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Multipurpose prevention technologies: Call for innovative strategies to address critical priorities and gaps

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Multipurpose prevention technologies: Call for innovative strategies to address critical priorities and gaps

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Editorial: Multipurpose prevention technologies: call for innovative strategies to address critical priorities and gaps

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Editorial on the Research Topic
Multipurpose prevention technologies: call for innovative strategies to address critical priorities and gaps

When developing new drugs and healthcare interventions, we often focus on the technical challenges. Development of new therapeutics and preventives is difficult and even developing products based on existing technologies poses a challenge. Beyond the scientific hurdles, there are numerous other challenges including fluctuating levels of funding and general underinvestment in certain conditions, socio-behavioral aspects that can affect uptake and product acceptability, and a challenging regulatory, manufacturing and reimbursement environment (1). For products such as multipurpose prevention technologies (MPTs)—which aim to simultaneously prevent HIV, other sexually transmitted infections (STIs), and/or unintended pregnancies—these challenges can be even greater as they combine multiple active pharmaceutical ingredients (API) or drugs into a single product and face complex and sometimes uncharted development pathways.

Building on research on contraception and prevention of HIV and other STIs, the MPT field was launched in 2009 to address these intrinsically linked risks (2–4). As the field matured, field-wide partners refined priority action areas and expanded our focus to encompass the many factors needed to ensure widespread and timely uptake of MPTs when they become available (Table 1) (5). Improved outcomes and equitable access can only be achieved if products reach the hands of end users and these action areas reflect this understanding of the entire product lifecycle. The papers in this special issue are organized around five priority areas; they provide updates, lessons learned, and discussion around what the MPT field can do in order to continue advancing product development and distribution in an efficient and equitable manner.

While the action areas reflect a focus beyond the scientific challenges inherent in product development, research and development continues to be a significant focus

TABLE 1 Priority areas to advance MPT development and corresponding articles.

1. ***Stimulate a productive ecosystem of MPT research and development (R&D)***
   - End-to-end approach to ensuring equitable access to multipurpose prevention technologies in low- and middle-income countries Cameron et al.
   - Key programmatic and policy considerations for introducing multipurpose prevention (MPT) methods: Reflections from healthcare providers and key stakeholders in South Africa Kutywayo et al.
   - Innovations in monoclonal antibody-based multipurpose prevention technology (MPT) for the prevention of sexually transmitted infections and unintended pregnancy Dohadwala et al.
2. ***Improve understanding of reproductive biology for the purpose of new pharmaceutical development for MPT R&D***
   - Common ground: the opportunity of male contraceptives as MPTs Vahdat & Nickels
3. ***Expand understanding of socio-behavioral research considerations, particularly among groups who have traditionally been underrepresented in MPT research***
   - Biomedical, socio-behavioral, and implementation science gaps in multipurpose prevention technology research Cummins et al.
   - Program impact and potential pitfalls of multi-purpose technologies (MPTs) for HIV prevention and contraception Latka et al.
   - How might we motivate uptake of the Dual Prevention Pill? Findings from human-centered design research with potential end users, male partners, and healthcare providers Nyagah et al.
   - End-user research into understanding perceptions of and reactions to a Microarray Patch (MAP) for contraception among women in Ghana, Kenya and Uganda El-Shah et al.
4. ***Expand understanding of market considerations to help ensure successful commercialization and uptake of MPTs***
   - Estimating the costs and perceived benefits of oral preexposure prophylaxis (PrEP) delivery in ten counties in Kenya: a costing and a contingent valuation study Forsythe et al.
   - The role of economic evaluations in advancing HIV multipurpose prevention technologies in early-stage development Chapman et al.
5. ***Enhance understanding of innovative approaches for MPT clinical trials that address regulatory and ethical challenges of testing multiple indications in the same trial***
   - Efficient regulatory approval of two novel HIV prevention interventions in a resource-limited setting: experiences from Zimbabwe Murombedzi et al.

(Action Area #1). According to a World Economic Forum analysis, at the current rate of investment, it will take 132 years to close the global gender gap between men and women—due in significant part to high rates of preventable morbidity during pregnancy and maternal mortality (6). This gender gap is exacerbated by underinvestment in health conditions that primarily impact women's health. A recent analysis of NIH funded work found that nearly 75 percent of research on conditions that disproportionately affected one gender vs. another found either underfunding of research for conditions that are more prevalent in women or overfunding of diseases that affect more men (7). While the NIH is a significant funder and supporter of MPTs, only 3% of the 2019–2020 NIH budget was devoted to female contraceptives and non-HIV STIs (8). Similarly, a 2020 analysis of biopharmaceutical investment found that only 5% of industry investment was in women's health with only 1% of global biopharmaceutical investments dedicated to non-cancer health conditions in women (9).

This lack of robust and diverse investment in women's and reproductive health is a broad challenge impacting MPT product development. Developing a safe, effective product is but the first step and the context in which researchers are working is challenging. In this special issue, Dohadwala et al. present advances in the use of monoclonal antibodies (mAbs) for the prevention of infectious diseases and highlight the fact that the MPT field pioneered the use of topical mAbs. However, they also note the high cost of development and manufacturing will be a significant constraint. Complementing this paper is the work by Cameron et al., examining equitable access to MPTs, and a second paper by authors Vahdat and Nickels from the Male Contraceptive Initiative. The limited funding for contraceptive and MPT research has been heavily focused on female end-users and Vahdat and Nickels outline steps and challenges needed to expand the field to include male end-users, including potential areas of synergy where working collaboratively could yield multiplicative advances in both fields.

One of the hurdles constraining the rapid development of MPTs is the traditional focus on lower- and middle-income countries (LMICs) where industry investment has been limited. As noted by Cameron et al., it takes an average of eight to ten years after HIV medicines receive approval in the United States to reach LMICs. This delay highlights the critical need to engage stakeholders across the research, manufacturing, distribution, and procurement spectrum from the beginning, a strategy that they refer to as end-to-end approach predict, prevent, and remove potential roadblocks to product development and access.

Having a better understanding of market considerations to ensure successful commercialization and uptake of MPTs is one of the action areas that builds on the end-to-end approach. In this issue, three articles examine market considerations. Forsythe et al. discuss willingness to pay for oral pre-exposure prophylaxis (PrEP)—a key component of many MPTs under development. They found low willingness to pay for oral PrEP among adolescent girls and young women, a key population for MPTs, suggesting that it may be difficult to use traditional market driven approaches for coverage and distribution of MPTs. Chapman et al. underscore the importance of incorporating economic evaluations to inform early-stage development and to mitigate potential market failures. Kutywayo et al. highlight the fact that healthcare providers serve as critical gatekeepers and can either stimulate or diminish demand. All three papers help inform our understanding of the challenges the field will need to confront in order to support a robust market for MPTs.

Four additional papers examine the importance of socio-behavioral research in understanding the potential for product uptake and use. Having a clear understanding of end-user needs and preferences is critical for developing a successful market strategy. The aforementioned disparities in research and funding for women's and reproductive health have been driven in part by regulatory policies that previously excluded women of childbearing age in clinical trials. In 1977, the U.S. Federal Food and Drug Administration (FDA) banned women of "childbearing potential" from participating in clinical trials (10). While this policy was formally rescinded in 1993 and the number of women participating in clinical trials has increased, infectious disease research continues to have one of the lowest relative ratio of female to male enrollment (−18.68% relative difference) (11). These historic exclusions have driven our

limited understanding of the social-behavioral considerations around women's a health, and knowledge gaps in reproductive biology and differences in male and female pharmacokinetics and pharmacodynamics.

In their commentary, Cummins et al. provide a high-level summary of environmental and structural barriers to MPT uptake, including the need to better understand socio-behavioral considerations, adherence, and gaps in implementation science that can either drive or impede effectiveness of MPTs Cummins et al. Responding to this, Latka et al., provide a framework for understanding the interplay between user characteristics, method efficacy, use effectiveness and the importance of developing a diverse array of products that can meet changing values, preferences, and needs across a person's life course. In line with this framework and referencing back to the end-to-end research approach characterized by Cameron et al., Nyagah et al. present their findings from a human-centered design approach and reinforce the importance of treating end-users as a diverse and heterogenous collection of individuals with sometimes conflicting and competing identities and values. Putting these theories to practice, El-Sahn et al. conducted in-person interviews to provide actionable feedback from potential end-users to product developers.

The MPT field faces a challenging regulatory pathway. MPT candidates include diverse delivery platforms and drug combinations representing both approved and new drugs. MPTs may need to meet US federal requirements for safety and efficacy testing of combination products although some product developers have pursued regulatory approval in only ex-US settings. While these alternative pathways may speed approval, the multiplicity of regulatory agencies makes it challenging to get approval for clinical testing and trial design to provide safety data on multiple indications. Individual indications of an MPT must also meet accepted efficacy standards for each of its indications. In our special issue, Murombedzi et al. detail strategies to reduce the approval time in Zimbabwe from a median of several years (516–1,673 days) to register a drug to 133 days for registration of the dapivirine vaginal ring and 159 days for the long-acting cabotegravir (CAB-LA) by leveraging innovative regulatory pathways and capacity strengthening. Although the MPT regulatory and approval pathway is inherently more complicated than single drug examples we can use these lessons and begin to look for efficiencies in the regulatory pathway for MPTs.

The MPT field faces a myriad challenges, but these products offer the possibility of revolutionizing women's health by offering prevention for multiple indications in single products- a feature most women favor (12–14). While women represent more than half of the world's population, many women across the world face tenuous access to healthcare (15–17). Increasingly scientists, governments, and multilateral organizations recognize the positive impact that reproductive health and family planning have on entire communities and even larger macro trends such as climate change (18–21). While still modest compared to what is needed, investment and attention to and investment in women's reproductive health is increasing (22). To realize the full potential of MPTs, we must strategically work to move promising products from the laboratory to end-users, improving the diverse health needs and wants of women globally.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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End-to-end approach to ensuring equitable access to multipurpose prevention technologies in low- and middle-income countries

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Introduction

With less than half of the 15-year Sustainable Development Goal (SDG) agenda remaining, progress toward the goal of ensuring healthy lives and promoting wellbeing for all has slowed, stalled, and in some cases reversed. UNAIDS has targets of 95% of people at risk of human immunodeficiency virus (HIV) infection using appropriate, prioritized, person-centered and effective combination prevention options and 95% of women of reproductive age having their HIV and sexual and reproductive health service needs met by 2025 (1). However, in 2021, there were 1.5 million new HIV infections, far from the 2025 target of 370,000 (2); 121 million unintended pregnancies, nearly half of all pregnancies globally (3); and 374 million new infections with one of four curable sexually transmitted infections (STIs) (4), compounding the risk of HIV acquisition. Most of this burden is borne by low- and middle-income countries (L/MICs). The COVID-19 pandemic pushed progress further off-track. For example, an estimated 12 million women were unable to access family planning services due to the pandemic, resulting in 1.4 million unintended pregnancies (5). With additional factors such as climate change driving migration and conflict, and the cost-of-living crisis constraining budgets, there is even greater need for streamlined services and improved, affordable technologies to meet diverse health needs across different contexts (6).

Novel forms of multipurpose prevention technologies (MPTs) are a game-changing innovation for the simultaneous prevention of unintended pregnancy, HIV, and/or STIs. By addressing multiple health needs at once, MPTs have the potential to better meet the needs of the populations they seek to serve and accelerate progress toward global goals. However, technological innovation alone is insufficient to achieve global impact. Addressing timely and equitable access is key for novel technologies to reach populations in need and realize their full potential. There is an opportunity to learn from other technologies that have emerged in recent decades. On average, it has taken eight to ten years for HIV medicines approved by the United States Food and Drug Administration (US FDA) to become accessible in L/MICs (7). With the urgent need

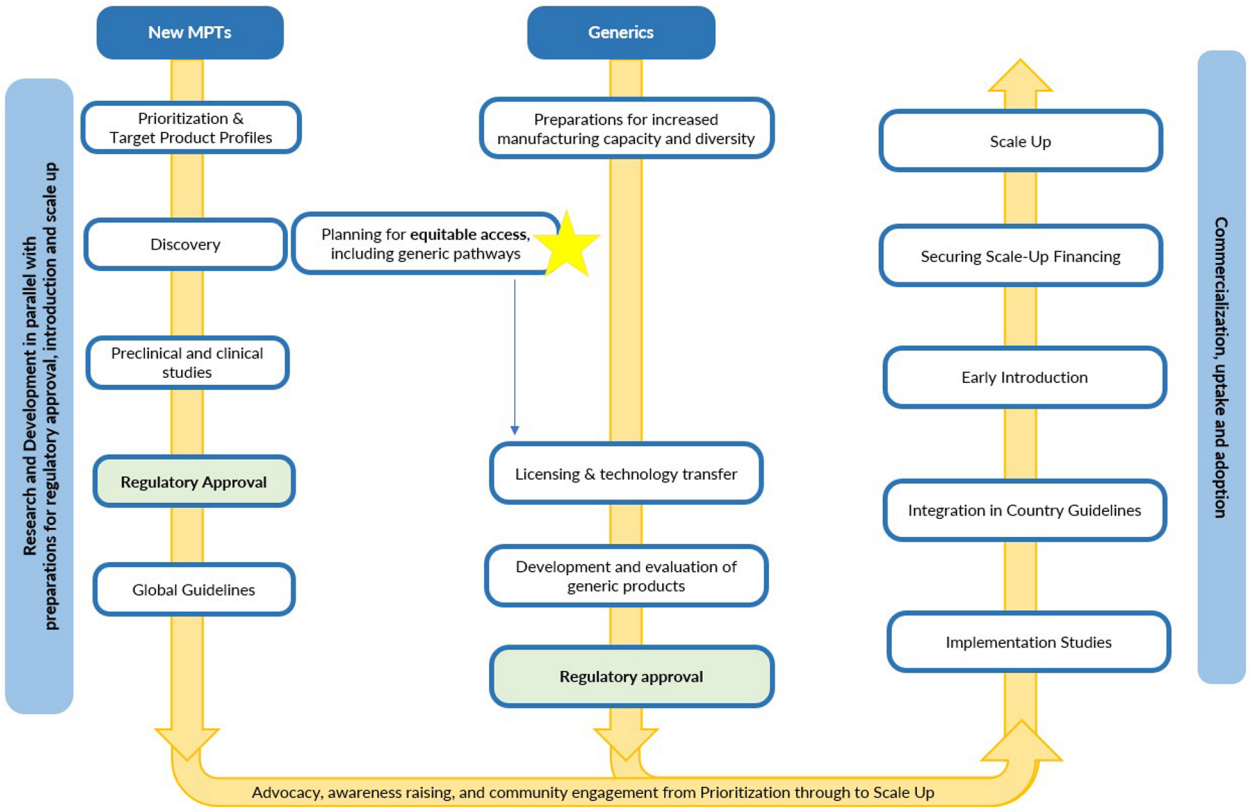

FIGURE 1
Planning an E2E approach.

to accelerate progress toward SDG3[1] (8), we cannot afford preventable mortality and morbidity caused by this lag in access.

E2E approach to access in L/MICs

An end-to-end (E2E) approach in the context of addressing health innovations aligns relevant stakeholders across sectors, including product developers, generic manufacturers, funders, regulators, health agencies, governments and communities, on a common strategy to bring a product from research and development to uptake and adoption by communities (Figure 1). An E2E approach has a holistic view of the actions and commitments necessary to facilitate equitable access and must be initiated at the earliest stages of product development. Waiting until products reach the market to plan for equitable access often leaves it too late to address the root causes of high prices and slow commercialization in L/MICs (7). The full potential of any given MPT can best be realized if an E2E approach is taken to ensure the conditions to achieve equitable access are established rapidly—including in advance of products being available—and in a sustainable manner.

An E2E approach goes beyond advancing products in pipeline and looks ahead at the roadmap to suitable, affordable and quality supply for accelerated introduction and adoption. This approach prevents and removes potential roadblocks associated with intellectual property, facilitates timely regulatory approvals; anticipates supply pathways; coordinates with country stakeholders for integration into guidelines; and maximizes the engagement of affected communities (6). The following sections outline key considerations for an E2E approach for MPTs, divided into the phases before, during and after regulatory approval.

Figure 1 is a linear depiction of the steps required, however in practice many of these steps overlap to expedite timelines.

