTC, levonorgestrel, and EE (a 3-week supply) plus 7 tablets of FTC and tenofovir disoproxil fumarate (a 1-week supply). As with conventional oral contraceptives, the product would involve a daily dosing of one pill per day, which is readily trackable by the end-user. This Viatris development effort has advanced to a bioequivalence study and is in pre-market approval stage of development [72]. Please refer to Section 6.4 below for more information about the DPP product roll out strategy.

### 4.3.2. Long-acting injectables

**TABLE 7.** Long-Acting Injectables (n=1) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Long-Acting Injectables (n=1)</b>				
Antiretroviral/levonorgestrel long-acting injectable	integrase inhibitors (TBD), levonorgestrel	HIV, Pregnancy	Early Preclinical	3-6 months



Scott, Nicola. (2015). Contraceptive Injection [Photograph]. The Mix. <https://www.themix.org.uk/sex-and-relationships/safer-sex/contraceptive-injections-4569.html>

Long-acting injectable (LAI) products have several advantages for prevention indications. First, injectables do not involve a daily, or coitally dependent compliance schedule for the end user. Secondly, the injectable dosage form is well established among AGYW in many L/MICs, particularly in high-risk areas of sub-Saharan Africa. Also, several end-user preference studies have established a high degree of acceptability for LAI in target populations [2], [73]. However, the LAI product option also has some potential negative issues as well. For example, the LAI product

cannot be removed once it has been injected. Depending on the drugs and associated safety data, it may be necessary to use an oral drug roll-in for users prior to an actual injection. Also, depending on the drug elimination kinetics, it possible that there can be detectable levels of the injected drugs for prolonged periods after they have fallen to levels below what is efficacious. This creates the hypothetical possibility that there could be selection for resistance if there is indeed infection during the period of insufficient drug for efficacy. Importantly, this risk has yet to be established for HIV prevention drugs delivered in any dosage form. Further, clinical efficacy studies with the LAI cabotegravir product have shown significant efficacy for HIV infection prevention when compared to oral PrEP with Truvada [74]. This is likely due to the reduction in end-user compliance with the injectable relative to the daily oral PrEP option. Thus, LAIs represent an MPT dosage form already well established for contraception, strongly efficacious in prevention of HIV infection, familiar to and preferred by primary target population end-users, and relatively safe, thus providing a potentially meaningful option for MPT products going forward.

The one MPT LAI candidate product listed in the IMPT database is being developed by **CONRAD (USA)** and is in early-stage preclinical development and involves an undefined integrase inhibitor ARV for HIV prevention and levonorgestrel (progestin) for contraception. Injectable progestins for contraception are widely used in the target countries and populations for MPT that couple HIV prevention and contraception. The development effort is targeting a six-month duration of effect. Currently, progestin-based contraceptive products are effective for 2 or 3 months, and the LAI cabotegravir product noted earlier was trialed at a two-month duration for HIV infection. There is limited information on the development timeline, but is targeting a pre-Investigational New Drug (IND) submission in early 2022.



### 4.3.3. Implants

**TABLE 8.** Implants (n=2) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Implants (n=2)</b>				
Subcutaneous Contraceptive + HIV Implant Engineered for Long-Acting Delivery (SCHIELD) device	unspecified	HIV, Pregnancy	Early Preclinical	N/A
Ultra-Long Acting MPT In-situ Forming Implant (ISFI)	hormonal contraceptive (TBD), antiretroviral (TBD)	HIV, Pregnancy	Phase 1 Clinical Trial	6 months



Health Information Brochures. (2019). Contraceptive Implant [Photograph]. Sexual Health and Family Planning ACT. <https://www.shfpact.org.au/sexual-health/info-sheets/31-contraception/58-implanon>

Although implants for various medical indications are commercially available, here we focus on subdermal eluting devices that systemically deliver reproductive health drug(s) over an extended period of time (months to year(s)). Non-biodegradable contraceptive implants in the form of single or multiple rods have been commercially available for decades [75] and are the technological basis for the development of HIV PrEP implants and MPT implants. Other architectures for PrEP implants in development

are also being explored [21]. Several potent ARVs are being evaluated in preclinical or early clinical stages for long-acting PrEP indication including tenofovir alafenamide, a potent prodrug of tenofovir [76] (Oak Crest Institute of Science, Houston Methodist, RTI, Intarcia) and the integrase strand transfer inhibitor cabotegravir (SLAP HIV) [77] and Islatravir (ISL) [78]. Like injections, implants are provider administered. However, unlike long-acting injectables, implants are retrievable throughout duration of drug delivery, a critical feature in cases of adverse reaction or desire for discontinuation. Additionally, implants offer an improved, sustained pharmacokinetic profile compared with pills. There are two different types of MPT implants currently in development:

- i. Subcutaneous Contraceptive and HIV Implant Engineered for Long-Acting Delivery (SCHIELD) (RTI International, USA).** Leveraging the aforementioned HIV PrEP implant, RTI international is developing a MPT implant that can be inserted sub-dermally with existing contraceptive trocars [21]. APIs evaluated include ENG and levonorgestrel for contraception and potent ARVs (Tenofovir alafenamide (TAF) or ISL) for HIV prevention [21]. The drug(s) are formulated in a reservoir device for sustained (zero order) release of drugs for 6-12 months. The thickness of the device walls can be engineered for tunable drug release rate, through a process of tube extrusion, with the FDA approved biodegradable polymer polycaprolactone. The biodegradability feature allows to leave the implant in place once inserted, to minimize clinic interface and the more invasive surgical procedure needed for non-biodegradable implant removals [75]. The technology is in late preclinical development (NHP studies currently ongoing). Possible MPT implant configurations include separate rods for the contraceptive and PrEP indications or co-formulated implants housing a hormone and an ARV in a single rod [79], [80]. In the case of an

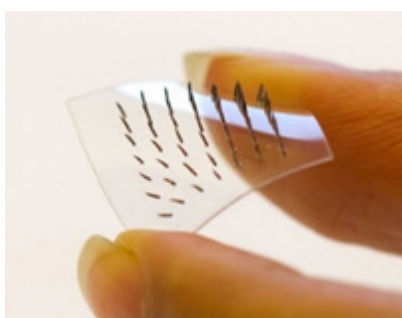
integrated co-formulated approach, the release profile of each drug will have to be evaluated along with appropriate alignment for duration of each indication, along with ascertainment of no DDI between co-formulated drugs.

