

Multipurpose Prevention Technologies for the Developing World: U.S. Investment Is Critical

By Heather D. Boonstra

Over the past 50 years, U.S. government investments in research and innovation have played a major role in improving the lives of women, children and families worldwide. Investments in sexual and reproductive health technologies, including contraceptives, vaccines, diagnostic tools and therapies, enable women and couples to have the number of children they want, when they want them; to deliver their babies safely and have healthy newborns; and to have healthy sexual lives.

Despite these remarkable gains, there is still much work to be done to provide essential health services to the poorest and most vulnerable people. Far too many women continue to have unintended pregnancies, STIs and pregnancy-related complications that could have been prevented.

In the face of these health challenges, the global community has been working toward better linkages between different types of sexual and reproductive health services in the developing world. As awareness of the need for linked services has increased, the need for new technologies that combine protection against unintended pregnancy, HIV and other STIs has become a research priority.

This drive—to develop new multipurpose prevention technologies (MPTs)—is now a rising priority on the health agenda of many of the leading government agencies and nongovernmental organizations (NGOs) worldwide; however, experts believe that these products may never reach the market without robust U.S. investment and intensified collaboration between government and the private sector. The U.S. government is the world's largest funder of global health research and development,

HIGHLIGHTS

- *There is a compelling need for new technologies that protect sexually active women against multiple sexual and reproductive health risks, especially in countries heavily burdened by HIV and by maternal and infant mortality.*
- *Multipurpose prevention technologies (MPTs) are products that combine protection against multiple risks, such as unintended pregnancy, HIV and other STIs.*
- *More research is needed to discover and develop new MPTs, but private industry is largely absent from the field because MPTs—designed primarily for use in low-resource settings—have not carried the allure of financial returns; U.S. government investment is, therefore, essential.*

and this leadership will be critical in pioneering and advancing MPTs.

Simultaneous Risks

Women who are sexually active may be exposed to multiple health risks, including unintended pregnancy, pregnancy- and childbirth-related complications, HIV and other STIs. The use of modern contraceptive methods has risen greatly in developing regions, from negligible levels 50 years ago to 57% among married women aged 15–49 in 2014.¹ And yet, the level of unmet need for modern contraception is remarkable: An estimated 225 million women—or one in four of those living in developing regions who are at risk of pregnancy but want to delay or avoid having a child—are not using a modern contraceptive method.

An unplanned pregnancy can be an emotionally wrenching experience for any woman. In absolute

numbers, an estimated 74 million women in the developing world experience an unintended pregnancy each year. These unintended pregnancies result in an estimated 28 million unplanned births, 36 million abortions (20 million of which are unsafe), eight million miscarriages and nearly one million stillbirths.

In many regions of the world, women of reproductive age are also at high risk of HIV. An estimated 37 million people are living with HIV worldwide²—14 million of whom are women aged 15–49 in developing regions.¹ Young women have been particularly hard hit by the epidemic: In Sub-Saharan Africa, 71% of all new infections among 15–19-year-olds are among women.² HIV prevalence among adolescent women is two times that of their male peers across the region.

The proportion of people living with HIV who receive antiretroviral therapy has expanded substantially in recent years. But large gaps remain: For example, roughly half of women aged 15–49 in developing countries living with HIV do not receive the antiretroviral therapy they need.¹ In addition, the challenges of retaining HIV-positive individuals in treatment are beginning to emerge. Many women know they have HIV and are eligible for treatment, but do not return for subsequent stages of treatment.

STIs other than HIV receive relatively little attention, even though they take an enormous toll on women's reproductive health. In developing regions, an estimated 204 million women each year contract one of the four major curable STIs (chlamydia, gonorrhea, syphilis and trichomoniasis); however, most do not know they are infected and do not receive STI services. These STIs can have serious consequences for women. For example, syphilis or herpes simplex virus increase women's risk of acquiring HIV threefold or more; some types of human papillomavirus (HPV) can progress to cervical cancer; and gonorrhea and chlamydia can lead to pelvic inflammatory disease, which often leads to infertility if left untreated.³ And for newborns, mother-to-child transmission of STIs can result in low birth weight, prematurity, congenital deformities and even death.