Pre-regulatory approval

The research and development phase for MPTs is a critical time for developers to consider end-user preferences and to chart a product's access pathways to ensure the final product will be both acceptable and accessible to all who could benefit. Investors will similarly need to prioritize which products to support based

[1]Sustainable Development Goal 3 is to ensure health lives and promote well-being for all at all ages. This includes targets relevant to MPTs such as target 3.3 (fight communicable diseases) and 3.7 (universal access to sexual and reproductive care, family planning and education).

on end-user preferences and access profiles. User preferences vary widely, however some studies have shown a general preference for discreet and familiar provider-administered long-acting products, such as injectables and implants (9). That said, as one MPT will not meet the needs or preferences of all potential users, this prioritization needs to be balanced with the objective of having a range of MPTs available to enable choice. Condoms are the only MPT currently available, and while they have been and continue to be pivotal in the global agenda to prevent HIV, STI, and unintended pregnancy, they do not meet the preferences of all potential users. This speaks to the need to have a range of different MPTs available, and to establish feedback mechanisms from users to inform the design of future products.

Identifying and mitigating potential barriers to access for end-users, such as affordability and availability, also needs to be initiated by product developers and those financing these innovations in parallel with research and development efforts. The complexity of combining active pharmaceutical ingredients and the technologies involved in MPTs may imply cost differences with the standard-of-care products they aim to replace, especially for formulations with extended release, and may also limit the number and location of manufacturers able to produce them (9). Cost-effectiveness estimates and potential impact need to be considered from early stages to inform which MPTs in the pipeline are prioritized, and developers may need to be incentivized by global health funders to investigate cost-reduction strategies. Global health funders can play an important role by embedding access terms, such as sharing of intellectual property, into funding agreements for research and development or considering market shaping support, such as guaranteeing minimum volumes of procurement in early introduction phases (see Box 1).

BOX 1 Long-acting contraceptives have demonstrated the potential for partnerships to catalyze a healthy market for L/MIC access.

The Implants Access Program (IAP) was a partnership between industry, procurers, donors, and implementers that began in 2012 with volume guarantees for two contraceptive implants, resulting in a price reduction of approximately 50% (10). This, in combination with efforts to improve supply chain coordination, service delivery, and knowledge and awareness, was key in facilitating rapid scale-up in L/MICs (11). Between 2010 and 2018, there was a tenfold increase in implant procurement in the 69 lowest income countries with 27 million women using implants in L/MIC in 2019 (11, 12, 13). Effective collaboration at global and country levels contributed to institutionalizing mechanisms to maintain lower prices for long term sustainability (11).

Intellectual property may also limit who can manufacture MPTs, especially considering the additional intellectual property involved compared to single-indication products. Early planning by developers to establish licensing mechanisms that enable a generic manufacturing base will not only help overcome intellectual property barriers and improve supply security; it will also enable greater affordability. For example, the Medicines Patent Pool (MPP), an organization founded by Unitaid, employs a model that facilitates non-exclusive, voluntary licensing of life-saving medicines for L/MICs (14). While MPTs would require special considerations for voluntary licensing, this model could help address such access barriers. Engagement between industry partners and MPP prior to regulatory approval accelerates access once approval is obtained. Voluntary licenses may not enable access for all L/MICs, however, and other mechanisms may need to be explored to overcome intellectual property barriers (15)[2].

Planning for regulatory approval

Early planning is necessary to ensure regulatory pathways do not cause delays in access to MPTs. Regulatory requirements for MPTs are yet to be clearly defined, which may cause challenges for MPT developers as they are planning what data to generate for approvals. There have been reviews of key regulatory guidance documents and their applicability to MPTs, however there will not be one single regulatory pathway for MPTs (9). Regulatory approval requirements often differ across Stringent Regulatory Authorities and national regulators in L/MICs, and requirements will also vary across MPTs depending on the components. For example, the Dual Prevention Pill under development only requires a bioequivalence study, rather than Phase 3 safety and efficacy trials because both oral dose products are separately approved and their drug-drug interactions well-studied (16).

Developers and regulators are therefore encouraged to engage early on in these discussions, so that approval processes can be executed without delay once products in the pipeline reach this stage. Developers are also encouraged to engage with the World Health Organization (WHO) technical areas regarding guidance recommendations; and the WHO Prequalification program (17) including the WHO Collaborative Procedure for Accelerated Registration (18), to accelerate access to and registration of critical quality-assured products in L/MICs. It is generally expected that developers widely register and supply quality-assured products soon after a recommendation or approval is obtained by a normative body and/or regulatory entity.

Planning for post-regulatory introduction and scale up

In order to have rapid introduction and scale up once approved, both supply and demand side strategies need to be considered including policy and implementation guidance (see Box 2). MPTs

[2]Note that while this resource refers to COVID-19 therapeutics, the mechanisms outlined to overcome intellectual property barriers can be applied to other products.

BOX 2 Lessons learned from delayed access to HIV treatment and prevention.

There are many lessons that can be learned from antiretroviral-based therapies and preventatives for HIV. When highly-active antiretroviral therapy first emerged in 1996, prohibitively expensive prices meant that AIDS-related mortality declined by 75% in three years in the United States but continued to rise in L/MICs. It wasn't until 2001, when lower-cost generic versions became available, that mortality started to decline in L/MICs (19). Similar patterns were seen with the emergence of fixed-dose combination therapies, which took nine years following approval by the US FDA to have generic versions available in L/MICs (19).

Daily oral HIV pre-exposure prophylaxis (PrEP) also faced delays reaching L/MIC populations after initial regulatory approval by the US FDA in 2012. By 2016, the US had nearly 100,000 PrEP initiations (virtually all of the 102,446 initiations worldwide), whereas South Africa had 380 (20). It wasn't until 2021 that South Africa and the US had reached roughly the same number of initiations (approximately 200,000) (20). This was largely due to challenges related to acceptability of the product among potential users and providers, low community awareness and motivation to seek preventative services, and health system bottlenecks (21). The experience of oral PrEP highlights the importance of early consideration of user preferences, advanced demand generation, and planning for post-approval activities that are designed and coordinated to inform decision-making at the national and global levels (21).

will break the mold of the silos that healthcare systems typically operate in. Supply chains for family planning and HIV commodities are currently disconnected, and financing and procurement streams are typically separated by governments and donors as well. Establishing the budget, procurement mechanisms, and supply and delivery pathways for MPTs will require collaboration among diverse stakeholders, including industry, governments, global health funders, and procurement agencies. This will have major implications for the scope of responsibilities of health departments as MPTs become available, ranging from monitoring and evaluation to health provider training. In addition to the adaptations country health systems will need to make to integrate MPTs, country-specific efforts will also be required to obtain national market authorization and guidelines for sustainable implementation in national programs. Implementation research in early adopter countries will play a critical role in generating real-world evidence to inform recommendations at the national and international level and enable broader scale up. In parallel with research, MPT awareness-raising by and with policymakers, medical associations and advocates through convenings, publications and interest group formations can accelerate uptake once products achieve government commitment to scale (9).

Discussion

Meaningful innovation requires more than new and improved products; it also necessitates finding novel strategies to collaborate and overcome barriers to equitable access for products to have global impact (6). This article highlights the need for a range of stakeholders to collaboratively address product and market characteristics, such as affordability, supply capacity, intellectual property, regulatory pathways, and ease of use, to enable prompt community adoption. While lessons can be learned from existing products, some considerations will be unique to MPTs and it is imperative that the global community align on how to address these and plan far in advance so that MPTs can reach L/MICs without delay once available. Platforms that bring together donors, agencies, governments, affected communities and advocates to ensure an accelerated, sustainable, and collaborative approach is taken to making MPTs equitably accessible will be essential. If planning to remove access barriers does not start early on, there will be a myriad of challenges impeding timely uptake and scale in L/MICs. As the pipeline of MPTs continues to grow and advance, now is the time to plan for an E2E approach to equitable access.

Author contributions

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Program impact and potential pitfalls of multi-purpose technologies (MPTs) for HIV prevention and contraception

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The overlapping epidemics of HIV and unplanned pregnancy disproportionately affect adolescent girls and young women (AGYW) in sub-Saharan Africa. Prevailing dynamics driving benefits of any prevention method at the population level depend on: 1) population size, risk profile, and prevalence of method use, 2) method efficacy, and 3) method use-effectiveness. Adding a multi-purpose technology (MPT) to prevent HIV and pregnancy to this three-part equation results in scenarios that may enhance HIV population impact, even with methods that exhibit less than "perfect" method efficacy, by extending protection among existing users and attracting new users, resulting in greater population coverage. However, the interplay of epidemic drivers is complex and the greatest population benefit of such a MPT would be realized among those most at risk for HIV and pregnancy, and could be harmful if successful contraceptive users switch to a method with lower use–effectiveness. While MPTs are highly desired, and may offer considerable individual, population, and system-level public health benefits, there is no "magic bullet", nor single prevention method–MPT or otherwise–that will end the HIV epidemic nor fully resolve unmet need for family planning. All methods have inherent tradeoffs and women have varied reproductive and HIV prevention needs across their life course. Key programmatic features to maximize the potential of MPTs include offering them among a range of safe and effective methods with comprehensive information about their features allowing women to make a fully-informed method choice. Programmatic follow-up should support consistent and correct use to maximize use-effectiveness, and then monitor for potential untoward effects.

KEYWORDS

multi-purpose technology, HIV prevention, contraception, unplanned pregnancy, use-effectiveness, method efficacy, adolescent girls, sub-Saharan Africa

Introduction

Multipurpose prevention products (MPTs) under development include a range of delivery platforms such as rings, implants, injectables, films, enemas, and vaginal and rectal inserts for HIV, other sexually transmitted infections (STIs), and contraception (1,2). Currently, condoms are the only MPT available for protection against STIs, HIV, and pregnancy. Condom use is challenging, especially for adolescent girls and young

women (AGYW) in sub-Saharan Africa (SSA) (3). Men's and women's desire for children, gender inequality, domestic violence, and stigma hinder agency for use. Warfare, corruption, poverty and competing morbidities create unstable backdrops for HIV prevention programming. Product development funding and product cost also present challenges. These prevailing societal norms and realities challenge introduction and use of any new prevention method. The majority of MPTs in development target HIV and pregnancy (1). Women's reproductive health and HIV are related, with HIV exacerbating the maternal mortality epidemic and mother-to-child transmission significantly contributing to the HIV epidemic in SSA (4). A biomedical MPT preventing HIV and pregnancy could have substantial health benefits for AGYW in SSA. The HIV epidemic disproportionately affects AGYW in SSA with 63% of incident infections occurring in females aged 15–24 (5). Further, across 30 SSA countries, the prevalence of unmet need for contraception is 27% among partnered AGYW aged 15–24, and 32% of pregnancies among women in SSA are unplanned (6,7).

A MPT for HIV and pregnancy–even one with less than perfect method efficacy for HIV prevention–holds potential for enhanced public health impact due to the interplay of three drivers of protection: 1) the population's size, risk profile, and method use prevalence; 2) method efficacy and; 3) method use-effectiveness. Adding MPTs for HIV and pregnancy to this three-part equation results in scenarios that may enhance HIV population impact. However, epidemic drivers are complex, and some MPT introduction scenarios for HIV and pregnancy may detract from net population benefit. The greatest potential population benefit and efficiencies for such a MPT would be realized among those most at risk for HIV and pregnancy.

Three drivers of population benefit

With respect to factors that public health practitioners can influence, drivers of population benefit involve the interplay of three broad elements (Figure 1). First are the population's size, risk profile (whether the group is epidemiologically at high risk for HIV and the total fertility rate), and prevalence of preventive method use in at-risk populations. Second is method efficacy which is the method's ability to prevent the outcome under ideal conditions, such as efficacy observed during pre-clinical challenges or in as-treated analyses in efficacy trials when a method is used consistently and correctly (8). Third, is use-effectiveness which is the effectiveness of a method realized under real-world conditions, where factors such as uptake and consistent and correct use influence the ultimate protection conferred (8).

A highly efficacious method only provides benefit if used consistently and correctly. A widely-used prevention method with only moderate method efficacy may still have population impact as was seen with the use of withdrawal (coitus interruptus) for contraception that contributed to the demographic shift in family size at the end of the 19th century (9). The interplay of method efficacy and user adherence, an element determining use-effectiveness, is demonstrated by the mixed findings of oral PrEP (TDF/FTC) to prevent HIV among women (10). High method efficacy alone is not sufficient to shift an epidemic. The role of the user, their risk profile, their access to methods, and ability to consistently and correctly use a method, are important drivers of protection. Long-acting cabotegravir (CAB-LA) has demonstrated high method efficacy for HIV prevention in clinical trial settings (11). Method efficacy for CAB- LA is derived from select women who met inclusion criteria, received reimbursements for study visits, and were cared for by proactive staff reminding them of injection

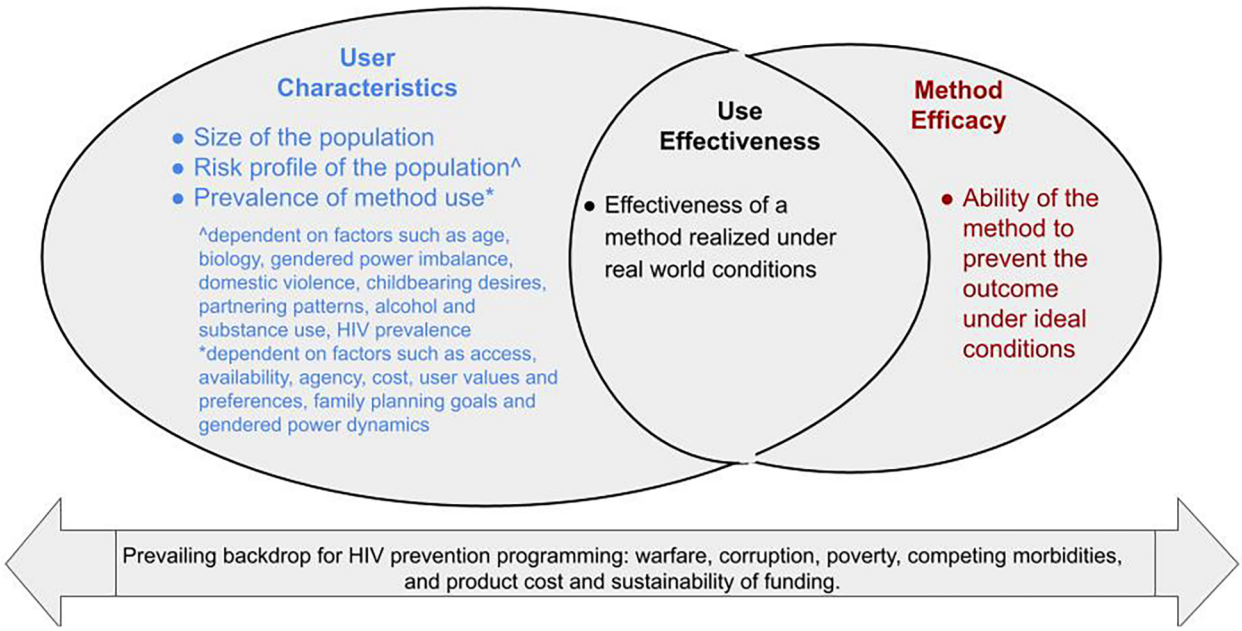

FIGURE 1
Drivers of population benefit.

visits. While many women in SSA state preferences for injectable HIV prevention (2), the use-effectiveness of CAB-LA to protect women from HIV under real-world scale-up is yet to be characterized. Further, at a population level, if new CAB-LA users are those migrating from successful daily oral PrEP use, population impacts on the HIV epidemic may be moderate if one method is simply supplanted for another without a net gain in prevention coverage for those at risk for HIV. The Catalyzing Access to New Prevention Products to Stop HIV (CATALYST) study, will evaluate a multi-product service-delivery platform offering daily oral PrEP, the monthly dapivirine ring, and CAB-LA at public clinics across five countries in southern and eastern Africa and will provide data on use-effectiveness of these single-indication methods and describe the programmatic impact of offering choice (12).

Three drivers + a MPT for HIV and pregnancy

Adding a MPT for HIV and pregnancy to this three-part equation may result in beneficial scenarios by adding new users with unmet need for both indications resulting in a net increase in population coverage, or by expanding protection for a second indication among existing users with unmet need. Increasing uptake for new users holds promise as MPTs are highly desired with 96% of women surveyed in SSA preferring HIV prevention products with multiple indications compared to a single-indication product (2). Preference for multiple over a single indication outweighed preference for type of delivery method (i.e., injectable, pill, implant, etc.) (2). Further, in a worldwide survey of method preference, women were most interested in products offering both HIV and pregnancy prevention (82%) compared with single indications for HIV (76%) or pregnancy only (64%) (13).