- ii. **The Ultra-Long-Acting MPT In-situ Forming Implant (ISFI) (University of North Carolina-Chapel Hill, USA)** is a first-in-line, ultra-long-acting injectable implant MPT that offers durable and sustained protection from HIV transmission, high efficacy of contraception, increased user compliance, and the ability to be removed. It consists of a liquid MPT formulation utilizing excipients that form a biodegradable depot after subcutaneous injection (in-situ forming implant). It is in preclinical development with limited publicly available details to date.

#### 4.3.4. Microarray Patches

**TABLE 9.** Microarray Patches (n=1) Candidates in the Pipeline

Product Candidate	APIs	Indications	Stage of Development	Target Duration
<b>Microarray Patches (n=1)</b>				
MPT Microarray Patch	cabotegravir, norelgestromin	HIV, Pregnancy	Early Preclinical	1 month or longer



KTH Royal Institute of Technology. (2016). Microneedle-Covered Skin Patch Offers Alternative to Injections [Photograph]. R&D World. <https://www.rdworldonline.com/microneedle-covered-skin-patch-offers-alternative-to-injections/>

Microarray patches (MAP) are a novel technology that involves transdermal delivery of APIs via a patch applied to the skin. Unlike earlier generation patches for drug delivery, this generation involves the delivery of small needle-like protrusions from the film surface which are fabricated from the drugs and transferred into the skin, allowing for removal of the patch, as drug is delivered from the dissolving drug needle embedded in the skin. MAPs have shown the potential for increased thermostability, thus reducing the cold chain burdens and facilitating access in remote areas, improving ease-of-use, and facilitating self-administration or delivery by lesser-trained

health care workers [81]. This delivery concept has been applied for HIV prevention and contraceptive drugs [82]. Although this technology would be very consistent with the needs for drug delivery as an MPT product, it should be noted that as of now, there are no approved MAP products for any indication [82].

At present there is only one MAP in development as an MPT (PATH, USA; Queen’s University, Belfast). This MAP is designed to deliver two drugs, cabotegravir (HIV prevention) and norelgestromin (contraception) [83]. The patch contains hundreds of drug needles that are micron scale projections amassed on the baseplate, which is applied to the skin and removed leaving the drug needles in the skin. The latter degrade over time, releasing the drugs. Thus, the use of the MAP will not be visible on the surface. This MPT MAP is targeting at least one month of drug delivery per application and is currently in early preclinical development.

## 5. CONSIDERATIONS FROM END-USERS

### Highlights from Assessment of End-user Considerations

- Incorporating **end-user research early** and throughout the R&D has become increasingly recognized as a critical part of the product development process to optimize and align products with end-user preferences and needs.
- Numerous end-user studies of biomedical HIV prevention product preferences, based primarily on theoretical product use and conducted in sub-Saharan Africa and the United States, have confirmed that women would **prefer an MPT over single-indication products**. This preference for multipurpose products seems to outweigh preference for a particular delivery type.
- While user preferences vary and are dependent on many factors, among women in sub-Saharan Africa there is generally a **preference for discreet and familiar provider-administered long-acting products** (i.e., injectables and implants) over less familiar user-controlled or on-demand delivery forms of MPTs. For novel user-controlled methods, end-users prefer to have initial training by health care providers before managing self-administration and a built-in feedback mechanism to increase confidence that the product is working correctly.

### 5.1 MPT end-user research: Introduction

Globally, most women of reproductive age state a preference for MPTs over single indication prevention products, according to a recent review of contraceptive and HIV MPT products [21]. Preference for MPTs was also reported by heterosexual men, male partners, or heterosexual couples [84]. This prevailing preference for MPTs over single indication products is evident across populations and geographies. These findings stem from a range of data collection methodologies, such as surveys in the U.S. and in West, Central and Southern Africa, and discrete choice experiments to assess stated preferences in Kenya, South Africa, and Zimbabwe [85]. In a large multi-country survey across Uganda, South Africa, and Nigeria, 93% of reproductive age women selected an MPT over a single indication product, with a preference for familiar provider-administered, long-acting products (injectables or implants) over user-controlled or on-demand delivery forms (intra-vaginal film or ring) [86]. Other surveys conducted in the U.S. and throughout sub-Saharan Africa with direct elicitation of preferences similarly showed that the majority of women surveyed (between 83% in the U.S. and 96% in Kenya and South Africa [87], [88]) preferred an MPT over single indication products [3], [4], [73], [84], [85].

Discrete choice experiments along with qualitative explorations have revealed heterogeneous preferences across settings and populations with regard to product attributes (including dosage frequency/duration of protection) and delivery forms [89], [90], highlighting the importance of advancing a variety of MPT options and offering a method

mix to users. The following paragraphs emphasize the nuanced cultural and circumstantial realities experienced by end-users that inform preference for a variety of MPT products.

Among Kenyan and South African women aged 18-30 who participated in the TRIO clinical study, a monthly injection was preferred and chosen by 62% of women, compared to daily oral pills (15%) and monthly rings (12%). However, in a follow-on survey conducted at the same site among 536 women, when the injection only prevented HIV and the comparator ring and pills were MPTs, the preference shifted to the MPT ring in South Africa (55%) and to the MPT pill in Kenya (34%), providing clear evidence of user interest in MPTs. In South Africa, among a sample of 600 diverse men and women, a conjoint analysis forecasted that the demand for an HIV prevention method would increase for all groups if a contraceptive indication was incorporated [91], [92].

Key perceived benefits of combined HIV and contraceptive MPTs over single indication products include convenience and simplified access for users through fewer clinic visits and improved product positioning to mitigate the stigmatizing topics of HIV prevention and sexual promiscuity with a partner [3, 84]. Main perceived barriers of MPTs include misalignment of indications when a desire to conceive arises (in which case a non-contraceptive product option may be desired), concerns about increased side effects (from a multidrug product), fear of the unfamiliar with new biomedical technologies (including unfamiliar delivery forms), and community misunderstanding around MPT use by women [3], [73], [85], [93]. Additionally, menstrual perturbations caused by hormonal contraceptives are disliked for MPTs [3] and a main cause of contraceptive method discontinuation, suggesting that non-hormonal MPTs are also likely to increase in appeal in the future.