In many of the world's poorest countries, these health challenges are not independent problems. In Sub-Saharan Africa, where 12 million women aged 15–49 are living with HIV, millions of women lack essential sexual and reproductive health services.¹ More than four in 10 reproductive-age women in the region want to avoid a pregnancy;⁴ however, more than half of these women—55 million—are not using an effective contraceptive method (see chart, page 64).^{1,4}

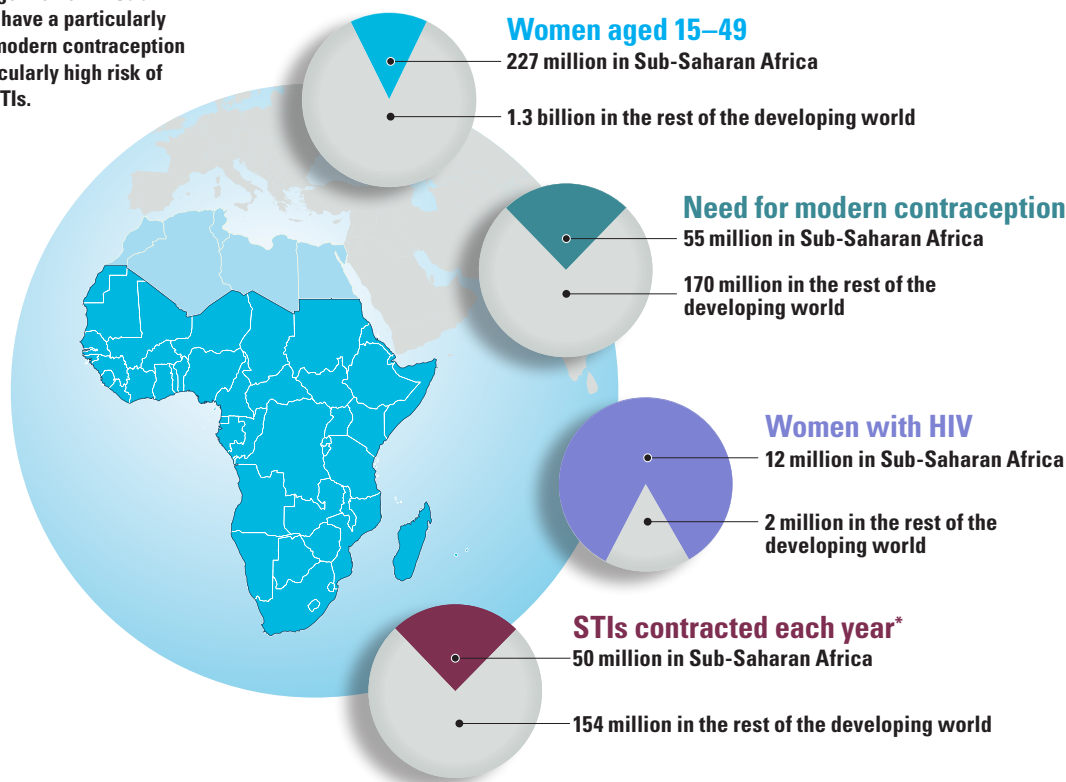
Need for New Technologies

Simultaneously meeting women's needs for both family planning and STI prevention is critical, and yet most contraceptive methods offer no protection against STIs, including HIV. Condoms (both male and female) are currently the only methods that protect against both unintended pregnancy and STIs; however, for many men and women, condoms are less than ideal. One disadvantage to condoms is that women have to negotiate use with their partner. Even the female condom, which has been hailed as a female-initiated method, requires a woman to obtain her partner's cooperation to use it. In many societies, especially those with an unequal gender power balance, women are simply unable to control when condoms are used.^{5,6}

Condoms have other drawbacks as well. They are not an option for women who want to become pregnant while protecting themselves against infection. Moreover, men and women worldwide report having issues with the fit and feel of male and female condoms, and that condoms interfere with sexual pleasure and are a barrier to intimacy and trust. To this point, studies from many regions show that women at high risk of STIs due to having multiple partners are much more likely to report using condoms than those with one partner. Still, only a minority use condoms consistently.¹ And condom use typically declines with relationship duration: Although condoms may be seen as acceptable and even necessary in the early stages of a relationship, they are often abandoned over time as intimacy between a couple grows.^{5,6} This, too, can make it difficult for women to discuss condom use with their long-term partner without raising suspicions of infidelity.

DISPROPORTIONATE RISKS

Reproductive age women in Sub-Saharan Africa have a particularly great need for modern contraception and are at particularly high risk of HIV and other STIs.