In both scenarios above–either attracting new users or expanding coverage to those with unmet need for a second indication–additional benefit is realized so long as the added coverage occurs among women at high risk for the outcomes as suggested by cost effectiveness modeling. Analyses scaling a MPT for HIV and pregnancy found pregnancy prevention would be cost effective if rolled out to women at high risk of HIV (e.g., serodiscordant couples, AGYW or female sex workers) but not to a general population of women (14,15). Notable was that a MPT for HIV and pregnancy was cost effective among populations at high risk for HIV even with HIV method efficacy ranging from 45% to 75% (15). Modeling of the dual prevention pill (DPP) found that scaling the DPP was sensitive to both risk of HIV in the population and adherence (e.g., use-effectiveness), where if adherence was low, the health risks from unintended pregnancy could outweigh the health benefit of HIV prevention (14).

MPT potential benefits and pitfalls for individual users and public health

Expanding protection for the dual outcomes of HIV and unplanned pregnancy would be especially beneficial among AGYW in SSA who are disproportionately at risk for HIV, have unmet contraceptive needs, and face well-established barriers to accessing sexual and reproductive health services (16). The availability of a MPT may ease how AGYW interface with the healthcare system by meeting dual health care needs with only one health encounter which may be less stigmatizing if focused on reproductive health compared with HIV prevention, and by reducing multiple disclosures about HIV and sexual activity (2, 17). Additionally, use-effectiveness for a HIV and pregnancy MPT may be enhanced if women are highly motivated to use the method consistently and correctly in order to avoid unplanned pregnancy as self-perceived risk for HIV is often inaccurate (18,19). However, there are potential pitfalls for a MPT highly dependent on adherence, such as the daily oral DPP. As per DPP cost-effectiveness modeling, expanded population coverage achieved could be outweighed by poor adherence and lowered use-effectiveness, as daily pill taking may be more challenging than using longer-acting methods (14). Since the average probability of conception is higher than HIV transmission, poor adherence to the daily oral DPP could be offset by unplanned pregnancy without necessarily increasing HIV protection.

The introduction of a MPT for HIV and pregnancy, especially among AGYW in SSA, has the potential to offer health dividends not just for the individual user by reducing HIV incidence and unplanned pregnancy in adolescence, but may also improve maternal and child health outcomes. Pregnancy in adolescent girls is associated with disproportionately high maternal mortality, low infant birth weight, severe neonatal outcomes, as well as decreased education and censored socioeconomic potential impacting the welfare of both mother and child (20).

A MPT for HIV and pregnancy may have the additive effect of streamlining and integrating service delivery for over-burdened providers and public health systems, a need which has long been noted (21–23). Most family planning and HIV clinics are overburdened and may not have capacity to provide separate but overlapping services yet several models for integrated care have been proposed (24,25). Integrated service delivery settings are associated with increased method uptake, enhanced client satisfaction, reduced HIV-related stigma, and may facilitate the involvement of men and improve joint decision making around protection (21, 23, 26). Yet, the development of a biomedical MPT for HIV and pregnancy will be challenging, as it requires meeting safety and efficacy thresholds for two indications while regulatory standards for a dual-indication product remain unclear (1, 27).

Discussion

Adolescent girls and young women who bear a disproportionate burden of HIV and unplanned pregnancy have much to gain from a MPT for HIV and pregnancy. While such MPTs are highly desired and have considerable potential for public health impact, like single-indication products, there is no single MPT, regardless of method efficacy level, that alone, will stem the twin epidemics of HIV and unplanned pregnancy. The

most effective method is the one that gets used consistently and correctly. While continued efforts should focus on developing MPTs offering high method efficacy for intended indications, a MPT for pregnancy and HIV, even with limited method efficacy, has the potential to have significant epidemic impact if used among those at high risk for HIV. Further, women need a range of prevention methods that can be varied across their lifetime, given that values, preferences, needs and risks vary across the life course. The contraceptive field has shown that offering a choice of methods, even with a range of method efficacy, lessens the burden of unmet need for family planning because values and preferences of users are varied (28). Contraceptive method decision-making is influenced by a variety of factors beyond efficacy including reproductive health events, relationship status, partner approval, childbearing desires, and societal norms which all affect the ultimate ability to adopt and use a method. Key programmatic features that would maximize the potential of MPTs include offering MPT as part of a range of safe and effective contraceptive and HIV prevention methods with full information about their features such as indications addressed (single, dual, multiple), method efficacy, use-effectiveness, mechanism of action, potential side effects, return to fertility, duration, and respectful support in how to use. This would allow women to make a truly informed method choice. Offering an array of both single and dual methods for contraception and HIV and ensuring providers have strong integrated counseling guidelines and training may mitigate against pitfalls, such as inducing women to switch to a less-effective MPT. A method array that includes multiple and single indications, locally-acting and systemic products, as well as on-demand, medium-, and long-acting methods is necessary to address women's complex and evolving needs.

USAID is investing in the development of an array of biomedical HIV prevention products for AGYW, and a few of these products are being developed as MPTs for HIV and pregnancy. Additionally, many USAID service delivery initiatives are underway to streamline and decentralize HIV services in high HIV-burden countries. In the short term, USAID supports moving to integrated care models for sexual and reproductive health, including moving more services into primary care, which is important for sustaining and simplifying service delivery. In the absence of MPTs available for implementation, additional testing of co-delivery models providing existing HIV and pregnancy prevention methods (e.g., the administration of injectable CAB-LA along with contraception) are needed given the promising association that integrated service delivery has on dual method use. In the longer term, sustained investments to make safe, effective, acceptable, and scalable MPTs a reality should continue.

Data availability statement

The original contributions are included in the article. Further inquires can be directed to the corresponding author.

Author contributions

ML, and KV contributed to the conception and design of the study. ML wrote the first draft of the manuscript. KV wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version. All author contributed to the article and approved the submitted version.

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Biomedical, socio-behavioral, and implementation science gaps in multipurpose prevention technology research

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There is strong global need for the development of Multipurpose Prevention Technologies (MPTs) that prevent HIV, pregnancy, and/or other sexually transmitted infections (STIs). However, despite decades of research focused on the development of MPTs, numerous research gaps remain, contributing to reproductive health disparities. This commentary will highlight biomedical, socio-behavioral, and implementation science gaps in MPT research. Biomedical gaps and barriers include limited dosage forms, challenges around drug selection and stable coformulation of multiple drugs, and an unclear regulatory pathway. Behavioral, social, and structural gaps include lack of research around MPT preferences for some subgroups of potential end users, lack of knowledge around whether MPTs improve uptake, adherence, and persistence vs. separate products, and a need to further understand how social and cultural factors might impact MPT interest and use. Gaps in implementation science research will need to be addressed to better understand how to implement MPTs to maximize effectiveness and benefit. This commentary will also identify opportunities for integrating biomedical and behavioral science around MPTs.

KEYWORDS

multipurpose prevention technology, sexually transmitted infections, contraception, socio-behavioral, drug co-formulation, regulatory affairs, end-user preferences, implementation science

Introduction

Globally, increasing reproductive health options for women will address health disparities and further opportunities to address gender inequality. There is an unmet need for contraception among women, and concurrently, an unmet need for prevention of HIV and/or other sexually transmitted infections (STIs) among women. The HIV prevention landscape has been transformed with FDA approval of Truvada (TDF/FTC) as oral PrEP in 2012, Apretude (CAB-LA) as long-acting injectable PrEP in 2021, and more recently with approval of the dapivirine intravaginal ring in several countries in Eastern and Southern Africa. Indeed, the development of Multipurpose Prevention Technologies (MPTs) to prevent pregnancy, HIV, and/or other STIs is an opportunity for collaborative and innovative efforts among product developers, regulatory bodies, biomedical

researchers, behavioral and implementation scientists, and most importantly, end users. Although advancements in both contraception and HIV/STI prevention methods offer potential platforms for MPTs, significant barriers persist that impact their real-world effectiveness. In this commentary, current advances in MPTs are briefly summarized and challenges, gaps and further research directions are identified.

Biomedical gaps and development challenges for MPTs

Selection of drugs and dosage forms, co-formulation of multiple drugs, and product scale-up/manufacture

The pace of MPT development has trailed that of non-vaccine biomedical HIV prevention with biomedical gaps and development challenges that include a limited number of drug choices, concerns around drug potency and drug loads that impact long-acting formulations, the physiochemical compatibility of co-formulating multiple drugs, the potential for drug-drug interactions, and challenges around scale-up and manufacture of novel dosage forms (i.e., formulation delivery platforms). In fact, these challenges have impacted development of MPTs with activity against HIV or non-HIV STIs, in combination with contraception, since multiple drugs are required. As a result, there are fewer innovative dosage forms in late clinical testing (oral pills and vaginal gels) compared to more innovative dosage forms in early clinical testing (intravaginal rings and fast dissolving inserts) or preclinical development (vaginal films, implants, and microarray patches).

Approved drugs are typically used to expedite the drug development process and rapidly advance a formulation into early clinical testing. A majority of MPT products in development contain licensed or approved antiretroviral drugs (ARVs) for HIV in combination with licensed contraceptives (1, 2). However, there are MPTs in development for non-HIV STIs that contain antivirals specific for HSV (TFV, TAF, and acyclovir) or broad-spectrum agents (Yaso-Gel, VivaGel, and Q-Griffithsin) with activity against both bacterial (gonorrhea and chlamydia) and viral (HPV and HSV) pathogens (2). The two most advanced products in clinical testing are Dual Prevention Pills (DPPs): a daily oral capsule containing two pills, TDF/FTC pill + LNG/EE pill (3), and a daily bilayer oral tablet containing TDF/FTC and LNG/EE (4). Despite their potential for rapidly taking an MPT to market, these DPPs may not represent the ideal MPT given their large size and possible issues around adherence to a daily capsule or tablet.

Several novel MPT dosage forms in development have their own unique challenges. More potent drugs are often required for long-acting formulations (e.g., IVRs, implants, and patches) to ensure drug loads that will deliver sustained concentrations over longer periods of times (i.e., weeks to months or longer) with minimal delivery volumes (5). Most current drugs are not potent enough to ensure minimal volumes and sizes that are acceptable to end users. As a result, product developers are now using prodrug chemical modifications (e.g., drug-polymer conjugates) to modulate physiochemical and pharmacokinetic (PK) properties or novel drug delivery platforms (e.g., biodegradable hydrogel depots) as approaches to address drug potency and control extended drug release (5, 6). It remains to be determined whether these approaches will result in viable next generation MPTs that deliver multiple drugs over longer periods.

While diverse preferences have driven a range of contraceptive types, dissatisfaction with current contraceptives indicates that there is considerable room for new and improved products (7). There is a need for more discreet options with fewer sides effects, including non-hormonal options and long-acting formulations (7). There will likely be a more complex regulatory pathway for new drugs or alternative contraceptive technologies to be considered for MPTs when these are used in combination with other licensed drugs.

It can be difficult to combine multiple drugs into a single product formulation that can deliver stable, sustained release of each drug and maintain the PK/therapeutic targets over extended periods – particularly when drugs have different physiochemical properties. While *in vitro* systems and animal studies are often used to assess and evaluate prototype formulations, there are no universally accepted protocols for evaluating novel drug delivery platforms in *in vitro* release studies (8) or relevant animal models, particularly those that assess vaginal products (9). The potential for drug-drug interactions should not be underestimated – particularly when certain drugs are known to induce metabolizing enzymes that could result in increased hormone metabolism – thus possibly impacting contraceptive effectiveness (8). MPT developers will need to consider multiple approaches to address these challenges and generate preclinical data that is acceptable to regulatory authorities and informative for early clinical testing.

As product developers focus on more novel drug delivery platforms (next generation IVRs, implants, and microarray patches), there may be challenges around transfer and scale-up of these MPT products due to limitations in current manufacturing processes. Technological considerations should be considered early in the drug development pathway to ensure viable end products by identifying and overcoming potential downstream issues related to material choices, drug compatibility, drug loading, and controlled release parameters (8).

Unclear US regulatory pathway

The MPT community has benefitted from increased communication between funding bodies, multidisciplinary conversations between basic, clinical and socio-behavioral scientists, and increased collaborative engagement from the FDA to clarify regulatory requirements (10). Despite improvements, a clear path to FDA approval remains elusive and, in looking at the global landscape, many of the same challenges are likely to impact regulatory approval of MPTs outside the US. Young Holt et al. offer a primer for regulatory considerations amidst a strategic path forward for the field (11, 12), and Hemmerling et al. outline many of the unique regulatory hurdles faced by MPT developers (10).

Although the FDA has drafted new bioequivalence guidance, knowledge gaps remain, including whether bioequivalence will be a suitable surrogate for efficacy studies.

Ethical quandaries can arise when working with vulnerable populations and testing experimental contraceptives. For example, effective contraceptive use is often a requirement of HIV trials, yet cessation of contraception is needed to assess the contraceptive indication of a new combination product (13). Combining two unrelated indications into a single trial requires a design that may be prohibitively complicated. Thus, some developers may choose to seek approval for a single indication while gathering exploratory data and then repeat the approval process for an additional indication, but there are drawbacks to this approach (increased time and money).

Another gap lies between the discovery of new products and translating them into a clinical success. While an IND/IDE represents an early milestone in the product development journey, it is never too early to consider the target market, ideal product attributes, and engage experts in a regulatory strategy. The potential high profits of the US market are often the focus of product development yet, for MPTs, early efforts to include a strategy for introducing a product to the global market will be beneficial, including a consideration for applying to the WHO Prequalification of Medicines Programme (PQP)[1]. Increased collaboration is key for the success of MPTs, as they have the potential to benefit countless users worldwide.

Several briefs authored over a decade ago are still relevant today for MPT developers seeking regulatory perspectives. Romano et al. (14) propose scenarios based on FDA guidance that illustrate nonclinical testing needs, regulatory considerations, and routes toward approval. While the FDA has since issued clarifying documents for combination products (defined by 21 CFR 3.2e[2]), many principles discussed remain true, including the reminder that the journey for each pharmaceutical product will be different. Concrete answers to generalized questions on MPT guidance are likely unobtainable, so adaptability to a changing landscape is key. The road map at the outset will not be what is in the rearview mirror at the end. Brady and Park (15) provided a guide to key regulatory documents from FDA, EMA and ICH, which are still relevant even though guidance such as Principles of Premarket Pathways for Combination Products[3] (FDA) and Clinical Development of Fixed Combination Medicinal Products[4] (EMA) have been added.

Brady (16) noted that the uncertainty of the regulatory environment for MPTs disincentivizes investment and thus advancement, but the potential impact of these products is too important to forgo. From 2018 to 2022, biomedical research funding provided by the NIH eclipsed any other funder for HIV, HPV, and other STIs (17). During this same period, the NIH remained one of the top two funders for research on contraception and development of contraceptive-containing MPTs (17). However, even with this investment, the NIH alone is not equipped to usher products from discovery to market. With the vast array of products in the current pipeline (2) and the aforementioned underinvestment in this area, public-private partnerships and other funding sources are imperative for MPTs to succeed.

FDA decisions and guidance, such as primary mode of action (PMOA) for combination products, may be simplified if a product exists for comparison, but until then primary jurisdiction for premarket review and regulation of a combination product will be assigned based on an algorithm (21 CFR 3.4[5]) (18). Once several different MPTs are established, MPT advancement will be enabled by the path elucidated by these trailblazing products. Until then, the FDA urges developers to have conversations via request for designation (RFD) or pre-RFD avenues. In fact, a unifying theme for the information available about MPT regulatory matters and combination products is communication, including but not limited to requests for clarification and conversations to fill knowledge gaps with regulatory agencies as soon as possible during development and often thereafter. Hopefully, developers will continue to communicate lessons learned while navigating the regulatory environment (see: MPT Regulatory Pathways: Case Studies from MPT Product Developers[6]), so the long sought-after MPT regulatory road map can be created collectively.

Socio-behavioral gaps

Preferred MPT characteristics

Both women and men are highly interested in novel MPTs and indicate they would prefer a combined product over separate methods for the prevention of HIV, STIs, and/or pregnancy (19, 20, 21). The only MPTs currently available are male and female condoms, which protect against pregnancy, HIV, and other STIs. However, there are numerous barriers to condom use, including concerns over loss of pleasure, stigma, and concern that condoms signal a lack of trust in the relationship; additional barriers to use of the female condom include concerns about the size, lack of partner acceptance, and difficulty with insertion (22, 23, 24). Despite the ease of a single medication for both purposes, fertility desires and perception of HIV/STI risk may change over time, and users may no longer desire one of the MPT indications.