Overall, the attributes of MPTs for which users indicate the greatest preference include methods that are easily accessible, long(er)-acting, partner-approved and/or discrete (can be used without partner knowledge), have no impact on sex, and have few side effects. Preference also goes to de-medicalized methods that are easy to store and transport and are packaged in a visually appealing way [3]. Other recommendations from end-users or providers for novel user-controlled methods (e.g. rings, MAPs, films) include preference for initial training by a health care provider at a clinic before managing self-administration [2], [94], [95] and desire for a built-in feedback mechanism to increase confidence that the product “works” (i.e. the drug is being released) or that the product has been applied correctly (e.g., in rings, MAPs and implants [95], [96]). Such efforts can mitigate user concerns regarding unfamiliarity with new biomedical technologies as well as community misunderstandings around MPT use by women. Typically, previous contraceptive experience increases comfort with a given delivery form and thus may influence preference for a particular MPT type, indicating that preferences tend to align with product familiarity.

Another important end-user population is health care providers, yet, only a few studies have explored their interest in MPTs. Among 42 providers from Malawi and Zimbabwe, over three quarters were interested in a vaginal MPT, although they believed that non-contraceptive HIV PrEP options should be made available too, acknowledging the continuous need to prevent HIV and the fluctuating contraceptive needs and fertility intentions over time [93, 21]. In the TRIO study, 24 providers were interviewed in Kenya and Zimbabwe. Providers were eager to offer a product that prevents both HIV and unintended pregnancy in young women, and simultaneously recognized that MPTs may put additional burden on the provider and would require product-specific training. Provision of MPTs also has potential benefits for the health system itself, such as streamlining access at a single location, time

saved by limiting interactions with multiple providers for different health needs, and reduced time to dispense a 2-in-1 product versus multiple single indication products.

An important research gap is to assess acceptability of actual MPT products in the general population, something that will likely be possible soon, given that several MPTs are now in clinical trials (e.g., rings and pills) [6].

## 5.2 Topical MPT product candidates

### 5.2.1. Vaginal rings

Several recent studies among women in L/MICs have reported high overall acceptability and ease of use of rings as a drug delivery system for diverse indications. In a recent meta-analysis that included both L/MICs and high-income countries, the favorable acceptability pooled prevalence of rings was 85.6% (95%CI: 81.3, 89.0) and acceptability was higher in Europe and Asia compared to Africa [97]. In addition to high overall acceptability, a systematic review across 25 L/MICs showed high ease of use (including insertion and removal) of rings for diverse indications [97]. The meta-analysis also suggested that larger ring size and diameter were associated with less comfort for both partners, lower ease of use, and more expulsions. Importantly, several end-user studies found that acceptability with less familiar delivery forms like the ring, which initially engendered ambivalent reactions or adverse attitudes, improved over time both within studies (as women gained experience inserting rings) and, in general, over time (as rings became more familiar in the setting). This highlights the strategic importance of evaluating suitable information, education, and communication messages, as well as individual-level tools to support informed decision-making when offering MPT options to women [89], [97].

A 3-month MPT ring containing levonorgestrel and tenofovir was assessed in two safety trials in the U.S and Kenya, showing high acceptability and comfortability. In a small phase I trial of another 3-month MPT ring containing dapivirine and levonorgestrel, menstrual perturbations were frequent and non-scheduled ring removals were reported by over a quarter of the participants, despite high overall adherence [41]. Ring expulsions and removals are reported (albeit infrequently) in all ring studies, highlighting the importance of building in forgiveness for “imperfect” use, particularly for fully user-controlled MPT methods like rings.

While the focus of this report is on MPTs for L/MIC populations, an end-user study done in alignment with clinical trials in the United States indicated that a 3-month ring was preferred over a 1-month ring. While there were reservations about the hygiene and safety of the 3-month ring, including discomfort with use during menses, these were usually outweighed by increased convenience of the longer ring dosage [98, 99]. Similarly, some ambivalence was reported regarding an extended duration ring in QUATRO, a clinical and preference study among young women (ages 18-30) in Zimbabwe and South Africa, to assess four different placebo vaginal products (rings, films, gels, and inserts) [100].

### 5.2.2. Other Topical Products (Films, Gels, and Inserts)

In CUPID, an MPT preference study of 400 heterosexual couples in Uganda and Zimbabwe, dosage frequency was a key product attribute. On-demand and weekly/monthly dosages were preferred over daily dosage for all delivery forms assessed (oral

pills, vaginal film, inserts and rings). In Uganda, the effect of topical products on the vaginal environment (i.e. increased wetness) was an important positive consideration whereas, in Zimbabwe, concerns about side effects and menstrual disruption were more salient [84, 90]. In the QUATRO study, there was no clear product favorite and acceptability ratings changed after participants tried each product [100], [101]. Zimbabwean women most often chose the film (45%) and South African women most often chose the vaginal insert (34%), although adherence with the ring was higher than with the on-demand products. Specific negative product attributes that emerged during a follow on preference survey and qualitative assessments included difficulty inserting topical products, hygiene concerns, excessive leakage (gel), discomfort with insertion of foreign object (ring), interference with sex (insert, gel, ring), and inconvenient, stigmatizing packaging (gel, insert) [101]. Product appearance and shapes were important as well, with the insert often perceived as looking too much like an antiretroviral therapy, the ring being too big, and the square film looking like plastic that could poke the vagina with its angled edges [59], [85], [101].

In the U.S., an online marketplace survey of 835 young (ages 18-30) sexually active women found that they were most likely to want to use a long-acting MPT in the form of an injection (46%), however 33.7% were interested in on demand vaginal gels [87]. This again suggests important variations in appeal for different delivery forms in different geographies.

### 5.3. Systemic MPT product candidates

#### 5.3.1. Microarray patches

Recent usability testing of MAPs showed promising results, with participants experiencing little to no pain with product application on the skin, no pain after one hour, and only faint erythema which faded after one hour. Furthermore, for a contraceptive indication, participants preferred the MAP to monthly injections or daily pills [82]. In another study, positive feedback was also received for use of MAP for HIV PrEP or treatment [82]. Providing a longer duration of protection (greater than one month) was the most salient feature of the MAP in an exploratory qualitative study of prototypes MAPs across a variety of stakeholders conducted in South Africa and Uganda [95]. Other important features included preference for a smaller size patch, 30-minute duration of wear time (although larger size or longer wear time would be acceptable if the product provided a longer duration of protection), and the inclusion of a feedback mechanism to improve end-user confidence that the patch was applied to the skin correctly. In the case of self-administration, upper arm or thigh were the preferred body site for application. Perceived benefits (such as ease of use, convenience, reduced clinic burden, discretion, and painlessness) as well as concerns (such as proof of drug administration, efficacy and safety) are being addressed in ongoing efforts to refine MAP formulation [95].