* One of four major curable STIs: chlamydia, gonorrhea, syphilis or trichomoniasis. *Note:* Numbers are among women aged 15–49 for the most recent year available. *Source:* Guttmacher Institute.

Service-level challenges have also worked against more widespread condom use. In many regions, access to condoms is limited, knowledge about prevention of HIV, other STIs and unintended pregnancy is not detailed, and myths are common. Moreover, for many years, separate HIV and family planning funding streams, advocacy and staffing have largely inhibited discussion of the need for dual prevention of unintended pregnancy and HIV.⁷ Family planning providers tend not to prioritize condom counseling because the contraceptive effectiveness of condoms is lower than that of other modern methods, and because dual use is not widely promoted. And HIV providers tend to focus on condoms for disease prevention, but often ignore the importance of fertility counseling and contraceptive services for their patients.

While more should be done to increase access to condoms, scientists and advocates have long argued that new and especially female-controlled

means of prevention are desperately needed. MPTs are designed to address two or more sexual and reproductive health indications simultaneously. For example, researchers are testing a drug that has the potential to protect against HIV and genital herpes. Vaginal rings for the prevention of unintended pregnancy and HIV are also in development, along with many other products (see table, page 65).⁸

Ideally, MPTs would also address some of the limitations of the contraceptive methods currently available. An analysis by the Guttmacher Institute found that women in developing countries have unmet need for contraception because they lack access to supplies and services, but that is only one of the many reasons women give for not using a method.⁹ Women also frequently report nonuse because they are concerned about health risks or side effects, have sex infrequently (and, therefore, believe themselves unlikely to become pregnant) or have a partner who is opposed to contraceptive use.

MULTIPURPOSE PREVENTION TECHNOLOGIES IN DEVELOPMENT

| Type of Product | Designed to Prevent | Number of Products by Status | | |
|-------------------|--|------------------------------|-------------------------|---------------------------|
| | | Preclinical Development | Phase I Clinical Trials | Phase III Clinical Trials |
| VAGINAL RING | HIV + pregnancy (hormonal contraception) | 1 | | |
| | HIV + pregnancy (nonhormonal contraception) | 1 | | |
| | HIV + genital herpes | 1 | 3 | |
| | HIV + genital herpes + human papillomavirus (HPV) | 2 | | |
| | HIV + genital herpes + pregnancy (hormonal contraception) | | 1 | |
| VAGINAL GEL | HIV + genital herpes | 1 | | |
| | HIV + genital herpes + HPV | 3 | 1 | |
| | HIV + genital herpes + HPV + chlamydia + gonorrhea + pregnancy (nonhormonal contraception) | 1 | | |
| | HIV + genital herpes + bacterial vaginosis | 1 | | |
| | Gonorrhea + pregnancy (nonhormonal contraception) + bacterial vaginosis | 1 | | |
| VAGINAL FILM | HIV + genital herpes | | 2 | |
| VAGINAL NANOFIBER | HIV + genital herpes + HPV | 1 | | |
| VAGINAL TABLET | HIV + genital herpes | | 2 | |
| FEMALE CONDOM | HIV + genital herpes + HPV + chlamydia + gonorrhea + pregnancy (nonhormonal contraception) | | | 1 |

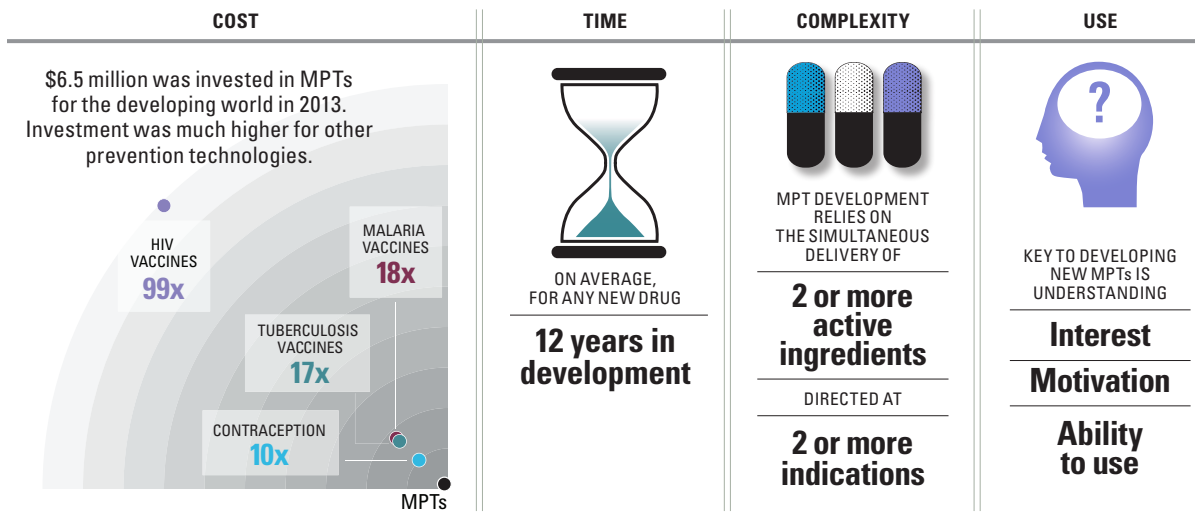
Note: Drugs typically go through three phases of clinical trials before approval: Phase I (testing safety), Phase II (testing efficacy), Phase III (large-scale testing). *Source:* Initiative for Multipurpose Prevention Technologies.