[1]https://www.who.int/news-room/fact-sheets/detail/prequalification-of-medicines-by-who

[2]https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=3.2

[3]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-premarket-pathways-combination-products

[4]https://www.ema.europa.eu/en/clinical-development-fixed-combination-medicinal-products-scientific-guideline

[5]https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-3/subpart-A/section-3.4

[6]https://theimpt.org/mpt-regulatory-pathways-case-studies-from-mpt-product-developers/

Research is needed to understand how preferences for MPT use change over time, and how switching from an MPT to a single indication product (and vice versa) can be supported.

Behavioral science research has begun to identify the preferred characteristics of an MPT, which can help guide MPT developers in the types of products in which they invest development resources. There are three main lines of research from which we have learned about product preferences: qualitative interviews, often conducted after participation in early stage MPT trials, discrete choice surveys (a survey in which participants are presented with a pair of products that differ in their attributes and asked to choose which product they prefer, across multiple product pairs), and placebo studies.

Qualitative studies have found that factors such as discreetness, reversibility, longer duration of protection, and community acceptance are important characteristics of MPTs (25, 26, 27, 28). A discrete choice survey of couples conducted in Uganda and Zimbabwe investigated couple preferences for an MPT, as well as how individual preferences for an MPT differ from couple preferences. This study found that the combination of product form and dosing frequency was most important; other important attributes included side effects, changes to the vaginal environment, and changes in menstrual bleeding, although the importance of those attributes differed by country (19). For the majority of couples, either both members had similar individual preferences or, where individual preferences differed, there was equal decision-making around MPT preferences during a joint couple DCE (29). The TRIO study randomized women to a placebo MPT delivery form (injection, tablet, and ring) for one month for each form, and then allowed participants to choose one of these products for an additional two months. During the choice period, the majority chose injection, with no difference in the percentage choosing tablet and ring (30). In addition, mean ratings for how much one liked using the product increased after use (31).

While these findings may help product developers better understand end-user preferences, there are still several socio-behavioral research gaps that may help inform the path forward for MPT development. First, partners have been infrequently included in MPT preference research. Although for some users MPT choice may be an independent decision, with a preference for products that can be used discreetly without partner knowledge, for other users MPT use and preferences may be decided on as a couple. Understanding which users make decisions about MPTs on their own vs. as a couple, and how these decisions are jointly made, is an important research gap. Second, although there are data on MPT preferences, additional research is needed to better understand whether preferences differ over time and across subgroups of women. For example, preferences may differ across adolescents vs. older women of reproductive age, women in long-term relationships vs. those not in a relationship, during breastfeeding, or those in rural vs. urban areas, where easy access to a health facility and product storage may be important considerations. Developmental, social, and cultural considerations may also influence product preferences and should be addressed, particularly given concerns around community acceptability (26) and differing preference findings by country (19, 30). Another aspect of MPT preference not well studied is how potential differential rates of effectiveness for HIV/STI prevention and contraception may impact product preferences. Providers are another type of MPT end user, and their preferences in prescribing MPTs over separate methods is not well-studied.

Research could also benefit from better integration of end user preferences as products are being developed. This integration of behavioral research alongside product development may be beneficial because it: (a) may help product developers better target resources towards developing products that people want and will ultimately use and persist on; and (b) allows for easier product modifications, as even minor changes to a product can be expensive and difficult to make once a product has received regulatory approval. Where possible, it may be important to allow user testing of prototypes, as perceptions of a product may change once a product is actually used (31). For example, the USAID-funded MATRIX project is using an innovative "Design to Delivery (D2D)[7]" approach to integrate end user and key influencer feedback into early stages of product development in an iterative way to inform product-related decisions.

Uptake, adherence, and persistence on MPTs

Even if an MPT is highly acceptable and includes preferred product attributes, it will be important to study whether there is indeed improved uptake, adherence and persistence over that for separate products (32). MPT adherence, the extent to which the product is used as intended, encompasses an understanding of timing of MPT use, dosage, consistency and duration of use (33). Another factor impacting adherence may be the level of discreteness or confidentiality an MPT affords over separate methods. Further, an MPT that includes a contraceptive purpose may help to reduce stigma associated with products that prevent only HIV/STIs, potentially additionally improving product uptake and adherence relative to HIV/STI prevention products. Interventions and/or tools to address adherence facilitators and barriers will also need to be built into research studies to optimize the effectiveness of MPTs. Such approaches could also be coupled with qualitative research to understand what product characteristics women, couples and providers like and dislike over time, as well as how to best discuss changing needs, to be informative for future generations of MPT product development.

Implementation science gaps

MPT implementation

Once an MPT has been developed and found to be effective, implementation science can help clinicians, program managers, and policy makers best understand how to implement the MPT

[7]https://www.matrix4prevention.org/activity-hubs/design-delivery-d2d

to maximize product delivery and use. First, researchers can identify how to best help patients make informed choices about whether an MPT fits with their values, goals, and lifestyles, for example, through the development of shared decision-making tools (34) that can be used to guide patient-provider discussions. Once multiple MPTs are available, these shared decision-making tools can be expanded to help patients decide which, if any, MPT is the best option for them.

A key area for implementation science research will be to identify barriers and facilitators to implementation of an MPT and to develop implementation strategies that are feasible and effective. Identification of barriers and facilitators to implementation can be investigated through qualitative interviews or focus groups with end-users, including patients, providers, and policy makers. Some of this work can begin even without an available MPT; for example, interviews around barriers and facilitators can be conducted during clinical effectiveness trials. One major challenge for implementation will be to identify the best setting(s) in which to deliver MPTs, particularly for MPTs that address both pregnancy and STI/HIV prevention, as family planning providers may not be comfortable prescribing HIV prevention, and STI/HIV providers may not be comfortable prescribing contraception. Research is needed to understand barriers to product switching and product distribution in different settings; for example, STI/HIV providers may be willing to prescribe an MPT but may not be comfortable prescribing contraception only if someone wants to switch to a single use contraceptive product. Implementation science can help to understand the barriers to MPT delivery, can devise and test strategies to overcome these barriers, and can work with patients and providers to understand their preferences for MPT delivery settings, to ultimately inform the delivery of MPTs when available. Timely implementation research is important in the early stages of product roll out, to inform subsequent larger scale-up.

Discussion

MPTs hold strong promise for preventing HIV, other STIs, and pregnancy. However, several research gaps must be addressed to ensure MPTs can realize this potential. The development of combination products for multiple therapeutic indications has trailed behind other products as researchers grapple with co-formulating multiple drugs into innovative dosage forms while addressing potential drug-drug interactions and manufacturing challenges. Yet, the potential public health impact of overcoming these issues with innovative solutions is immense. Because blanket regulatory guidance does not exist, researchers and developers could consider the following steps: communicate with regulatory bodies, read regulatory guidance, think globally, consider the entire development pathway as early as possible, seek partners and collaborators, prepare for change, know the market, and communicate with the field. End-users have indicated a strong preference for prevention technologies with multiple indications. However, additional research on end-user preferences integrated into early product development is needed, including research focused on individuals, partners, and providers. Research is needed to understand MPT uptake, adherence, and persistence, as well as social factors that may impact these outcomes. Finally, implementation research is needed to understand barriers to implementation and to test strategies to overcome those barriers.

Author contributions

JEC and TES contributed to conception and design of the article. JEC, CLA, SL, and TES conducted literature review, wrote manuscript, and edited manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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How might we motivate uptake of the Dual Prevention Pill? Findings from human-centered design research with potential end users, male partners, and healthcare providers

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Introduction: Multipurpose prevention technologies (MPTs) combining contraception with HIV prevention offer a promising solution to uptake and adherence challenges faced with oral pre-exposure prophylaxis (PrEP). The Dual Prevention Pill (DPP), which combines oral PrEP with an oral contraceptive pill (OCP), could address unmet need for family planning (FP) and HIV prevention. This study aimed to identify barriers and motivators for DPP uptake to inform the development of a DPP demand generation strategy and broader introduction efforts for MPTs.

Materials and methods: Qualitative, ethnographic research employing human-centered design techniques was conducted in Kenya, South Africa, and Zimbabwe. A research consortium conducted 45 immersions, 34 key informant interviews, and 12 friendship circles with potential end users, male romantic partners, healthcare providers (HCPs), and cultural commentators. Creative concepts were subsequently co-created and validated in workshops with end users, male partners, and HCPs.

Results: Four major themes emerged. Women struggled to balance personal motivations with societal expectations. Relationship goals strongly influenced sexual and reproductive health decisions, particularly related to financial security and social status. Negative experiences, such as untrustworthy partners, were significant triggers for OCP and PrEP use. Lastly, male partners were concerned about the DPP upending gender norms but held more positive individual attitudes. Five initial audience segments for the DPP were identified: women seeking enjoyment outside of their primary relationship; new mothers adhering to social norms; women wanting to maintain romantic relationships; women at risk of unintended pregnancy; and women with unfaithful partners. Segments informed the development of three communication themes, with the preferred route highlighting the DPP as a tool to prepare for life's unpredictability.

Discussion: To effectively generate demand for the DPP, several strategies should be considered. Connecting with women's diverse identities and goals and celebrating their individuality is crucial. Linking the DPP to relationship goals reframes it as a means to protect relationships rather than a risk. Leveraging negative triggers through targeted media campaigns empowers women to take control of their sexual health during challenging moments. A balance in channel placement is necessary to raise public awareness while using more discrete channels for potentially controversial messages with male partners and wider communities.

KEYWORDS

pre-exposure prophylaxis, oral contraception, HIV prevention, family planning, multi-purpose prevention technologies, end users, human-centered design, demand generation

1. Introduction

HIV and unintended pregnancies continue to pose significant challenges for women of reproductive age, particularly in sub-Saharan Africa, with a notable unmet need for effective prevention options. In 2021, women and girls accounted for 63% of all new HIV infections, with 82% of these infections occurring among adolescent girls and young women (AGYW) aged 15–24 (1). Furthermore, there is a persistent challenge of unmet need for family planning among women of reproductive age in sub-Saharan Africa, with an estimated 24.2% of married or in-union women having an unmet need for modern contraception (2). Among AGYW globally, younger AGYW (15–19 years old) exhibit higher levels of unmet need compared to older AGYW (20–24 years old) (3).

Over the past decade, several biomedical HIV prevention modalities have become available, including tenofovir-based oral pre-exposure prophylaxis (PrEP), the dapivirine vaginal ring (PrEP ring), and injectable cabotegravir (CAB for PrEP). Studies such as the TRIO (Tablets, Ring, Injections as Options) study in Kenya and South Africa and the CUPID study in Uganda and Zimbabwe have found that participants would prefer a combined product for HIV and pregnancy prevention over separate products (4, 5). Discrete choice experiments have also shown higher demand for multipurpose prevention technologies (MPTs) among women interested in HIV prevention compared to single-indication products (6).

MPTs that combine contraception and HIV prevention have the potential to address the challenges of uptake, adherence, and societal stigma seen with oral PrEP (7, 8). The Dual Prevention Pill (DPP), which combines oral PrEP and an oral contraceptive pill (OCP) in a single, co-formulated, daily pill, is the MPT closest to market. The first-generation DPP will have a 28-day regimen with 21 combination PrEP/OCP tablets and 7 PrEP-only tablets, which maintain protection against HIV while allowing for monthly bleeding (**Figure 1**). The DPP, as the first MPT containing PrEP, could help address the unmet need for family planning and increase oral PrEP use, thereby reducing the risk of HIV infection (9). Moreover, the development and rollout of the DPP will lay the groundwork for future MPT options in the research pipeline (10). As the number of biomedical PrEP modalities increases, it is critical to understand the individual-level drivers and barriers to PrEP uptake, as well as the factors influencing decision-making in this context (11). Lessons from past demand generation efforts for HIV prevention and family planning have shown that increasing awareness and understanding of new product options alone is not sufficient to drive uptake and sustained use. Additional strategies are required to address barriers and shape attitudes towards prevention. Demand creation for PrEP should recognize the individual, interpersonal, sociocultural, and structural factors that contribute to decision-making on sexual health, and be grounded in a socio-ecological model that considers end users and their relationships to people, organizations, and their community (12). Lessons from oral PrEP rollout highlight the need to create appealing and easy-to-use products tailored to people's stated concerns and desires and to build a supportive environment in which users can make decisions (13). Engaging key influencers, such as male partners, families, peers, community, and healthcare providers (HCPs), is critical to promoting HIV prevention products for women and girls (14). Finally, empowering communities through participatory approaches and involving them in the design and implementation of demand generation strategies can improve acceptability and uptake of sexual and reproductive health (SRH) products and services (15). A successful demand generation strategy for the DPP will employ a layered approach to increase general awareness, mobilize communities, and provide support to clients and HCPs at the point of care. Employing successful approaches that include research, audience segementation, and human-centered design (HCD) can ensure that demand generation for the DPP is

FIGURE 1
First-generation DPP tablets.

evidence-based, contextually relevant, and responsive to the diverse needs of the target population.

2. Materials and methods

2.1. Primary research

2.1.1. Research design

AVAC and M&C Saatchi World Services led a consortium to undertake qualitative HCD research in Kenya, South Africa, and Zimbabwe from April to July 2022 to uncover potential barriers and motivators to uptake of the DPP. To inform the design of primary research, the study team first conducted a desk review of available literature to surface findings and evidence gaps. The desk review included 25 articles of 750 screened, a quantitative re-analysis of DHS datasets, and an analysis of social media conversations on key terms including birth control, contraceptives, and relationships in the three key markets using Brandwatch (16), to understand the following questions:

1. What are the values, day-to-day lives, and lifestyles of end users, and how might these be leveraged to encourage uptake of the DPP?
2. What are the opportunities and occasions in end users' lives where the DPP brand can drive relevance?
3. Where are end users having conversations about SRH and which channels will penetrate in these locations?
4. What is the end user's network of influence and how does this network influence decisions around sex, relationships, and SRH?
5. Which products do current OCP and oral PrEP users access, purchase, or use alongside OCP and/or oral PrEP, and what opportunities could these afford for DPP marketing?

Subsequently, the primary research aimed to fill gaps and deepen the field's understanding of the key learning questions. Participants were recruited using convenience sampling based on target audience profiles, leveraging venues in selected localities where these audiences were likely to convene within the context of study parameters (e.g., healthcare facilities, community centers). The recruitment sample included women aged 20–40 who were current OCP users, current oral PrEP users, and non-users of OCP, oral PrEP, and long-acting reversible contraceptives (LARCs). Men recruited were all in a current relationship with a woman and reflected a mix of attitudes toward the acceptability of PrEP and contraceptive use by female partners. HCPs recruited were currently providing contraception and/or HIV prevention services and represented a cross-section of cadres, including doctors, nurses, pharmacists, and providers working for non-governmental organizations (NGOs). Cultural commentators were selected for their ability to provide insights on trends, nuances, and idiosyncrasies that define how sex, relationships, and SRH are conceptualized and discussed in their local cultural contexts.

One urban and one rural location was selected in each country. Regions and provinces were shortlisted based on where the Total Addressable Market for Contraception (TAMC) for women ages 15–49 constituted a relatively large proportion of the population, and had a relatively high HIV prevalence rate for women ages 15–49 (17). These locations were reviewed by the study team to identify preferred regions and provinces, after which local field research teams recommended specific districts to conduct the research based on whether the area was a DREAMS district (PEPFAR-funded public-private partnership aimed at reducing rates of HIV among AGYW in the highest HIV burden countries) and other logistical factors.

Research was guided by an ethnographic approach to build trust and understanding between researchers and participants through repeat engagements in the field and the pursuit of a holistic understanding of participants within their cultural contexts. Because implicit motivational drivers of decision-making are not always conscious (18), a research approach that aimed to draw out responses deeper than surface level was preferred. The ethnographic process was conducted in two 3–4-hour long sessions with each participant, which provided participants space to reflect on their responses without the time pressures often associated with a single-session research process. Because research participants often struggle to have open conversations about sex, relationships, and SRH, owing to the oftentimes sensitive and private nature of these subjects, within each session, researchers employed a variety of HCD exercises designed to facilitate these discussions and ensure that all insights were grounded in an empathetic understanding of the lived realities of participants. Institutional Review Board (IRB) approval was obtained in Kenya, South Africa, and Zimbabwe. The ethnographic participant then became the lead participant in the friendship circles, comprising friends with whom the lead participant was comfortable engaging on SRH conversations. This provided an additional layer of emotional and psychological comfort during the potentially sensitive conversation.

2.1.2. Data collection

A total of 45 ethnographic immersions, 34 key informant interviews (KIIs), and 12 friendship circles were conducted across the three countries (**Table 1**). In each country, ethnographic immersions were conducted with 13 potential end users and two male romantic partners; intimate group discussions were held with two male and two female friendship circles; and KIIs were conducted with eight HCPs. In addition, KIIs were conducted with three cultural commentators in Kenya and South Africa, respectively, and four in Zimbabwe.