#### 5.3.2. Injectables and implants

Qualitative exploratory research conducted with 110 young women (parous, nulliparous, and female sex workers) and 17 providers in South Africa and Zimbabwe indicated a strong interest in MPT implants among potential end-users. This was the case despite concerns around discreteness once the implant was inserted sub-dermally, as well as pain and scarring resulting from rod removal [102]. Preferred implant duration differed by demographic characteristics, with 3-year implants preferred among post-partum women and shorter duration implants

(1-2 years) preferred among nulliparous women, especially in Zimbabwe [103]. Interest was expressed for independent retrievability of the HIV and contraceptive components of the implant, in case a woman wants to conceive, or if menstrual side effects are not tolerable, suggesting that co-administration rather than co-formulation of each indication may be favored [103]. To help simplify administration, a majority of providers favored biodegradable implants to avoid removals and other attributes (e.g. pre-loaded inserters and a single rod). They also recommended adequate training for providers and thorough counseling to clients [96]. Importantly, for provider-administered methods, the critical gatekeeping role of clinicians should not be minimized and, in the case of implants, challenges experienced with past contraceptive implant rollout were perceived to taint providers' and patients' perspectives on future PrEP or MPT implants. These 'lessons-learned' should be carefully addressed when implant rollout occurs [104]. Another exploratory study conducted with 24 AGYW and female sex workers in South Africa for a PrEP implant highlighted similar findings, including preference for a longer-acting implant that is discreet and dissolvable (does not require removal) [105]. A follow-up preference survey with 600 diverse South African women showed that effectiveness was the most important attribute of the implant, followed by minimal side effects (insertion pain only), longer duration, and single insertion if more than one rod was placed (like for Jadelle®).

Currently, there are no co-formulated MPT injections, but co-administration of a PrEP injection and a contraceptive injection would be feasible if timing is aligned (e.g., CAB-LA and Net EN). Co-administration of injectables was evaluated in the TRIO study using twice monthly saline injections in the gluteal muscles [2]. In TRIO, injections were the most preferred delivery type among many end-users and were chosen by 62% of the clinical study participants, with 100% successful administration at the scheduled visits. When all products were MPTs, the injection received the highest preference shares in the conjoint analysis: 72% in Kenya and 54% in South Africa, respectively [4]. Some of the main benefits of injections included invisibility, low burden on daily life, peace of mind ('set it and forget it'), ease of visiting clinics bi-monthly, and ease of receiving 2 shots in one clinic visit [86].

Among 807 youth (ages 18-24) near Cape Town, South Africa who participated in a preference survey, all participants preferred a longer duration HIV PrEP product. Interestingly, among the 401 female participants, stated preference for injectables was stronger (1 or 2 injections) compared to an implant, even if the implant provided longer protection [106]. However, injections may not be the optimal fit for all: among 89 US women in a qualitative study, those with a history of recreational injection drug use were averse to injectable medications [107].

### 5.3.3. Oral pills

Daily use of products can be challenging to remember, and this has resulted in major barriers to adherence among contracepting women or women in HIV prevention randomized controlled trials such as FEMPrEP or VOICE [12]. In the TRIO study, daily pills as MPTs were least preferred among young women (18-30) who tried 3 different placebo options (tablets, rings, injections). Furthermore, over 40% of the sample would not consider using a MPT pill in the future [2], [108]. In a preference survey conducted at the same study sites, preference for daily pills as MPTs was higher in Kenya (16%) than in Republic of South Africa (11%) compared to the 2 other dosage forms, and preference for an MPT pill increased to 34% and 17% at each location, respectively, if the injection (the preferred dosage form overall) was no longer an MPT [89].

The preference for lower dosage frequency with pills (weekly or monthly) was highlighted both in TRIO with actual placebo products and in CUPID with hypothetical MPTs where MPT pills were most familiar and most preferred compared to vaginal dosage forms like the ring, film, and insert [3], [84], [90].

The effort to develop a DPP for HIV and contraception is currently led by a large consortium of organizations [72]. Human-centered design and exploratory research was conducted in South Africa and Zimbabwe on perceptions, barriers, and motivators of end users, providers and influencers as they relate to the DPP [109]. Findings highlighted initial appeal (with reservations) for the DPP. Indeed, women will likely balance side-effects and convenience when making DPP use decisions. Many of those already on a current contraceptive method have chosen it by “trial and error” after they had experienced side effects with other methods. These women expressed reticence to change method. This may be a general consideration that all current contraceptive users that are considering switching to a MPT (in the future) may have. In South Africa, most women on contraceptive oral pills or oral PrEP were interested in the DPP, depending on what side effects they would have. In Zimbabwe discreet use of the DPP so that husband is unaware was contingent on willingness to use. Overall, women also wanted support for using the DPP and overcome their anxiety and fear, which encompassed being better informed/knowledgeable about the method, providing ways to use the DPP discreetly (to avoid partner conflict) and changing the social environment so DPP can be used more publicly, by minimizing social judgment [70]. Preliminary findings from health care providers and women highlighted several potential benefits of DPP including women’s empowerment and method control, reduced frequency of clinic visits, user convenience and lower burden. Potential challenges include pill attributes (size, forgetfulness and fatigue with daily dosage for PrEP and oral contraceptives, exacerbated side effects, partners’ lack of approval, and fear of the unknown) [110].