One goal, therefore, is that MPTs would cause few or no systemic side effects. Another goal would involve having a suite of products to meet the differing needs of different women: Some could be used on-demand, around the time of sex, which may appeal to women who have sex infrequently; others could be long-acting for women who would rather not worry about remembering to use a method each time. MPTs would be within a woman's personal control and have the potential to be used without her partner's permission or knowledge. And most MPTs in development have the advantage over condoms of allowing for direct

physical contact—and some may even enhance sexual pleasure.

In addition, MPTs would not require a woman to admit to herself or others that she considers herself at risk of HIV or other STIs. (In fact, for many women, avoiding an unwanted pregnancy is a more pressing concern than preventing HIV or another STI,¹⁰ and they may be more inclined to use MPTs for pregnancy prevention rather than STI prevention.) On the flip side, MPTs that prevent STIs but have no contraceptive benefit would be an important breakthrough for women who

CHALLENGES IN DEVELOPING MULTIPURPOSE PREVENTION TECHNOLOGIES



want to prevent disease but also want to have a child, as well as for couples (including men who have sex with men) who engage in anal sex and, thus, are at risk of STIs but not pregnancy.

Research Challenges

Despite the importance of new MPTs, research and development has been inadequately financed and painfully slow. In this respect, MPT research shares many of the same difficulties that exist in any frontier of science. However, the field faces a number of unique challenges as well (see chart).

Lack of Private-Sector Support

Drug development in the United States is typically supported by both the public and private sectors. Public-sector funding—mostly through the National Institutes of Health (NIH)—is often used to support basic science and early-stage discovery and development, while the private sector provides the kind of applied research and development needed to get drugs approved for marketing.¹¹ Both sectors are crucial for advances in science.

In the case of MPTs, however, the natural engines that usually drive drug development have stalled. NIH has supported important research to evaluate the building blocks of MPT products, and several private-sector companies have made drugs available to others for development. But no large

pharmaceutical company has a significant program in MPT research.^{12,13} The fact that a major goal of MPT research is to develop low-cost products for use in developing countries has made some investors concerned that their financial investments will never be recovered from sales, especially given the high cost of clinical trials. As a result, the field overwhelmingly relies on public-sector support, even in the later stages of development.

MPTs are not alone in this regard. Other global health challenges—including malaria, tuberculosis, HIV, family planning and child and maternal survival—also lack commercial incentives to fully engage the private sector. To address this, the U.S. Agency for International Development (USAID) invests in research and development for global health, and has a portfolio that focuses mostly on later stages of development and bringing products to launch in developing countries. For example, USAID investments have contributed to the development of more than a dozen contraceptives on the market today, including copper and hormonal IUDs, implants, injectables, and new vasectomy and female sterilization techniques that have increased safety and accessibility worldwide.¹⁴

Scientific Hurdles

Most MPTs in development rely on the simultaneous delivery of two or more active ingredients, directed at two or more clinical indications.

Aligning the component parts, their release time, duration and efficacy, while ensuring no interactions among drugs, is not a simple matter. Related to this, the regulatory review process is likely to be much more complex than what is typically involved with a single-agent, single-indication product.¹⁵ An MPT candidate could conceivably require review and approval by as many as three separate divisions of the U.S. Food and Drug Administration, depending on whether it is designated as a drug, biological product or device—or a combination of these.