Fieldwork was conducted by 1–2 lead ethnographers in each country. Three HCD research tools were employed:

- **Social network mapping** was used to investigate who male and female immersion participants would seek advice from (and who they would avoid) in different scenarios, in order to understand who influences them and their level of trust in different people in their networks. Participants were invited to arrange cards representing different people in their social network on a map of concentric circles. Proximity to the center of the map correlated with how trusted that person was

TABLE 1 Primary research sample and methods per country.

Research method		Immersion (2× sessions per participant)				Friendship circle (Participant + friends)		Key informant interview	
Country	District	Current OCP users	Current PrEP users	Non-users of OCP/PrEP	Male romantic partners	Female circle	Male circle	HCPs	Cultural commentators
Kenya	Nairobi (Urban)	3	2	2	1	1	1	4	3
	Areas around Kisumu (Rural)	3	2	1	1	1	1	4	
South Africa	Johannesburg (Urban)	3	2	2	1	1	1	4	3
	Districts in KwaZulu-Natal (Rural)	3	2	1	1	1	1	4	
Zimbabwe	Harare (Urban)	3	2	2	1	1	1	4	4
	Areas around Bubi (Rural)	3	2	1	1	1	1	4	
Total participants		18	12	9	6	6	6	24	10

in a given scenario: the closer to the center, the more trusted and likely that the participant would be to seek advice from them.

- **Journey mapping** was used to understand how participants came to use oral PrEP and/or OCP and their experiences using the product. The exercise explored triggers that led participants to consider and ultimately decide to use the product; experiences at different points on their journey; sources of information (people, HCPs, and media) used throughout their journey; and the places visited at different points in their journey. Participants were provided with a journey template and a set of prompt cards to populate the template. These prompt cards required the researcher (or the participant, depending on literacy level) to write descriptions on the cards of what happened and how they felt at each stage of the journey and arrange them in a visual representation on the map.
- **Mini-Me** was used to explore the personal values and relationship goals of male and female participants. Participants were provided with a template on which to draw and annotate themselves (their 'mini-me') and their partner. Researchers asked questions to encourage participants to capture their personal values, aspirations, roles, and responsibilities, as well as the values and roles they wished for their ideal partner.

All ethnographic sessions were recorded with digital audio recorders and transcribed into English where relevant, with appropriate permissions. Photographs were taken to capture visual data relevant to the research with permission from participants, including the final outputs from each HCD exercise. In addition, local researchers kept field notes that recorded their key findings and insights. KIIs were conducted in English using semi-structured discussion guides designed for HCPs and cultural commentators, respectively.

2.1.3. Data analysis

To maximize opportunities for the analysis process and benefit from the expertise and experience of field researchers, a series of data download sessions were convened. These sessions, led by the lead researcher, were attended by field researchers in each country and members of the study team. Three download sessions were conducted per country: one following initial pilot immersions, one mid-way through fieldwork, and one once all fieldwork was completed. During each session, field researchers provided an overview of the key findings emerging from the research. These findings were interrogated in an open discussion to identify implications for the rollout of the DPP, as well as considerations and recommendations for demand generation and marketing strategies. Each session lasted 2–3 hours; and was conducted via Zoom. Where permission was granted, photos were shared with the study team for further analysis.

Field researchers documented the final outputs from each HCD exercise through photographs. Responses to the Social Network Mapping exercises were transcribed to identify patterns in positioning of different influencers based on each scenario. HCD journeys were sorted based on their trigger points, and common themes were analyzed from the results. Values expressed in the Mini-Me responses were manually coded and analyzed.

2.1.4. Development of user personas and journeys

Based on the primary research findings, a total of five user journeys and personas were created. The study team initiated a rapid analysis of the values and aspirations of male and female immersion participants to gain insights into their key motivators and values. This analysis aimed to explore how these factors intersected with their SRH goals. The data utilized for this analysis included information derived from the 'Mini-Me' exercises and conversations with participants regarding their personal values.

Subsequently, the study team examined the barriers to the uptake and sustained use of SRH products that were reported at different stages of the research process. These barriers were identified through a combination of methods, including a desk review, discussions with male and female participants, HCPs, and cultural commentators, as well as social network mapping and user journey exercises.

To categorize the user journeys effectively, trigger moments for product entry were considered (Table 2). Additionally, a user journey matrix was developed to ensure that the final set of journeys encompassed the diverse data collected across nine dimensions (Table 3). Finally, each user journey was associated with a persona. The personas were created to highlight the most

TABLE 2 User journey sorting.

PERSONA		VICKY (New mother - planned pregnancy)	THANDIWE (New mother - unintended pregnancy)	FAITH (Untrustworthy partner)	LINDIWE (Maintaining relationship)	ELSIE (Seeking enjoyment outside of relationship)
Total ($n = 28$)		7	2	12	4	3
Product	OCP ($n = 15$)	7	2	1	3	2
	Oral PrEP ($n = 13$)	0	0	11	1	1
Country	KE ($n = 10$)	2	1	4	1	2
	SA ($n = 9$)	1	1	3	3	1
	ZIM ($n = 9$)	4	0	5	0	0
Location	Urban ($n = 13$)	3	1	5	3	1
	Rural ($n = 15$)	4	1	7	1	2

TABLE 3 User journey matrix.

Matrix dimension	PERSONAS				
	Vicky	Thandiwe	Faith	Lindiwe	Elsie
Trigger category	New mother - planned pregnancy	New mother - unintended pregnancy	Untrustworthy partner	Maintaining relationship	Seeking enjoyment outside of relationship
Product used	OCP	OCP	PrEP	PrEP	PrEP + OCP
Awareness of options at trigger moment	High	Low	Low	Low	High for OCP, low for PrEP
Primary influence on preferred product	Partner, HCP	Older female relatives	HCP	Sister, HCP	Close friend
Online research conducted?	Yes - to form initial preferences	No	No	Yes - to check what partner's medication is for	Yes - to look up how to manage side effects
Partner aware of product usage?	Actively consulted	No	No	Informed but not consulted	No
Side effects experience	Severe	Low	Moderate	No	No
Product switch?	Yes	Yes	No	No	No
Other factors	Obtain OCP from source other than clinic		Husband disapproves of condoms	Believes condoms reduce pleasure	

prevalent entry points, drivers, and barriers within specific categories. These personas provide valuable insights that can be leveraged in demand generation communications.

2.2. Co-creation and validation

Based on insights obtained from the desk review and primary research, the study team took three creative routes for DPP demand generation into the field beginning in September 2022, with the aim of refining and contextualizing the creative routes for localized appeal and relevance. In Kenya, South Africa, and Zimbabwe, respectively, seven co-creation workshops were conducted with current OCP/PrEP end users (×2), end users with an unmet need for HIV prevention/family planning (×2), male romantic partners (×2), and HCPs (×1). In each market, four workshops were held in urban locations and three workshops were held in rural locations (Table 4).

During the co-creation workshops, the three creative approaches were tested using visual identities that would be incorporated into various communication materials. Elements tested included campaign taglines and creative concepts (messaging and imagery) adaptable to different audiences. The results from the co-creation workshops helped narrow down the focus to a single creative approach for the DPP.

Following the co-creation fieldwork, revised creative stimulus was developed for the selected route, building out a range of scenarios, positioning, imagery, and messaging. The subsequent validation workshops comprised four sessions in each market: two sessions with end users (current OCP/PrEP users and non-OCP/PrEP users) in one urban and one rural location; one session with male romantic partners in an urban location; and one session with HCPs in an urban location (Table 5). This validation phase was convened to assess the likeability, relevance, persuasion, acceptance, believability, comprehension, and attractiveness of the stimuli. Workshop participants first completed individual questionnaires on stimulus preferences, then participated in a collective group discussion. HCPs had shorter sessions due to fewer executions but were prompted to discuss potential tools for increasing clients' adherence to a daily pill. The study team then refined the stimulus based on findings from validation workshops.

3. Results

3.1. Primary research findings

Across audiences, four major insights emerged, which have significant implications for the DPP demand generation strategy.

TABLE 4 Co-creation workshops recruitment sample.

Country	District	Current OCP/ PrEP users	Users with unmet FP and/or HIV prevention need	Male romantic partners	HCPs
Kenya	Nairobi (Urban)	4	4	4	8
	Kisumu (Rural)	4	4	4	0
Kenya total		8	8	8	8
South Africa	Johannesburg (Urban)	4	4	4	8
	KwaZulu-Natal (Rural)	4	4	4	0
South Africa total		8	8	8	8
Zimbabwe	Harare (Urban)	4	4	4	8
	Bubi (Rural)	4	4	4	0
Zimbabwe total		8	8	8	8
Total participants		24	24	24	24

TABLE 5 Validation workshops recruitment sample.

Country	District	Current OCP/PrEP users and users with unmet FP and/or HIV prevention need	Male romantic partners	HCPs
Kenya	Nairobi (Urban)	8	8	8
	Kisumu (Rural)	8	0	0
Kenya total		16	8	8
South Africa	Johannesburg (Urban)	8	8	8
	KwaZulu-Natal (Rural)	8	0	0
South Africa total		16	8	8
Zimbabwe	Harare (Urban)	8	8	8
	Bubi (Rural)	8	0	0
Zimbabwe total		16	8	8
Total participants		48	24	24

- When considering the hypothetical use of the DPP, women often find themselves grappling with different aspects of their identity and conflicting values. (Women were not offered the DPP to use as part of this research.) Societal stigma related to both PrEP and OCP meant that the DPP was frequently perceived as in conflict with societal expectations, limiting potential uptake even when the DPP was seen to support personal motivations.
- Relationship goals exert a stronger influence on SRH decisions than health risks, particularly when they are linked to financial security and social status. Women prioritize maintaining stable, secure, and loving relationships with their partners and upholding family values.
- Male romantic partners feel the DPP could threaten traditional gender norms, but hold more positive individual attitudes. While the prevailing view was that men would not be in favor of their own partners using the DPP, male romantic partners expressed generally supportive attitudes towards the DPP, saying that it was an innovation that could help address endemic issues of unintended pregnancy and HIV in their countries and communities.
- Triggers for OCP and PrEP use for women were largely negative. Instances of partner infidelity, discovery of a partner's secret HIV status, and other forms of untrustworthiness were significant factors motivating women to start using PrEP or OCP, and they strongly identified with the need to tackle risks beyond their control.

3.1.1. Women navigate a plurality of values and identities

Research found that male and female participants were driven by complex, diverse, and sometimes opposing sets of self-focused and community-focused values. Female participants, in particular, made decisions about SRH considering multiple values simultaneously, carefully weighing the benefits and risks of various SRH options in relation to their diverse goals.

Self-focused values revolve around personal development, achievements, pleasure, excitement, wealth, and prestige of the self. The most commonly expressed self-focused values by participants were (1) *empowerment values*, characterized by the pursuit of professional success and accompanying financial security, and (2) *enjoyment values*, encompassed by sexual pleasure, new experiences, and indulgence in "the finer things" in life. Female participants who highly valued empowerment were more likely to adopt prevention products like the DPP, seeing them as a means to protect their goals from being disrupted by HIV or unintended pregnancy. Younger participants were motivated by career and educational goals, while male participants tended to prioritize pleasure and enjoyment in their personal values and daily practices.

Across all three countries, both men and women emphasized the desire to comply with societal expectations through two community-focused values. (1) *Religious and traditional values* were especially important for Kenyan and Zimbabwean female participants, who underscored the importance of women dressing respectably and modestly, as well as rural male and female participants, who highly valued being prayerful, devout, and humble. Demonstrating (2) *social status and respectability* was important for women, who wanted to be seen as accomplished, well-groomed, fashionable, monogamous, married with children, and having a happy, successful husband. In all three countries, research participants commonly associated marriage with social status and viewed it as a marker of success for women. The performance of respectability led women to conceal their usage of SRH products out of fear of stigma from the community, and only discussed SRH with extremely close confidants. Given the importance of discretion to their public image, women often reported a preference for SRH products that could be used covertly, and viewed the DPP as offering a solution to social risks associated with condoms and oral PrEP.

Women reported performing a plurality of identities depending on the social context, such as presenting themselves as more

respectable with family and in-laws, while adopting a more outgoing, pleasure-seeking identity among close friends. Female participants in South Africa exhibited greater evidence of enjoyment values, including sexual pleasure, and ascribed greater value to the social status associated with being in a successful relationship. In Kenya, the desire for social respectability was linked to the fear of moral sanctions, and women sought "empowerment in secret," such as achieving equality in sexual relations. This was specifically linked to the awareness that a high proportion of male partners were unfaithful, and a desire to "get even" and find their own enjoyment outside of marriage or their primary relationship. In Zimbabwe, adherence to religious and traditional values took precedence for participants. Whereas male participants generally split their time between work and relaxation, female participants' daily lives consisted predominantly of either working for income or taking care of domestic and family duties, with less opportunity for indulging in leisure activities.

3.1.2. Preserving romantic relationships is central to decision-making on SRH

The research found that women often depend on their relationships with male partners to fulfill various values that are important to them, particularly (1) *relationship goals*, which emphasize maintaining a stable, secure, and loving romantic relationship, and (2) *family values*, typified by family security, caring for children, and upholding a positive self-image and relationship with siblings and parents. As a result, women may be disinclined to discuss SRH issues with their partners or engage in practices that may upset them, fearing the potential loss of the benefits provided by the relationship. Female participants described their ideal partner as someone who serves as their personal protector, financial provider, and someone who will give them access to luxuries in life. These descriptions depict how women often depend on male partners to meet their basic security needs, and their desires for wealth and enjoyment. At times, participants and field researchers also highlighted the transactional nature of romantic relationships.

Participants tended to weigh "short-term" risks more heavily than "long-term" risks, for instance, prioritizing a threat to their relationship due to its perceived immediacy over health risks that are seen as longer-term and easier to discount. Preferences for SRH products were often based on which posed the least risks to their relationships. Some female participants reported agreeing to not use a condom because their male partner did not want to, even when the female participant knew the implications of this decision. Women reported keeping usage of PrEP and OCP secret from a partner or family member, some using a product only when required in order to avoid chances of detection. Decisions on SRH product use carried implications about fidelity, with one female participant in Kenya noting: "*According to him, condoms should be used by those who do not trust each other and those that go outside [of the relationship]*."

The practice of concealing SRH product use from male partners was observed among female OCP and PrEP users, and was especially widespread among PrEP users. Women commonly stored SRH products alongside beauty products and medicines in their homes, and decanted pills into a container of their own choosing, rather than leave them in the original packaging. They felt strongly that the DPP should be designed, packaged, and branded to resemble a contraceptive or a beauty product to minimize associations with oral PrEP and make it easier to conceal from male partners who are not supportive of use. HCPs, noting similar concerns from clients, saw potential for the DPP to alleviate the social and relationship pressures that limit women from taking PrEP as a standalone product; for example, by enabling clients to obtain the DPP at a family planning clinic. One HCP from Kenya stated, "…*if they are taking one pill at the same time, for those who feel they want to hide because they are taking PrEP, it will be easier because they only have one pill to take and so 'no one should know what I am taking.*'" The DPP was thus widely perceived as a means for women to obtain HIV protection that posed less risk to their existing romantic relationship and their public image in the community and society at large.

3.1.3. Male partners felt the DPP could threaten gender norms, but held more positive individual attitudes

Male partners hold significant influence over SRH decisions and expressed concern that the DPP could threaten gender norms, particularly in rural locations. The majority of male participants said they would not support their own partners to use the DPP. By removing the risk that a woman may become pregnant or acquire HIV, some argued the DPP could enable women to "act like men" and be sexually adventurous with minimal risk of consequences. This in turn was expected to fuel fear and paranoia among men that their female partners might be using the DPP to be unfaithful to them.

Some male romantic partners saw a societal benefit in the DPP, viewing it as an innovation that could help address endemic issues of unintended pregnancy and HIV in their countries and communities. In a number of cases, male partner support for the DPP was caveated with a desire to be involved in DPP rollout, particularly in Kisumu, Kenya. The research indicated that male participants who were younger, urban, highly educated and had a higher socio-economic background would be most likely to support their female partners to use SRH products such as the DPP. Male participants belonging to higher socio-economic backgrounds expressed more progressive views around ensuring their female partner's independence. Urban male participants placed less emphasis on traditional and religious values in their relationships and held more positive individual attitudes towards the DPP. In Zimbabwe, male participants put the most emphasis on presenting as a leader and contributor within their communities. Evidence of positive deviancy highlights an opportunity for the DPP to identify and promote the minority of men who do support DPP uptake and adherence as role models for driving social change and acceptance of the DPP within their communities.