# 6. PATHWAY TO INTRODUCTION AND SCALABILITY OF MPTS IN L/MICS

## Highlights from Assessment of the Pathway to Introduction and Scalability of MPTs

- Large-scale **manufacturing capabilities and intellectual property status** will impact the complexity of each MPT product's regulatory pathway, manufacturability, availability, cost, and feasibility, key to ensuring uptake and a pathway to scale in L/MICS.
- **Implementation research and demonstration studies** should inform international and national recommendations, as well as practicalities for improved access and use for the end-users.
- Visibility on future uptake, including key elements for selection and **procurement by L/MICS and funders regarding emerging MPT products, would be required to timely inform development as well as plans for production at scale.**
- Careful and efficient planning, from end to end, is warranted to ensure that products that eventually prove safety and efficacy are quickly introduced in countries and brought to scale. **Learnings from introduction of long-acting contraception, current introduction of emerging options in long-acting PrEP, and ongoing efforts to integrate HIV and family planning services would support such strategic planning.**

## 6.1 Technical challenges for development and approval and opportunities

### 6.1.1. Combining APIs

As described above, an array of MPT candidates are in development, many combining approved single indication products. At the same time, single indication contraceptive, HIV prevention, and anti-infective products are in development that could be critical components of future MPTs [111], [112], [113].

There is a growing number of biomedical strategies and clinical trial designs being utilized for HIV prevention that can inform MPT development, including:

- The **dapivirine ring** for HIV prevention, in the process of gaining regulatory approval in individual countries [114].

- **Long-acting injectable cabotegravir** has been and is undergoing phase 3 trials in MSM, transgender women, and cisgender women, already showing strong efficacy and safety results [115]. It is submitted for regulatory approval.
- A growing number of **combination HIV prevention products** are in development that include two oral PrEP compounds approved for use: Truvada® for use by men and women containing emtricitabine and tenofovir disoproxil fumarate [30], [116], and Descovy® [117], containing emtricitabine and tenofovir alafenamide, which currently is not approved for use in persons assigned female at birth [118].

New approaches for prevention of non-HIV STIs include those which address growing concerns around the development of antibiotic resistant STI prevention [113], [119].

While advances in single indication products hold promise for MPT R&D, the development of MPTs that combine APIs poses additional technical complexities. A product's end goal shapes the approach to its API selection and design [120]. Complexities include competing metabolic pathways, differing drug release patterns in devices (i.e. rings) used to combine APIs with different chemical properties (i.e. hydrophobic and hydrophilic), and API compatibility with the polymers used in devices [120], [121].

A challenge for some MPT developers is identifying and accessing APIs and reference product from pharmaceutical companies, which often requires lengthy negotiation of technology transfer agreements. Recommended was the establishment of a registry of MPT-relevant drug compounds on the shelves of pharmaceutical companies and medicinal chemists. This could be accompanied by an intermediary entity that would assist MPT researchers/ developers in accessing specific drugs of interest.

### 6.1.2. Planning large-scale manufacturing

MPT developers may face specific challenges in translating products from bench scale to large-scale manufacturing, which may affect regulatory pathway, manufacturability, cost, and feasibility.

Many of the MPTs under development use complex technologies (rings, drug-device combinations) that may limit the number and location of manufacturing partners available to developers. The complexities of formulating multi-API compounds may also require additional or different processing steps than with separate APIs. Products containing hormonal APIs require specialized manufacturing controls, as may other APIs under consideration. Combining approved products may have intellectual property limitations affecting who can manufacture a new MPT. Conversely, where new intellectual property is generated, the intellectual property rights strategy may affect which manufacturing partners and investors may be interested.

Thus, early identification of potential commercial partners is warranted to maximize likelihood that the final product will be feasible to produce at the quality and cost desired. This is especially critical for products being developed by small developers or academia who may have limited experience in large-scale manufacturing.

### 6.1.3. Regulatory requirements

As a novel field, accepted standards for clinical trial design and regulatory pathways are still in development.

#### **Clinical Trial Design**

Designing later stage phase 3 clinical trials for MPTs requires careful consideration of a range of complex issues. These include the use of comparator groups, new standards of care for HIV prevention, a comprehensive set of outcome measures, study sequencing, identifying trial populations that can best represent priority users, and ethics. For example, as more single indication HIV prevention products become available, the less likely it will be that regulatory bodies will approve efficacy studies that are placebo-controlled. Regulatory requirements for future MPT trials will need to move beyond placebo-controlled designs toward superiority and non-inferiority trials that compare any new candidate against existing effective prevention options. This may conflict with the Pearl Index approach widely used in contraceptive trials. Furthermore, regulatory requirements for MPTs that combine drugs and devices (i.e. rings and implants) mandate the assessment of safety and efficacy in the combination product, and that the combination be at least as effective as the single agent products [122], [123], [124], [125], [126].

#### **Regulatory Processes**

As there have not yet been any MPTs that have received regulatory approval, regulators have not released formal guidance specific to MPTs. To address near-term concerns around pathways for MPTs, several reviews of key regulatory guidance documents and their applicability to MPTs outline key development elements necessary for various MPT configurations [127], [128].

Regulatory approval requirements can differ across stringent regulatory authorities and national regulators in L/MICs, which can affect the data that developers must generate for approvals. National regulators may have limited laboratory and other capacities to review new drugs, as may be the case for emerging MPTs. In addition to stringent national authorities and regional regulatory bodies (such as the African Medicines Agency), the WHO prequalification program offers a centralized mechanism widely recognized for accelerating and increasing access to critical quality-assured products that are affordable and adapted for markets in L/MICs [129].

## 6.2 Advancing MPTs from preclinical to clinical development

Shepherding potential high-impact MPT products through the R&D pipeline to clinical trials and approval will require significant financial investment from a more diverse funding base. Most preclinical MPT candidates are in development by academic research centers and small biotechnology companies in the United States, largely supported by the United States government and predominantly by the USAID and the NIH, with growing investment from philanthropic and private investors. [130] The average cost of phase 1, 2, and 3 anti-infective clinical trials is around \$4, 14, and 23 million respectively, with a subtotal of approximately \$41 million for anti-infective clinical trials through phase 3 [131]. The pharmaceutical industry traditionally avoids licensing and funding products until after phase 2 clinical development trials have been successfully completed to 'de-risk' the product.

Thus, a commonly encountered challenge for MPT product development is the progression from the end of preclinical drug discovery through phase 1-3 clinical evaluation. This process is often referred to as the 'valley of death,' since many preclinical products never reach clinical development [132]. While some of this loss is due to attrition, the development of many innovative and promising product candidates by academic laboratories and smaller companies often stalls due to insufficient financial resources, training, and regulatory expertise, resulting in major losses to drug development efforts. Multiple key informants echoed the need for expanded funding to support promising MPT candidates between phase 1 and phase 2 development, since pharmaceutical companies and investors require this for investment decisions. Establishing target product profiles and measures of success to inform Phase 1 funding decisions, could generate a tighter, but more promising pipeline, freeing up resources for Phase 2 trials.