Moreover, because MPT candidates for HIV prevention are almost exclusively based on existing antiretroviral drugs (traditionally used for treatment), scientists are grappling with the potential for drug resistance.¹⁶ Other major scientific obstacles for MPTs include the lack of new contraceptive agents (particularly nonhormonal methods) and non-antiretroviral HIV prevention compounds; the ethics and design challenges of conducting trials that include adolescents; and the safety of using MPTs during pregnancy.

Practical Barriers

As scientific efforts advance, researchers are focused on developing MPTs that will be used by women and their partners in the real world. Although research suggests that products with multiple prevention indications will have broad appeal, asking women to assess whether a hypothetical product will be acceptable to them is a challenge.¹⁷ Much depends on whether women perceive they are at risk of unintended pregnancy or disease, on their expectations related to product effectiveness and on their concerns about side effects. And women's needs and preferences change over their life span, and vary across geographic and sociocultural contexts.

So, while acceptability research has its place, women's preferences vary. What may be more important is developing a broad mix of MPTs so that each woman can make choices to address her concerns and needs at a given time in her life. As evidence on women's contraceptive use shows, the better a woman can match a method to her current needs, the more likely she is to use it correctly and consistently.¹⁸

Strategies to ensure that women use MPTs correctly and consistently are also a key challenge in product development. In recent years, experts have become increasingly concerned about "user adherence," because of data that emerged from microbicide trials.¹⁶ In these studies, only a minority of women in low-resource settings used the test product (a gel or oral tablet) correctly and consistently. The results were disheartening for many scientists and donors, and many have since shifted their focus to the development of longer-acting or "sustained release" MPTs, such as vaginal rings or implants, which can dramatically reduce user error.

Insufficient Financial Resources

Ultimately, many of these challenges could be addressed if adequate funding were available. New drug development is costly, and innovative products brought to market for the first time are particularly so. Tufts University Center for the Study of Drug Development estimates an out-of-pocket cost per approved compound (inclusive of the cost of failures) of \$1.395 billion: \$430 million in the preclinical stages and \$965 million in the clinical trial period.¹¹ Moreover, research and development takes years and requires a long-term commitment: The average time for new drug development is approximately 12 years.

And yet, in 2013 just \$6.5 million was invested in MPT research and development for the developing world, according to one analysis.¹³ And this one-year investment was spread over numerous products in development—not just one compound. USAID and NIH provided the bulk of these funds (\$5.8 million); the philanthropic sector and other governments provided the rest. To put this number into perspective, investments in MPTs are dwarfed by the already inadequate investments in other areas of preventive health for the developing world: According to the same analysis, in 2013, \$63 million was spent on contraceptive research and development, \$110 million on tuberculosis vaccines, \$119 million on malaria vaccines and \$642 million on HIV vaccines.¹⁹

Mobilizing Support

In 2009, CAMI Health, a project of the Public Health Institute, founded the Initiative for Multipurpose Prevention Technologies to catalyze the field by

bringing together scientists, product developers and advocacy groups on a regular basis to advance the MPT agenda.¹⁵ The initiative aims to promote collaboration across a broad cross-section of organizations and experts from around the world. These include agencies such as USAID, NIH, the World Health Organization and the United Nations Population Fund; foundations such as the Bill and Melinda Gates Foundation; research entities such as CONRAD, International Partnership for Microbicides, the Indian Council of Medical Research and the Population Council; and NGOs.

As one of its first priorities, the initiative led an assessment of the leading MPT products in development and prioritized the most promising candidates. It has also been working to galvanize political support for MPT research, with hope that this will eventually result in a significant infusion of new funding for MPT product development.

Looking ahead, U.S. policymakers have an opportunity to accelerate MPT innovation by increasing funding through NIH and USAID. At the very least, maintaining funding at current levels is needed

to continue the momentum behind the field. “There is little doubt that, with sufficient investment, MPTs could revolutionize how we approach prevention and the options women have,” says Bethany Young Holt, founder and executive director of the initiative.²⁰ “This is as true in developing countries as it is in the United States, where many women and couples are also at risk of unintended pregnancy and STIs. Let’s face it, though. MPT research and development requires a long-term commitment and more robust funding. And because private industry is largely absent from the field, the U.S. government will have to take the lead. But imagine the impact on a woman’s life if she could use one product that simultaneously prevented unintended pregnancy and disease. MPTs would be a true game-changer.” ■

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