3.1.4. Negative triggers motivate product uptake

Most trigger moments for OCP and oral PrEP uptake were associated with negative emotions, and as such, women strongly identified with the type of person who is prepared to take on risks that are often outside their control. In particular, initiation of oral PrEP was motivated by experiences of untrustworthiness in their male romantic partners, with one Kenyan participant affirming, "*I felt that since he started cheating, I have to protect myself.*" Out of the 13 female oral PrEP users consulted for this research, 11 began using oral PrEP after suspecting or discovering that their partners were unfaithful, and one user initiated oral PrEP upon learning that her partner had kept their positive HIV status secret during their relationship.

In Kenya, partner infidelity prompted some women to start their own affairs as a form of retaliation ("tit for tat"), while in South Africa, some participants cited broader incidences of untrustworthiness, such as male partners cheating on HIV tests or spending their money on extramarital affairs. In Zimbabwe, some oral PrEP/OCP users perceived their relationships to be high-risk. More positive triggers to product entry that participants mentioned included delaying children, for example due to financial burden or focusing on their current child.

3.1.5. DPP user journey and personas

The research gathered strong evidence from female participants, HCPs, and cultural commentators indicating that women develop preconceptions and preferences for oral PrEP and OCP well before actually using the products (Figure 2). Female participants described forming a preference based on observing what close family members or friends were using, or because of what they had learned in school. Along the user journey, beliefs were entrenched by peer preference and online information (including social media), which also served as the main source of myths, stigma, and misinformation. Consequently, there was no evidence that female participants changed their minds about a particular product preference if it had been formed before the trigger moment, nor in response to a recommendation by an HCP prior to the moment of initiation. Instead, preferences for a given product tended only to change after the original trigger moment of uptake, such as in response to side effects, and HCPs played a more critical role in supporting adherence.

User journeys demonstrated a general upward trend in the emotional states of the female participants, especially after they had the opportunity to experiment with a product and concluded that it would be suitable for their needs. This decision was often made after side effects had subsided, signaling that the participant had found a product that would be feasibly used in the long term. One participant in Zimbabwe described, "*I started feeling comfortable after using PrEP for a year with me using it and going to get tested over and over again. That is when I concluded that my pills were working.*"

These findings demonstrate the need to build DPP awareness and relevance among women prior to trigger moments. Potential triggers for DPP uptake informed the development of five initial DPP audience segments and their barriers and motivations (Figure 3).

Women **seeking enjoyment outside of their primary relationship** demonstrate the highest potential for DPP uptake, prioritizing self-focused values such as enjoyment or career goals. Triggers to PrEP/OCP initiation in this segment are often centered on discovering their male partner was having an extramarital affair and subsequently engaging in their own affair with another man. This persona is concerned about maintaining her reputation as a respectable woman and goes to great lengths to keep her extramarital relationship a secret.

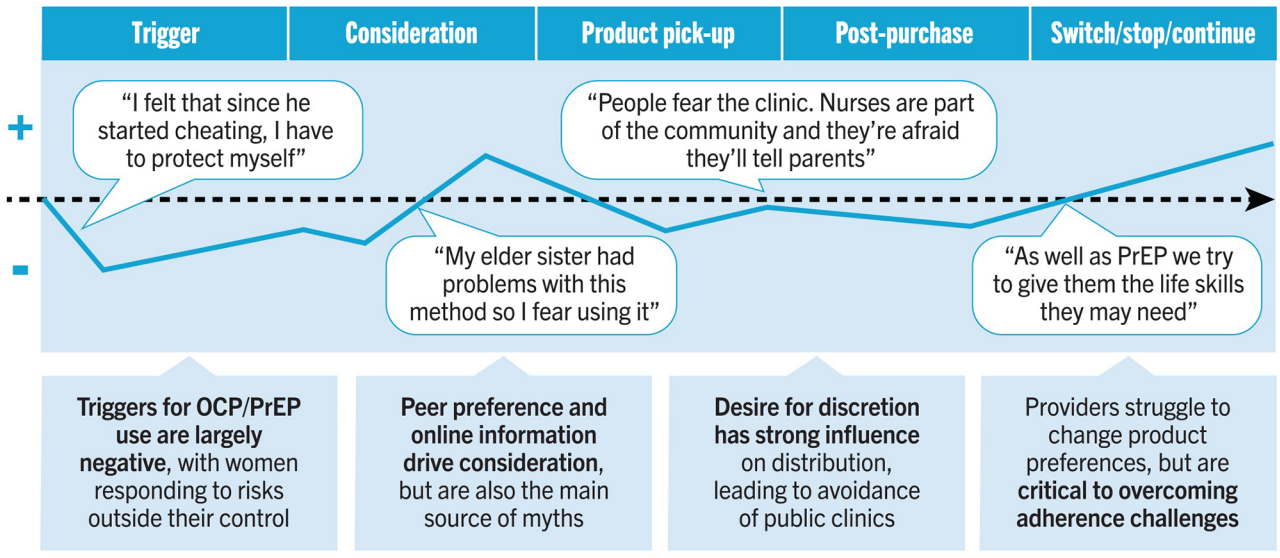


FIGURE 2
Potential DPP user journey.

DPP Persona	Description	Trigger Moment	Key Drivers to Uptake	Key Barriers to Uptake
 Elsie	Is **seeking enjoyment outside of her primary relationship** and prioritizes individual values such as enjoyment or career goals.	Discovered male partner having extramarital affair, then began her own affair to get even.	Pursuit of pleasure, stress relief, and companionship; desire to find empowerment in secret; business ambitions; knowing her partner is unfaithful; financial benefits from her own extramarital affair.	Pressure to hide PrEP use and her affair; concerns about keeping up the appearance of respectability and a stable relationship; fear of stigma and being labeled promiscuous.
 Vicky	**New mother** who is motivated to use SRH products to perform this role, in a way that adheres to the social norms of motherhood.	After giving birth to her first child, wants to space births of subsequent children.	Prospect of financial security and a positive future for her child; maintaining her marriage; public conformity to social norms around marriage and motherhood.	Low self-perception of HIV risk; pressure from partner to not use prevention; need to conceal her SRH product use; fear of side effects, particularly on mood swings, libido, and future fertility.
 Lindiwe	Wants to **maintain her romantic relationship**, in which she often has limited decision-making power and has to rely on her male partner.	Discovered partner was secretly living with HIV; does not want to lose security and social status that comes with a partner.	Protection from HIV acquisition; preservation of romantic relationship; conformity with societal expectations; enjoyment of sex.	Societal pressure to embody the image of the perfect couple; fear of HIV stigma; low awareness of and misconceptions about PrEP.
 Thandiwe	Has **experienced or is at risk of unintended pregnancy**, often compounded by low awareness of SRH options and limited locus of control with use of prevention products.	Unintended pregnancy postponed her plans to complete her studies and start a career.	Ambitions for her future; taking pleasure in "the finer things" in life; maintaining appearances; social status that comes with a successful partner.	Prioritizing her relationship and social status over SRH risks; lack of familiarity with SRH products beyond condoms; unwillingness to access healthcare services; fears of being perceived as promiscuous.
 Faith	Has **unfaithful male partner** and is motivated to protect her health, but finds it difficult to negotiate safe sex with her partner.	Suspected partner of infidelity; wanted to protect herself without the need for her partner's consent.	Protection against partner's infidelity, given challenges negotiating sex with a condom; keeping up appearances of social respectability in her community; validation from female peers in a similar position.	Fear of partner's reaction if her PrEP use is discovered; lack of familiarity with other prevention methods; having to pretend not to know about partner's infidelity; few trusted confidants she can talk to about her situation.

FIGURE 3
DPP user personas.

New mothers are motivated to use SRH products in a manner that aligns with the social norms of motherhood. This persona likely started using OCP after giving birth to her first child and wants to space the births of subsequent children. A notable barrier is that she does not see HIV prevention as relevant for her; she is also more likely to feel the need to conceal her SRH product use from her partner.

Women who aim to **maintain their romantic relationships** are primarily motivated by relationship goals, which often denotes greater influence of male partners over their decision-making. This persona begins using PrEP upon discovering her partner was living with HIV and does not want to lose the security and social status that comes with having a male partner.

Women who have **experienced or are at risk of unintended pregnancy** face challenges such as limited awareness and locus of control around use of SRH products. This persona began using OCP following an unintended pregnancy, which postponed her plans to complete her studies and start her career. Yet maintaining her relationship was also important to her, as her partner brought her social status and helped fund her lifestyle.

Women whose **male romantic partners are untrustworthy** are motivated to protect their health but struggle to negotiate safe sex with their partner. This persona began using PrEP when she suspected her partner of infidelity, enabling her to protect herself without the need for her partner's consent. She is concerned that a conversation about prevention will upset her partner by implying that she does not trust him.

While the research elucidated these five archetypes as potential DPP users, it is important to note that these personas aggregate many different data and are not based on a single individual. As such, many individuals do not fit into a single persona and can embody different personas or aspects of personas at various moments over the life course. Given this fluidity, the DPP demand generation strategy should be designed to flex across various audiences, leveraging but not always corresponding to the specific personas outlined above.

3.2. Creative route for the DPP

Research findings and user personas underscored the importance of finding a creative route for the DPP that resonated with participants' broader values and lifestyles and framed the DPP in relation to them, rather than approaching the DPP from a health lens, which occupied a smaller share-of-mind. The findings were used to develop three potential creative routes for the DPP, which were then tested and refined through co-creation workshops with end users, male partners, and HCPs (Figure 4).

3.2.1. Embrace every side

Embrace Every Side reflected the insight that women often experience a sense of duality in their lives, needing to balance societal expectations with their own motivations. Creative stimulus for this route depicted different moments of duality in women's lives, such as balancing career aspirations with being a supportive wife and mother; traditional values with wanting a different life than the previous generation; and pleasure and enjoyment with the appearance of respectability. The DPP was positioned as a dual pill with dual benefits that could help women navigate both sides of their lives.

The need to balance multiple sides of their identity resonated with all audiences in co-creation workshops. In particular,

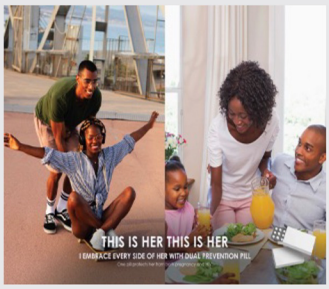
Creative route	Embrace Every Side	I'm Ready	Flip the Script
Based on the key insight that...	Women experience duality in their lives, balancing societal expectations with individual motivations	Women struggle with the unpredictability of life, often fueled by the actions of their partners	There is a wide gap between social stigma for OCP/PrEP and more positive attitudes held by individuals
Key question for testing	Could we help women live both sides of their lives to the fullest, when others are telling them they have to be one thing or the other?	Could we reach women when they experience positive or negative shocks in life and help them feel ready for anything by taking the DPP?	Could we flip the question from 'why would you' to 'why wouldn't you' and create a new set of positive associations for those who take the DPP?
DPP brand truth	The DPP is a dual pill with dual benefits, which helps you navigate both sides of your life	The DPP instills confidence that nothing will get in the way of living life the way you want	The DPP gives you peace of mind in your relationships and your life, protecting you when others take risks with their sexual health
Example of creative stimulus	 	 	 

FIGURE 4
Potential creative routes tested for the DPP in co-creation workshops.

career-focused women felt this message captured their everyday reality. Male partners felt that their own experiences balancing multiple identities were overlooked, as they were primarily portrayed as supporters of their female partners.

3.2.2. I'm ready

I'm Ready responded to the insight that women struggle with the unpredictability of life, often fueled by the actions of their romantic partners. Creative stimulus featured women who were ready to embrace life, rather than being consumed by the anxieties of SRH. This direction reflected the findings that protection from partners who engaged in risky behavior was more motivating than protection from HIV and a stronger association with women who were "ready for anything" than with women who actively seek to prevent HIV. The DPP was positioned as a product that could instill confidence in

women that nothing will get in the way of living the lives they desire.

Participants strongly connected with the need to prepare to weather shocks that are outside of their control. This route performed best when it connected to everyday moments and supported women to achieve career and family goals. Participants expressed concerns that associations with leisure and nightlife could be seen as encouraging promiscuity. Men appreciated being framed as "in it together" with their female partners but were less supportive when the route challenged traditional gender norms.

3.2.3. Flip the script

Flip the Script acknowledged the existing social stigma surrounding OCP/PrEP, contrasting it with more positive attitudes held by individuals. Creative stimulus reframed prevention behaviors as a set of positive associations, such as protecting against the actions of others rather than one's own, becoming a desirable partner instead of damaging the relationship, and shifting from the default notion of taking on risks to taking prevention "just in case." The DPP was positioned as offering peace of mind in women's relationships and lives, protecting them when others take risks with their sexual health.

Participants agreed that stigma around OCP/PrEP needed to be changed but expressed concerns that the selected imagery, which showed too much skin, could reinforce perceptions of promiscuity. However, participants resonated with written affirmations on the images, which they believed could help reduce stigma.

3.2.4. Selected creative route

After comprehensive testing, *I'm Ready* was found to be the preferred route across all markets and audiences. Creative stimulus was refined, expanded and tested in validation workshops with end users, male partners, and HCPs to understand if participants understood, liked, and connected with the creative concept, scenarios and messaging (**Figure 5**).

Comprehension of the scenarios and product benefits was consistently high across all audiences and geographies. End users underscored the need to avoid ambiguity in messaging, as headlines with a question-and-answer format (e.g., "Am I Ready? Yes") and messaging intended to be more discreet led to confusion. Participants related to most, if not all, of the scenarios and agreed that most executions would be appropriate in public spaces to increase reach and awareness. Male partners felt making the messaging accessible would help protect the women in their lives and foster conversations within friend groups and relationships. Scenarios addressing experiences of infidelity deeply resonated across groups, but participants preferred softer language to communicate this, as a female participant from Zimbabwe noted: "*We may not like how blunt the message is, but this is real- it's the reality.*"

Potential end users felt motivated by stimulus that celebrated their individuality as a woman, whether through a goal-oriented or self-care lens. Women appreciated a focus on how pregnancy and HIV impact their lives, and how protecting themselves benefits their current well-being and long-term goals. Both women who already prioritized self-focused values as well as those who felt they needed encouragement to do so responded positively to these messages.

In addition, end users appreciated references to intimacy, particularly where partners were depicted enjoying their sex lives regardless of HIV status, and they appreciated a broad range of messaging for diverse populations regardless of HIV status, life stage, and gender. End users requested more inclusive language to expand the applicability of enjoyment and pleasure scenarios, such as changing "husband" to "partner" or "campus" to a more general setting. Male partners were less supportive of inclusive messaging and responded negatively to scenarios featuring sero-discordant couples.

The stimulus made male partners appreciate the need for the DPP. Male partners across all countries most responded to messaging that positioned them as protectors of women in their lives who were not their romantic partners, recognizing that it was more difficult for them to discuss SRH with their wives. However, they felt positively about advising female friends and relatives to use the DPP and appreciated that these messages could help break down socio-cultural barriers around men speaking with female friends and relatives about sexual health.

Male partners also responded positively and enthusiastically to messages that focused on enjoyment, which appealed to their desire to not be affected by the consequences of their lifestyles. This message ranked highly among those they wished to see across public spaces because they felt it could prompt conversations in their friend groups. One male participant in South Africa affirmed, "*Everyone of us can relate to this scenario and we do want the best for the women in our lives.*"

HCPs preferred creative executions that focused on promoting empowerment and control, rather than narratives framing women as victims of infidelity by their male partners. HCPs found messages that positioned them as supportive of the priorities of their clients, such as spacing children to focus on their careers, would be powerful because they were both needed and relatable. HCPs underscored that messaging that made their clients feel confident in their choices would resonate, and requested additional information to support clients with side effects, continuation, and switching to this end.

Building on the primary research finding that HCPs wielded greater influence later in the user journey, HCPs were shown a range of adherence tools to understand which they felt would be useful to support clients to use the DPP. A daily reminder app to encourage adherence was highlighted as a particularly effective measure that could reach a large number of women and allow for discreet tracking. Discreet packaging was also preferred, potentially with a visual or mechanism to encourage adherence.