Given the high cost of research and development, limited resources, and diversity of supporting agencies currently investing in MPTs, rigorous standards are needed to guide strategic investment decisions and to prioritize the most promising candidates at each stage of the pipeline. The establishment of clear scientific, regulatory, and target product profile-driven criteria and standards to serve as benchmarks for MPT candidates would be valuable. For products that meet these benchmarks, a non-biased, standardized, evaluative process could then efficiently identify priority MPT candidates and support their progression through the development pipeline. The resulting objective, data-driven priority list of MPT product candidates could be made available for funding agencies, industry and other interested stakeholders to help guide MPT product candidate investments. The WHO has experience moderating these processes in related sectors of global health (e.g., Conference on Antiretroviral Drug Optimization (CADO) and Paediatric Antiretroviral Drug Optimization (PADO)) and could be similarly called upon here [130]. Given limited funding for the field, particularly to advance from preclinical to phase 2, key informants agreed with the need for product-agnostic benchmark criteria to help guide MPT product candidate investments and an external committee that can be reputable to donors to evaluate candidates based on such criteria.

### 6.3 Investment Case

MPT stakeholders, including Policy Cures, AVAC and the IMPT, collaborate to track and measure the MPT pipeline investment, as published in their recent reports [133], [134]. In 2018, global funding for product development for MPTs was \$48m, the majority of which was invested in MPT drugs (including microbicides), with a small portion supporting MPT devices and combination products, and other unspecified intended product type. To stimulate increased investment support that moves MPT product development forward, building a business case that reflects the needs of diverse stakeholders is essential, with health impact, return on investment and cost being key drivers to articulate. Product developers and their funders need to understand how L/MIC governments make decisions on product introduction, and the importance of reliable market assessment data to inform strategic decision-making.

#### Market Demand

The immense potential of MPTs to transform care will be crucial, if they become recommended, for people affected by HIV, STIs, and those without accessible contraception measures, the greatest burden of which is borne by populations in L/MICs. Therefore, the development of MPTs in the pipeline should be geared towards products that are fit for

purpose in these settings and that can be brought to scale. Several key informants noted that the potential market for MPTs is vast with a large customer base (women and AGYW, as well as potentially men concerned about HIV and other STIs). Product developers should invest resources in end-user, provider and policy research to quantify the market potential of their MPT.

### **Government Decision-Making**

Cost and efficacy were mentioned as key policy considerations for product introduction and rollout by many L/MIC health ministries and donor agencies. Critical is the assessment of what impact the product would have (e.g., product efficacy), the public health benefit, and if the product will be cost-effective to promote. Other key policy considerations will include alignment of new products with user behaviors and preferences, health system readiness (e.g., number of patients, sites, providers trained in HIV and family planning, high level of/potential for integration), and scalability. One key informant noted a second 'valley of death' that can result from high manufacturing costs after proof of concept and product efficacy has been demonstrated. However, there may be overall cost-benefit of products with multiple indications that are more acceptable to the end-user, and efficient to access and distribute [135]. Procurement cost must therefore be analyzed in comparison with the potential savings to programs and health care systems due to increased effectiveness and efficiency of delivery. Some health economics modelling on MPTs suggests that they will have the potential to be impactful and cost-effective, but such models are limited [91], [136], [137]. Product developers may want to consider whether co-administration or co-packaging could be more cost-effective for health systems to deliver, prior to embarking on an expensive and challenging development pathway.

### **Product Cost**

The cost of manufacturing MPTs may be greater than single-indication products. The need to combine APIs and the technologies involved, especially for those formulations seeking extended release, would imply potential cost differences with the standard-of-care products they aim to replace, at least until the market becomes well-established and scale allows for further cost reduction.

Product cost-estimates are needed early in development to best inform go/no-go decisions and refined as further information becomes available. Estimating large scale commercial manufacturing costs based on phase 1 scale costs is, however, challenging, and thus involving a manufacturing partner early in the R&D process can be helpful.

Approaches that can lower the cost of goods and create more efficient production lines are becoming available, which could aid in reducing the launch price of these products. Enabling an extended supply base, including through a generic pathway, will also be key to affordability as well as to ensuring supply security. Encouraging and supporting product developers to identify development and commercialization partners and establish access strategies early in product development can accelerate the pathway to cost reductions. To address such challenges, the Medicines Patent Pool (MPP), funded by Unitaid, is collaborating with academia and developers of several long-acting products (including for Unitaid-funded long-acting products in development [138], [139]) to voluntarily license their product to generic manufacturers.

### **Financing**

In L/MIC, and particularly in sub-Saharan Africa, the majority of HIV and STI prevention products and contraceptives are subsidized by donors and governments, although an

important portion of contraceptives are also funded out-of-pocket. MPTs are likely to need similar financing strategies; several key informants noted as well the potential importance of mixed funding models. Budgets and financing streams for family planning and HIV procurement are often separate within donors and governments. Establishing who is paying for and procuring MPTs may be more challenging than single indication products, particularly where the costs of the two indications are quite different.

However, development assistance for health has flatlined in recent years [140]. This has resulted in donors and non-governmental organizations (NGOs) increasingly focusing on “innovative financing” mechanisms aimed to generate additional development funds beyond traditional funding from established donors. These mechanisms include leveraging both public and private sector capital, including corporate social responsibility (CSR) approaches.

KIIs also discussed market strategies focused initially or in parallel on MPTs in less constrained markets, which may create a return on investment and offset the cost for MPT R&D and introduction in L/MICs. market size and substantial.

## 6.4 Product roll-out strategies

The potential health impact of MPTs can only be realized if a holistic approach is taken as early as possible to secure access to these innovative products for those most in need. Without early consideration and intervention, emerging MPTs will face challenges that impede timely uptake in L/MICs where many of the primary target populations are located.