4. Discussion

Taken together, findings from this research provide a strong creative foundation for designing a comprehensive demand

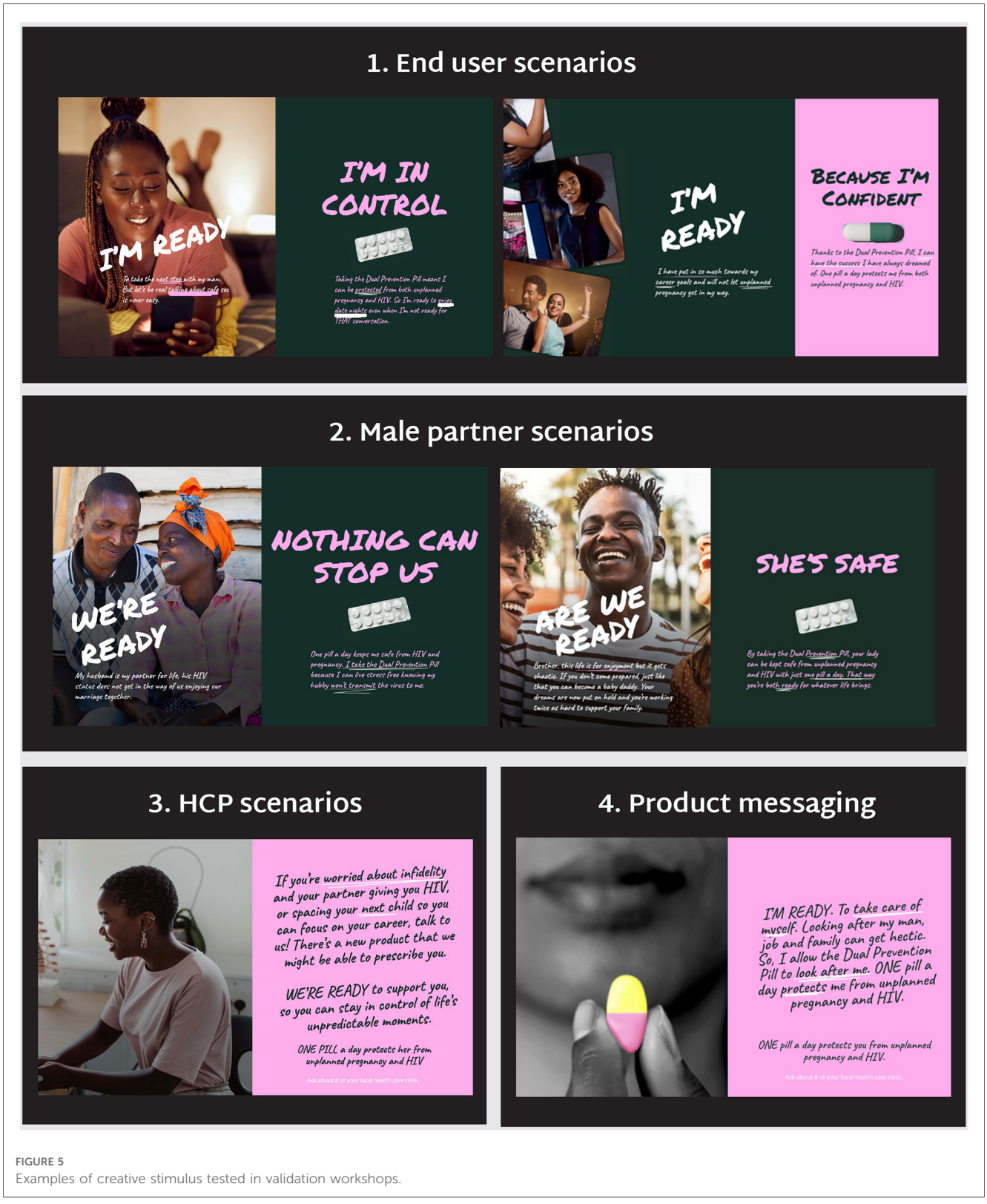


FIGURE 5
Examples of creative stimulus tested in validation workshops.

generation strategy for the DPP. Four key recommendations surfaced for generating demand for the DPP, which are elaborated on in this section.

Connect with women's diverse identities and aspirations: The research findings point to an opportunity for highly distinctive communications on the DPP that reflect the interplay of different values, rather than focusing on a singular value, which risks diluting the complex lived realities and multiple goals of end users. Focusing on women in their diversities aligns with a notable shift in the broader SRH field away from risk-

based communications and towards communications that elevate values, goals, and needs that may appeal to end users, particularly around self-care and women's empowerment (19, 20). For instance, the Kotex "She Can" campaign in Kenya demonstrates the importance of balancing aspirational messages with people's lived reality, as it was criticized for being overly positive (e.g., women can do anything on their periods) and downplaying the realities and challenges of having a period (e.g., pain, social stigma) (16). There is an opportunity to position the DPP as a product that makes it easier for women to juggle competing values without having to make trade-offs for their SRH, and could even enhance their enjoyment and intimacy. Finding the right balance between reality and aspiration will be critical for DPP communications.

Link the DPP with relationship goals: The research found that OCP and PrEP are viewed as products that can put people's romantic relationships at risk, and that women value maintaining their relationships above SRH goals. Other studies across sub-Saharan Africa have similarly found that relationship goals are more relevant than HIV prevention for women, and in particular AGYW, and they will prioritize the needs and preferences of their romantic partners over their own (21, 22).

Discussion of male partners as barriers to women's PrEP and contraceptive use is widespread in the literature. Examples include anticipated and actual accounts of behaviors that limit a woman's capability, opportunity, and motivation to initiate and adhere to prevention products, including contraceptive sabotage, intimate partner violence (IPV), and threats of divorce (23–26). In particular, literature highlights women's concerns that discovery or disclosure of PrEP or contraceptive use will be interpreted by their partner as distrust or implications of unfaithfulness (25), and has found discretion to be a highly valued product attribute (27). Several studies highlight the importance of facilitating covert access to and use of contraception and PrEP as strategies for avoiding stigma while remaining protected from unintended pregnancy and/or HIV (23, 24, 27). Moreover, studies suggest that a lack of communication about prevention use can decrease adherence among women who try to hide their use of products, and conversely, that disclosure, when successful, can increase adherence (27–29).

Some male participants recruited for this research may have been positive deviants with respect to the dominant social norms and practices of their communities, as the positivity of their responses to the DPP was in contradiction to what the literature dictates. Yet romantic relationships are not monolithic, and some are more conducive to women's use of prevention products. A recent qualitative study in South Africa identified four distinct relationship typologies, each with different likelihoods of adoption of HIV self-testing (25). Several studies highlight the heterogeneity of male attitudinal and behavioral profiles related to HIV prevention (30). Literature also indicates that, when supportive, male partners can play an invaluable role in encouraging their partners to use and adhere to products like the DPP, for example by creating an accepting environment and reminding them to take their daily dose (27, 29, 31). Perspectives are mixed on the extent to which men should be involved in women's SRH decision-making as a trade-off to potentially increasing acceptability (32), and DPP messaging should be careful not to reinforce existing stigma around women's agency to make their own decisions on SRH.

Previous HCD research on the DPP found that women do not want to have to be discreet with their product use, and a saw a role for mass media campaigns to combat societal stigma around prevention (33). This research revealed a consensus view among HCPs and cultural commentators that men needed to be proactively targeted to support the DPP in order to limit the risk of product stigmatization among men. Placing DPP campaigns in public spaces were found to be a strong potential entry point to transform male attitudes towards prevention in the broader community, especially when messaging positioned men's support for the DPP as a way to protect women in their lives, given that men were largely resistant to the DPP in the research. Men felt scenarios depicting their own enjoyment could catalyze conversations on sexual health with their peers, indicating that DPP campaigns should seek to reach men with potential for positive deviancy who could influence their peer networks. In addition, there is an opportunity to flip the perception that DPP use could put relationships at risk by showing that DPP users care about their partner and protecting their relationship. At the same time, communications can reframe the DPP as for women who are savvy about protecting themselves from the actions of others, thereby shifting stigma away from end users.

Leverage different triggers for media targeting: Most triggers to OCP and PrEP use relate to negative experiences, such as entry into an established risk group, including commercial sex workers, people with multiple sexual partners and sero-discordant couples, discovery or suspicion of a partner's sexual behavior outside of the relationship, and negative experiences with other prevention methods (29, 31, 34). Literature about how influencers in a woman's social network interpret prevention use tend to focus on negative trigger moments exclusively. Negative trigger moments are thus likely to be significant category entry points for the DPP that can be targeted through media placement. Relevant positive trigger moments, such as change in relationship status, starting university, or child spacing, can be leveraged too (25, 29, 35). Other point-in-time segmentations demonstrate how AGYW may transition in and out of need-states when they are more likely to use a product like the DPP (36, 37). There is an opportunity to position the DPP as helping women to overcome moments of uncertainty and navigate moments when they feel they need to take control of their sexual health, as well as to broaden the concept of "readiness" to apply to positive triggers for adoption, such as preparing for university, a night out, or marriage.

Strike a balance in channel placement: Research findings pointed to high potential for a multifaceted demand generation strategy for the DPP that simultaneously raises public awareness to create social acceptability and delivers more targeted, discreet communications to end users in safe and trusted channels for messaging that male partners and communities may view as controversial. In Kenya, the Jilinde project's "360-degree" marketing campaign targeting multiple levels to effectively shape

perceptions of PrEP country-wide, utilizing national mass media and local events to create widespread awareness and position PrEP as a product for anyone at risk of HIV helped to mitigate potential stigma (36). These campaigns were followed by a large increase in oral PrEP uptake in some counties. Other mass media campaigns have also been effective at creating acceptability and increasing uptake (38). More targeted efforts focused on reaching specific audiences have also been found to drive uptake and support amongst those groups, such as peer-to-peer approaches and men's engagement (36, 39).

5. Conclusion

This research provided valuable insights into the barriers and motivators for DPP uptake, which can be leveraged to develop demand generation strategies for the DPP. The use of HCD techniques ensured a deep understanding of participants' perspectives and cultural contexts, contributing to the relevance and effectiveness of the research findings. Moreover, research findings are applicable to MPTs as a product category, as they draw from both HIV prevention and family planning as well as on broader relationship and SRH dynamics. With a myriad of MPTs in the research pipeline, lessons from demand generation for the DPP can be leveraged to inform future MPT introduction, enabling prevention products and services to reach more end users through their preferred channels and approaches.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Daystar University Ethics Review Board; Human Sciences Research Council; and the Medical Research Council of Zimbabwe. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WN: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. KS: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. JF: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Validation, Writing – review & editing. AA: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. JM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. MM: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Corrigendum: How might we motivate uptake of the Dual Prevention Pill? Findings from human-centered design research with potential end users, male partners, and healthcare providers

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Text correction

In the published article, one of our contributors was omitted from the Acknowledgements section of the article. A correction has been made to **Acknowledgements**. This section previously stated:

"The authors are grateful for the generous support from the Children's Investment Fund Foundation (CIFF) for this research. The contents of this paper are the sole responsibility of the authors and do not necessarily reflect the views of CIFF. The authors would like to thank colleagues at AVAC and M&C Saatchi World Services for their guidance on the research and review of the manuscript, and members of the DPP Advisory Board and DPP Civil Society Advisory Group for providing feedback on the research at multiple stages throughout the process. Finally, the research would not have been possible without the critical contributions of field research teams and research participants in Kenya, South Africa, and Zimbabwe."

The corrected section appears below:

"The authors are grateful for the generous support from the Children's Investment Fund Foundation (CIFF) for this research. The contents of this paper are the sole responsibility of the authors and do not necessarily reflect the views of CIFF. The authors would like to thank colleagues at AVAC and M&C Saatchi World Services for their guidance on the research and review of the manuscript. Humanly supported the design of HCD research tools, trained field research teams, analyzed outputs of the HCD research, and helped develop the user

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The authors apologize for this error and affirm that this does not change the scientific conclusions of the article in any way. The original article has been updated.

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Common ground: the opportunity of male contraceptives as MPTs

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Multipurpose prevention technologies (MPTs) and male contraceptive methods are currently in development to address unique and critical needs facing the global reproductive health community. Currently, MPT products in development are exclusively female-focused due to the readily available nature and regulatory precedent offered by female contraceptive active pharmaceutical ingredients (APIs); however, the opportunity to explore codevelopment with male contraceptive methods, which are at a comparatively early stage of development, should not be overlooked. These fields face parallel challenges including research and development, commercialization, regulatory approval, and market uptake, and these parallels can inform strategic alignment between the fields. One challenge that precludes codevelopment, however, is the path to market and associated funding models for these innovative, yet underappreciated fields. Without candid review, reconsideration, prioritization, and innovation led by the donor and investment communities, product developers will have no compelling reason to consider accepting the added regulatory and fiscal burden associated with combining development streams.

KEYWORDS

male contraception, multipurpose prevention technologies, contraception, MPTs, pharmaceutical development, global access

1. Introduction

Multipurpose prevention technologies (MPTs) are innovative products in development which combine anti-infective and contraceptive properties, presenting an opportunity to revolutionize public health by simultaneously addressing rates of unintended pregnancies and sexually transmitted infections (STIs). However most, if not all, MPTs in development are meant for use by those that can become pregnant, rather than those that produce sperm. This is a direct reflection of the fact that the majority of marketed contraceptive methods are also designed for women, while novel male contraceptive technologies are still in development. Since most MPTs in development consist of a combination of existing, previously-approved active pharmaceutical ingredients (APIs), MPTs for men are comparatively underrepresented, with no active programs in development.

2. Status of male contraception

The development of male contraceptive methods is not a new concept. Scientists have been exploring options for male contraceptives for over 70 years (1). These explorations were overshadowed by the launch of the first female contraceptive method in 1960, when "the pill" and indeed the very concept of contraception, became synonymous with women's reproductive and social autonomy. While these benefits cannot be understated, the responsibility and burden of contraception also became firmly affixed to women.

Meanwhile, the only reversible contraceptive method for men continues to be the condom (ironically, the only MPT currently available).

While development of male contraceptives has lagged behind female contraception, the field has seen marked progress in recent years with programs across multiple mechanisms of action advancing to clinical application. A daily-administered hormonal gel and a long-acting injectable hydrogel are currently in clinical trials and several potential products are anticipated to move into clinical trials in the next 12–24 months, including multiple non-hormonal oral pills. These comparatively late-stage programs are in addition to many other projects that are progressing through the earlier stages of development, (i.e., discovery, optimization, preclinical). These early-stage programs are often identifying drug-like compounds and have not yet begun to consider formulations or routes of administration, and therefore are theoretically well-positioned to investigate co-development with other APIs.

Given the evolving nature of the male contraceptive sector, it seems opportune to consider dovetailing MPT products into the existing product development pipeline rather than circling back to create MPT products after the contraceptive products have completed the full development and approval cycle. However, the idea of developing a dual-indication product is daunting both in theory and in practice. The male contraceptive field already faces extremely limited funding and uncharted regulatory pathways. It is understandable that the idea of further challenging the progress of products by attempting to integrate a second indication and API would not be inherently compelling.

3. Shared development and funding challenges

The many challenges facing the development of MPTs are well understood, have been recapitulated in multiple publications over the past decade, and are similar to those facing male contraceptives (2–5). Manufacturing and delivery system questions, how to efficiently and effectively design clinical trials, and navigating novel regulatory pathways are all problems faced by MPT and male contraceptive product developers alike. With this overlapping need, combining efforts to engage regulatory agencies to (1) increase awareness that these unique and complementary products are in development and (2) to identify the potential gaps in knowledge that will support the development of better-fitting regulatory guidance is critical. For example, there currently is no male contraceptive-specific guidance from the Food and Drug Administration (FDA). Instead, male contraceptive developers are left to consider existing, tangentially relevant guidelines, patchworking female contraceptive guidance (6) with additional input derived from testicular toxicity guidance (7). Similarly, MPT product developers can reference guidance structured for codevelopment of two or more investigational new drugs (8); however, whether or not this guidance is appropriate depends upon a subjective assessment of the proposed product against defined criteria. Without more tailored guidance it is nearly certain that these products, which address critical global public health needs, will face avoidable, unnecessary, and costly delays on their path to market. Unfortunately, these costs are likely to be passed on to consumers through higher product pricing, which, in turn, limits accessibility.

While the fields of MPT and male contraceptive product development can collaborate to develop strategies to address these challenges, the largest limitation for both is low levels of funding compared to other therapeutic areas. The lack of investment from the pharmaceutical industry, which normally works in concert with public-sector funders (9), has significantly stymied development in both the contraceptive and STI sectors for decades. The resulting gap in funding has partially been filled by the philanthropic sector, specifically foundations and other non-profit organizations; however, their combined fiscal efforts still pale in comparison to industry research and development (R&D) expenditures. For instance, in 2021, funding for MPTs and all contraceptive methods combined was $165 million (**Table 1**). Pharmaceutical sector investment accounts for 20% of this funding ($23 million) but represents a $16 million decrease from industry investment in 2020. By comparison, the annual budgets for the top 10 pharmaceutical companies in 2021 ranged from $7–$16 billion (11). The reasons for this lack of investment from the pharmaceutical industry likely derive from a perceived lack of market demand and/or from concerns regarding the distinctive regulatory hurdles and legal concerns associated with developing products for a preventative purpose, as is the case with MPTs and male contraceptives.