### Key Considerations

Product and market characteristics, such as affordability, supply capacity, intellectual property, regulatory pathways, adaptability, and ease of use are all key elements that need to be addressed in a timely manner to ensure delivery at scale. At a country level, national market authorization, inclusion in national treatment policies, and implementation across national programs are essential to drive demand and support introduction, and there may be additional factors to consider given MPTs’ positioning in multiple areas of the healthcare system. Implementation research and demonstration studies will play an important role in providing evidence to inform international and national recommendations, as well as practicalities for the end-users. Figure 4 is an overview of the South African introductory process for new biomedical HIV prevention products, portraying the range of activities that must occur from regulatory approval to availability of product to health care users.

**FIGURE 4:** Example of Introductory Process for new Biomedical HIV Prevention Products

Planning Process for Implementation of the Biomedical HIV Prevention Products			
Regulatory	Implementation & Financial Plannig	Service Delivery Preparation <small>Integrate with existing implementation tools</small>	Communication and Social Mobilisation
WHO PQ approval	Demand Forecast and Impact Models	Develop National and Provincial Implementation Plans	Dev Social Mobilisation & Demand Generation Strategy
SAHPRA approval	Investment Case	Identify and delivery sites and health care provider's required for delivery	Effective interventions for Uptake & Continued Use
National Policy and Guidelines	Costing and Budget	Develop M&E Indicaitions and Systems	Development of communication, education and social mobilisation materials
National Health Council Approval	Procurement/ Supply Chain/Tender	Develop implementation tools, job aids & Training Materials	Commerce implementation

Source: Reproduced with permission of Hasina Subedan, National Department of Health, South Africa.

### Unique MPT Challenges

Successful MPT product introduction will require addressing differences in how and where family planning, STI and HIV prevention services are delivered. Some key informants noted a disconnect between family planning services, which have in many contexts been increasingly de-medicalized, and HIV prevention, which has remained controlled and medicalized. These barriers, such as frequent HIV testing and clinical visit requirements, may need to become more flexible for MPTs to be a success from a self-care perspective. Several key informants discussed integrated approaches for ensuring that HIV and family planning providers are adequately trained on MPTs, while also minimizing additional burden on contraceptive services/delivery. This is also noted in the TRIO Study (see section 5). It was also suggested to deliver MPTs where target populations congregate (e.g., hair salons and schools), service delivery models that are being used for family planning products and PrEP.

### Leveraging Learnings

Learnings from similar products such as long-acting contraceptives or long-acting PrEP, now becoming a reality, can be applied to MPTs – in particular, understanding of the regulatory pathway and framework for getting these products into countries, demand generation and acceptability – although some aspects will be unique to individual MPT products. As noted by several key informants, the current and ongoing introduction of new single indication approaches may also lower the barriers for introduction of MPTs.

A critical learning has been the importance of investing substantial time and effort to engage and coordinate key stakeholders to enable rapid introduction and effective in-country rollout of emerging products. Examples of collaborative product introduction strategies for MPTs and relevant single indication products include:

- **The Dual Prevention Pill (DPP)** strategy follows a phased, coordinated approach, beginning with strengthening existing health systems, followed by pilot projects in public HIV and family planning clinics in Kenya, South Africa, and Zimbabwe [72]. Later phases of product introduction may include community-based distribution,

telehealth, universities, and private providers, but such approaches may be more complex. Critical activities for product introduction and rollout will also require: training of more providers to deliver integrated HIV/SRH services in family planning and HIV clinics; expanding demand generation activities for HIV prevention among contraceptive users; and facilitating integration of PrEP/family planning programmatic data at the national and clinic levels. [141]

- **BioPIC for long-acting injectable biomedical preventive methods** [142] takes an innovative, collaborative approach to product introduction to ensure activities are well-designed, well-timed, and well-funded to meet the needs of global and country decision-makers. Using CAB-LA as an example, it addresses key requirements for advancing long-acting preventive methods.
- **The dapivirine ring global action plan** aims to support coordination across partners for the planning, funding, and introduction of the dapivirine ring in Africa in the context of combination HIV prevention, including oral PrEP and integrated service delivery. It identifies five action areas to support ring introduction [143].
- The **Hormonal Intrauterine Device (IUD) Access Group** is a recent example from the family planning space where a consortium of global donors (including USAID, Bill & Melinda Gates Foundation, Foreign, Commonwealth & Development Office of the United Kingdom and UNFPA), governments, suppliers and partner organizations came together to explore concrete opportunities to ensure affordable, secure supply and support introduction of the hormonal IUD beyond pilot settings [144].

### 6.5 Additional insights from experts on the applications of MPTs in L/MICs

Additional themes emerged from the KIIs that offer insights for advancing the MPT field, as summarized below.

- **Choice:** The wider the array of MPT options that reach the market (in terms of delivery type and combination of indications), the more likely people will adopt and adhere to a prevention method that safeguards their own health and that of their families and communities. While we think about choice as inherently good, there is a risk with MPTs that there will be an overwhelming permutation of different options available. Thus, with choice should come education, training, and strong tools to help potential users identify which product (or mix thereof) meets their needs.
- **Socio-behavioral research:** More socio-behavioral data and granularity is needed to inform MPT R&D for different L/MIC markets, particularly beyond sub-Saharan Africa. Also critical is the timely integration of end-user research into early stages of product R&D when meaningful and cost-effective adjustments can be made. There is also a need for adherence monitoring in clinical trials, which should be integrated so product use is consistent throughout the study. Adherence may correlate with an individual's risk.
- **Self-care:** MPTs could play a key role in expanding self-care options for prevention. COVID-19 has taught us that service delivery models need to be redeveloped into more holistic approaches that empower people to obtain health care outside the clinic



environment. In this vein, the clinic may not be enough to reach end-users with MPTs and other prevention products. As with existing methods of contraception, it is also important to recognize that different MPT delivery types will have varied alignment with self-care. For example, methods like MPT rings and vaginal films may require an initial visit with a provider for blood work, clinical evaluation, and short training for users to learn to apply the device themselves and then have infrequent (e.g., annual) clinical follow up visits. MPT injections and implants, on the other hand, can be long-lasting but will likely need administration by a trained provider.

- **MPT demand creation:** It is important to consider demand creation early on to ensure rollout targets are met once products reach the market. Key aspects include MPT awareness-raising and promotion to help potential end-users start thinking about multipurpose prevention before MPTs reach the market.

## 7. CONCLUSIONS

As outlined in this report, the MPT field is dynamic and has greatly diversified over the past decade. A wide range of stakeholders has joined the movement for MPTs and contributed to major strides towards expanding the field. The MPT field builds upon advances in single indication products relevant to MPT development, including contraception and HIV PrEP.

While the MPT concept is compelling, the R&D for MPT products is scientifically and logistically complex. Most **MPT candidates** are being developed by **academic research centers and small biotechnology companies** in the United States, largely supported by the United States government and predominantly by the USAID and the NIH. **Industry involvement** in MPT R&D has been very limited. To reach the full potential of MPTs, financial investments and technical resources require greater optimization and diversification, as well as a focus on translation from research and development to evaluation and market entry of priority products that can also meet the public health needs of most vulnerable.

Although meaningful funding is necessary to advance MPT product development, it is not sufficient. These investments need to be in the context of vigorous evaluation of this work, successful achievement of critical milestones, and development strategies designed to identify and address challenges with the product as soon as possible, including those linked to future access and scaled-up use. This includes technical and regulatory risks, as well as end-user compatibility, and objective assessments of impact potential, market size, efficacy, and cost of goods to inform the advancement of the most promising MPT candidates.

To summarize the MPT R&D landscape, Table 10 provides a snapshot of key considerations regarding each MPT delivery type currently in the pipeline, acknowledging that the array of product candidates will change over time. This includes the number of products currently in development, the development stages, delivery route, type of administration (self vs. provider), and some high-level advantages and risks for consideration.

To avoid losing the momentum of the gains made to date and to maximize the potential of MPTs, the growing interest in and global support of this field must be acted upon. A strategic, coordinated, and well-funded response to the gaps and next steps outlined in this report can add rigor to the development process and advance the most promising products to the hands of end-users worldwide.

TABLE IO. Snapshot of MPTs in the R&D Pipeline (n=26)

Delivery Type	# Products in the Pipeline	Development stage	Delivery Route		Administration		Advantages	Risks	Other Considerations
			Systemic	Topical	Self	Provider			
Enemas (rectal)	1	Phase 1		✓	✓		Gender-neutral; MSM-focused; low manufacturing cost	Focus on rectum; low end-user adherence in some L/MICs	Potential for over-the-counter (OTC) delivery
Implants	2	Preclinical	✓			✓	Biodegradable implants may reduce health care provider (HCP) burden and improve user acceptability (e.g., less pain, scarring and no clinic visit when product termination is desired)	Higher level of HCP training required; small surgical intervention to remove; lack of invisibility once placed	Leverage contraceptive trocars for insertion vs. developing unique insertion devices
Rings	11	Preclinical Phase 1, 2		✓	✓		Can be self or provider inserted; immediately reversible upon removal; high acceptability among experienced users; rings exist for other indications (e.g. contraception, menopausal symptoms)	Unfamiliarity in target populations; partner detectability during sex; low prospective acceptability must be overcome with thorough education and training for first time users	May need HCP to administer first and/or verify placement; potential for OTC delivery
Long-Acting Injectables	1	Preclinical	✓			✓	High user compliance; discreet method; familiar delivery system	PK tail as relevant; silent infections; return to fertility concerns; pain at injection site	Access to qualified HCP for administration
Microarray Patches	1	Preclinical	✓		TBD	TBD	Discreet method	Denovo product; training for proper application; unfamiliarity in target populations; wait time at clinic prior to removal may be a concern	May need HCP to administer first and/or verify placement, or direct observation if self-placed at clinic
Oral Pills	1	Pre-market approval	✓		✓		Affordable; stable; manufacturing simplicity; familiar delivery system	Adherence; low forgiveness if skipping; home storage needed	Not available yet; pill and bottle/packet linked to HIV stigma
Gels (vaginal and rectal)	4	Preclinical Phase 2, 3		✓	✓		On-demand; affordable; stable; manufacturing simplicity	Adherence; messy; noticeability during sex	Potential for OTC delivery; delivered with reusable or disposable applicator
Films (vaginal)	2	Preclinical		✓	✓		On-demand; could be formulated as extended-release form	Adherence; Training for proper application; may stick to finger; unfamiliarity	May need HCP to administer first; potential for OTC delivery;
Fast Dissolving Inserts (vaginal and rectal)	3	Preclinical Phase 1		✓	✓		On-demand; can be dual compartment	Adherence	Potential for OTC delivery

# APPENDICES:

## APPENDIX A: List of Key Informants

We wish to thank our key informants for their time and invaluable expertise:

**Amole, Carolyn:**

Clinton Health Access Initiative (CHAI), USA

**Bateson, Deborah:**

Family Planning New South Wales, Australia

**Benhabbour, Rahima:**

University of North Carolina-Chapel Hill, USA

**Brett, Tracey:**

DKT International, South Africa

**Bukusi, Elizabeth:**

Kenya Medical Research Institute, Kenya

**Chidanyika, Agnes:**

UNFPA, USA

**Clark, Meredith:**

CONRAD, USA

**Caswell, Georgina:**

Global Network of People Living with HIV (GNP+), South Africa

**Delany-Moretlwe, Sinead:**

Wits RHI, South Africa

**Gaayeb, Lobna:**

Medicines Patent Pool (MPP), Switzerland

**Glover, Caitlin:**

CHAI, USA

**Jenkins, Sarah:**

CHAI, USA

**Johnston, Daniel:**

Eunice Kennedy Shriver National Institute of Child Health and Development, USA

**Lavreys, Ludo:**

Maisha Consulting, Belgium

**Lee, Dennis:**

Bill and Melinda Gates Foundation, USA

**Lepine, Marie Chantele:**

CHAI, USA

**Light, Benjamin:**

UNFPA, Belgium

**McCormack, Sheena:**

Medical Research Council, United Kingdom

**Machayo, Jean:**

Liberian Agriculture Company, Liberia

**Malcolm, Karl:**

Queen's University Belfast, Ireland

**Mann, Chastain:**

Mann Global Health, USA

**Moench, Thomas:**

Z-Mapp, USA

**Nhamo, Definate:**

Pangea Zimbabwe AIDS Trust, Zimbabwe

**Reinisch, Annette:**

Global Fund, Geneva, Switzerland

**Robles, Wilberto:**

WomanCare Global (WCG), Puerto Rico

**Subedan, Hasina:**

National Department of Health, South Africa

**Turpin, Jim:**

Independent Consultant, USA

**Watkins, Melynda:**

CHAI, USA

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