4. Discussion: re-evaluating the path to market

As reproductive health is not a priority for most major pharmaceutical companies, the onus lies on the donor and social sector investment communities to lead by example and take action to expand efforts to develop MPTs and the novel contraceptive methods that support them. Sponsoring MPT-specific funding opportunities, convening collaborative workshops to openly discuss regulatory experiences and needs, and advocating for additional funding for public sector grantmakers are all excellent steps, but in order to impart significant change and progress, a major shift in mindset and strategy is needed.

The current pharmaceutical industry model is not a fit for every therapeutic area and serious introspection is required to assess if it is the correct model to be targeting for the contraceptive and MPT sectors. In the current model, based on contraceptive products developed over the past 30 years, the pharmaceutical industry does not invest in R&D until a product has been sufficiently "de-risked". This model applies in other therapeutic areas as well, but with respect to contraception and MPTs there are a number of incompatibilities that make the traditional pharmaceutical development model unsuitable.

TABLE 1 Annual funding for MPTs and contraception (2018–2021) (10).

Funding	2018		2019		2020		2021	
	$USD (M)	% Total funding	$USD (M)	% Total funding	$USD (M)	% Total funding	$USD (M)	% Total funding
MPTs	54	0.32	33	0.19	30	0.18	48	0.29
Contraception	114	0.68	143	0.81	140	0.82	117	0.71
Male	9.1	0.08[a]	15.7	0.11[a]	15.4	0.11[a]	12.9	0.11[a]
Female	95.8	0.84[a]	110.1	0.77[a]	107.8	0.77[a]	83.1	0.71[a]
Multiple/Unspecified	9.1	0.08[a]	17.2	0.12[a]	15.4	0.11[a]	19.9	0.17[a]
Total Contraception + MPTs	**$168M**		**$176M**		**$170M**		**$165M**	

[a]% of total funding for contraception only.

First, there is no definitive milestone at which a product is deemed "de-risked" to the point of being commercially compelling to a pharmaceutical company. These decisions are made behind closed doors at pharmaceutical companies on a case-by-case basis, often weighing profit over impact, which is understandable as profit is the driving force behind the pharmaceutical industry. Second, despite considerable evidence (12, 13), there are still questions regarding whether there are sufficient markets for MPTs and male contraceptives to make pharmaceutical investment worthwhile. Finally, given the fact that the philanthropic and public sectors are essentially carrying these products through a significant level of development, their associated missions and interests become entwined with the products they are supporting. For instance, organizations like Male Contraceptive Initiative support missions for global access and affordability of products developed with their funds. This mission-driven approach can result in conflict with the traditional pharmaceutical sector approach which is driven primarily by profit. While efforts have been made over the past decades to find common ground (e.g., tiered pricing models, market shaping efforts in low- and middle-income countries) there are still significant delays in the time that it takes products to reach vulnerable populations (14).

While the lack of pharmaceutical investment is the most discussed financial barrier for the development of male contraceptives and MPTs, the current R&D model conflicts with the MPT and contraceptive sectors even earlier in the product development process. Venture capital (VC), often the precursor to pharmaceutical investment, is critically lacking. As with the pharmaceutical industry, one major challenge faced in attempting to attract investors is a lack of understanding or underappreciation of the potential markets for male contraceptives and MPTs. In addition, VCs traditionally move quickly with a general expectation of holding an investment in their portfolio for 3–8 years over a timeline from discovery to the end of Phase II clinical (15). It is about this point where the baton is often handed off to a pharmaceutical partner; the VC's willingness to assume early risk rewarded by return on investment derived from the pharmaceutical partner's investment to obtain licensing fees or direct purchase of an asset. As such, if either the VC or pharmaceutical partner (or both as is often the case in the contraceptive and MPT sectors) is not present, the handoff chain, as well as the path to market, breaks down dramatically.

This model presents a particularly conflicting expectation for contraceptive products designed to offer longer-term prevention, known as long-acting reversible contraceptives (LARCs). For any product designed to be a LARC, or in the case of MPTs that are combined with a LARC, there is an inherent impact on the development timeline, particularly during clinical phases. For instance, if a contraceptive is targeted for use over 3–5 years, then, generally speaking, trial participants will need to be followed for that period of time. If you add in recruitment and time and analysis, the traditional 3–8 year turn around for VC investment is quickly surpassed.

For these reasons, it is important to take a more pragmatic view of the situation facing product developers in the MPT and contraceptives sectors. Rather than continuing to spend the limited resources available on what may be a "square peg in a round hole" scenario out of fear of losing the little ground that has been gained, taking a beat to consider novel approaches may result in long-term gains, particularly in a global context.

5. Conclusion

Combining contraceptive and anti-infective agents to develop MPT products stands to offer considerable impact as a more efficient means of addressing two of the biggest challenges facing global health: unintended pregnancy and STI transmission. However, significant challenges lie ahead of these products before they can successfully make their way to the market. Two of the most critical challenges to be addressed are clarifying the regulatory pathway and exploring system-level change to move towards an alternative path in lieu of the traditional pharmaceutical industry and investment models. These challenges are particularly aligned for the male contraceptive and MPT sectors. As such, these sectors can and should combine efforts to: (1) engage regulatory agencies to establish product-specific guidelines to ensure time and cost efficiency, (2) highlight and communicate the ways in which

the current pharmaceutical model is not meeting the needs of the MPT and contraceptive sectors, (3) identify and propose modified or novel models to address this disconnect, and (4) and to solicit and educate investors on the unique needs and potential impact offered by the contraceptive and MPT sectors.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://policy-cures-website-assets.s3.ap-southeast-2.amazonaws.com/wp-content/uploads/2023/03/01082056/Snapshot-Contraception-RD-Broadening-Horizons-to-Meet-a-Diversity-of-Needs.pdf.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficient regulatory approval of two novel HIV prevention interventions in a resource-limited setting: experiences from Zimbabwe

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The global burden of HIV remains unacceptably high despite significant progress made in HIV treatment and prevention. There is an urgent need to scale up the comprehensive HIV prevention strategies that include pre-exposure prophylaxis (PrEP). Oral PrEP is highly effective in preventing HIV acquisition when taken regularly, but this remains a challenge for some at-risk individuals. Therefore, there is a need for other HIV prevention options. The dapivirine vaginal ring (DVR) and long-acting injectable cabotegravir (CAB-LA) are novel biomedical interventions that are safe and efficacious for HIV pre-exposure prophylaxis, as demonstrated in recently completed clinical trials. Timely roll-out and scalability of efficacious interventions depend on the registration process with the national medicine regulatory authorities (NMRAs). The Medicines Control Authority of Zimbabwe (MCAZ) was the first NMRA globally to approve the DVR in July 2021 and the first in Africa to approve CAB-LA for HIV prevention in July 2022. The regulatory review process for DVR and CAB-LA by MCAZ took 4.5 and 5.5 months, respectively. This efficient review process of the two interventions by MCAZ, a regulatory body in a resource-limited setting, provides important lessons to shorten timelines between the completion of the clinical development process and the registration of essential medicines.

KEYWORDS

HIV, pre-exposure prophylaxis, dapivirine vaginal ring, long-acting injectable cabotegravir, regulatory approval, Zimbabwe

1. Introduction

Remarkable progress has been made in HIV treatment and prevention in the last two to three decades. Since the 1990s, HIV incidence has been reduced by 90% in Zimbabwe, 45% in South Africa, and 44% in Kenya (1). Overall, AIDS-related deaths in Eastern and Southern Africa have decreased by 58%, and the number of new HIV infections has also decreased by 57% since 2010 (2). Notably, in sub-Saharan Africa (SSA), a 39% decrease in HIV incidence was reported among young women aged 15–24 years between 2010 and 2020 (1). Despite this significant progress, HIV/AIDS is still a major global public health threat, with 1.3 million new HIV infections and 630,000 AIDS-related deaths per year. In 2022, AIDS claimed a life every minute, and 4,000 adolescent girls and young women were diagnosed with HIV each week (2). Of all the new HIV infections in SSA in 2022, 63% were among

women and girls (2). Zimbabwe is at the epicenter of the global HIV pandemic, with an HIV prevalence of 12.9 % among adults, 15.3% among women, and 10.2% among men aged 15–49 years (3). The annual incidence of HIV was 0.45% among Zimbabwean adults aged 15–49 years, 0.67% among women and 0.23% among men. An estimated 31,000 new HIV cases occurred among Zimbabwean adults in 2020 (3). With the current rate of new HIV infections, the world will not meet the Global AIDS Strategy (2021–2026) target of fewer than 370,000 annual incident HIV infections by 2025 (1).

There is an urgent need to scale up comprehensive HIV prevention strategies that include the provision of pre-exposure prophylaxis (PrEP) options of oral Truvada, the dapivirine vaginal ring (DVR), and long-acting injectable cabotegravir (CAB-LA). This requires regulatory approval of the PrEP products before they can be made available. DVR and CAB-LA have not been approved in many countries yet, which limits the available PrEP options. Their prompt and easy regulatory approval has the potential to greatly decrease the rate of new HIV infections, especially in SSA, where the disease burden is the highest. Many countries in SSA have limited resources to conduct regulatory reviews of new drug applications. Countries with limited resources have reduced workforce and materials for efficient drug regulation. As a result, drug regulatory approvals in these countries are prolonged, and access to essential medicines is delayed. In this article, we aimed to describe how the National Medicine Regulatory Authority (NMRA) in Zimbabwe, a resource-limited country in Southern Africa, was able to approve DVR and CAB-LA in a short period.

2. Drug approval process: from clinical trials to scale-up

Proven safety, efficacy, and acceptability of new biomedical interventions from clinical trials do not guarantee access but are merely one step in ensuring the availability of the new agents. PrEP is the use of antiretroviral drugs to prevent HIV acquisition. Before being made available to the public, PrEP agents must be registered for use by the drug regulatory authority in the country where they will be distributed. The products must be scalable to reach people who could benefit from them most promptly.

Many countries took years to approve Truvada (emtricitabine/tenofovir disoproxil fumarate). Truvada was initially submitted to the Medicines Control Authority of Zimbabwe (MCAZ) in May 2006 for registration as an antiretroviral drug for HIV treatment and received approval in April 2009. The process took almost 3 years. Oral PrEP with Truvada was first approved in the United States by the US Food and Drug Administration (FDA) in 2012. The World Health Organization (WHO) recommended offering Truvada as part of a comprehensive HIV prevention package to individuals at substantial risk of HIV infection in 2015 (4).

Oral PrEP is highly effective in preventing HIV acquisition when taken regularly, but this remains a challenge for some at-risk individuals, especially women in SSA, for a variety of reasons such as pill burden, stigma, fear of violence from partners, religious beliefs, and dissatisfaction with the PrEP delivery services (5, 6). Therefore, there is a need for discrete, safe, efficacious, and acceptable longer-acting HIV prevention options, such as the DVR and CAB-LA.

2.1. DVR regulatory pathway

The DVR is a discrete, flexible silicone ring that is inserted into the vagina and works by releasing the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine, an antiretroviral drug, slowly over a month (7, 8). The DVR, developed by the International Partnership for Microbicides (IPM), has been extensively evaluated across several phase I–III trials (6, 9). The IPM, together with the Microbicides Trials Network (MTN), conducted two large phase III trials, namely, the MTN-020/ASPIRE and The Ring study, assessing the safety, efficacy, and acceptability of the DVR in 4,500 women from Malawi, South Africa, Uganda, and Zimbabwe. The DVR was shown to reduce the risk of HIV-1 acquisition via vaginal sex by about 30% among cis-gender women, and further analysis demonstrated an HIV-1 risk reduction of 50% or more for those who used the ring most regularly (5, 8, 9). Modeling data from two subsequent open-label studies (i.e., MTN-025/HOPE and DREAM) suggested a greater HIV-1 risk reduction of 63% or more for those who used the ring most regularly across both studies (8, 10). The DVR showed a strong safety profile and no evidence of NNRTI resistance among women who seroconverted across the four studies (8–11). The clinical trials were supported by qualitative work with women and their sexual partners to understand end-user preferences and concerns. In Zimbabwe, ASPIRE and HOPE were conducted at three clinical research sites at the University of Zimbabwe Clinical Trials Research Centre (UZ-CTRC) (8, 9).

Following the successful phase I–III clinical trials, the IPM applied to the European Medicines Agency (EMA) to review the DVR under EU-M4all in 2017. On 24 July 2020, using data from the two phase III trials, the EMA issued a positive scientific opinion on the DVR (12), a piece of evidence that the product should be authorized or approved for use. The DVR subsequently received WHO prequalification in November 2020. In January 2021, the WHO recommended offering the DVR as a safe and effective additional prevention choice for women at significant risk of HIV infection as part of a package of prevention options. The WHO added the DVR to the WHO list of prequalified (essential) medicines after this process (13).

After WHO's prequalification, on 23 February 2021, the IPM submitted the DVR dossier to MCAZ, NMRA in Zimbabwe, for review. The MCAZ Registration Committee did not conduct a full review. Instead, they used a reliance approach in line with the MCAZ Reliance guidelines (14). These guidelines allow the Registration Committee to rely on part or all of the decisions made by reference regulators. This is known as an abridged review (14). An abridged review enabled the process to be concluded in a shorter timeline than the normal review pathway. The positive scientific opinion from the EMA, the WHO

prequalification, and the prior "regulatory knowledge" of MCAZ about the product from the clinical trial approval and oversight stages of the Zimbabwe UZ-CTRC sites enabled the MCAZ to conduct an expeditious but rigorous review. On 6 July 2021, 133 days after submission by IPM, MCAZ approved the ring for registration, and Zimbabwe became the first country globally to register the DVR (15, 16). The regulatory process for DVR in Zimbabwe is shown in **Figure 1** adapted from AVAC (12).

2.2. CAB-LA regulatory pathway

Cabotegravir is a second-generation integrase strand transfer inhibitor (INSTI) antiretroviral drug with a high resistance barrier. The long-acting formulation, which is administered as an injection 1 month apart for the first 2 months and then every 2 months after that, was developed by ViiV Healthcare, a division of GlaxoSmithKline plc (GSK) (5). Two international phase IIb/III multicenter, randomized, double-blind, active-controlled studies, namely, HPTN 083 and HPTN 084, demonstrated the superiority of CAB-LA to Truvada for HIV prevention in individuals at high risk of HIV acquisition through vaginal and anal intercourse (6, 17). Compared to Truvada, the participants on CAB-LA experienced a 69% and a 90% lower rate of HIV acquisition in HPTN 083 and HPTN 084, respectively (6, 17). HPTN 084 enrolled 3,200 cis-gender women at 20 clinical research sites in Botswana, Eswatini, Kenya, Malawi, South Africa, Uganda, and Zimbabwe. The five sites of the University of Zimbabwe Clinical Trials Research Centre contributed almost 25% of the sample size (6).

Data from HPTN 083 and HPTN 084 supported the FDA regulatory approval for CAB-LA for PrEP on December 20, 2021 (18). In March 2022, the WHO recommended offering CAB-LA as an additional HIV prevention option. The EMA validated the marketing authorization application (MAA) of ViiV Healthcare for cabotegravir long-acting injectable for PrEP to reduce the risk of sexually acquired HIV-1 in October 2022 (19). This meant that the EMA had accepted the application and would begin the formal scientific review process. On January 28, 2022, GSK, the parent company of ViiV Healthcare, applied for registration of CAB-LA to the MCAZ. The FDA is one of the reference regulatory authorities (RRAs) that the MCAZ considers for reliance on the regulation of medicines. Being an innovative product from a "Stringent Regulatory Authority (SRA)," CAB-LA was eligible for the expedited review pathway. The MCAZ dossier assessors utilized the expedited review pathway before tabling for consideration during the monthly Registration Committee meetings. On July 6, 2022, Zimbabwe was the first African country and the first low- and middle-income country to approve CAB-LA for HIV prevention after the United States, as depicted in **Figure 2** (20).

3. Capacity and expertise that strengthened the MCAZ

It took 133 days in 2021 to register the ring and 159 days in 2022 to register CAB-LA in Zimbabwe. Prior to that, between 2003 and 2015, it took 516–1,673 median days to register a drug in Zimbabwe. Truvada took 1,045 days to be registered in

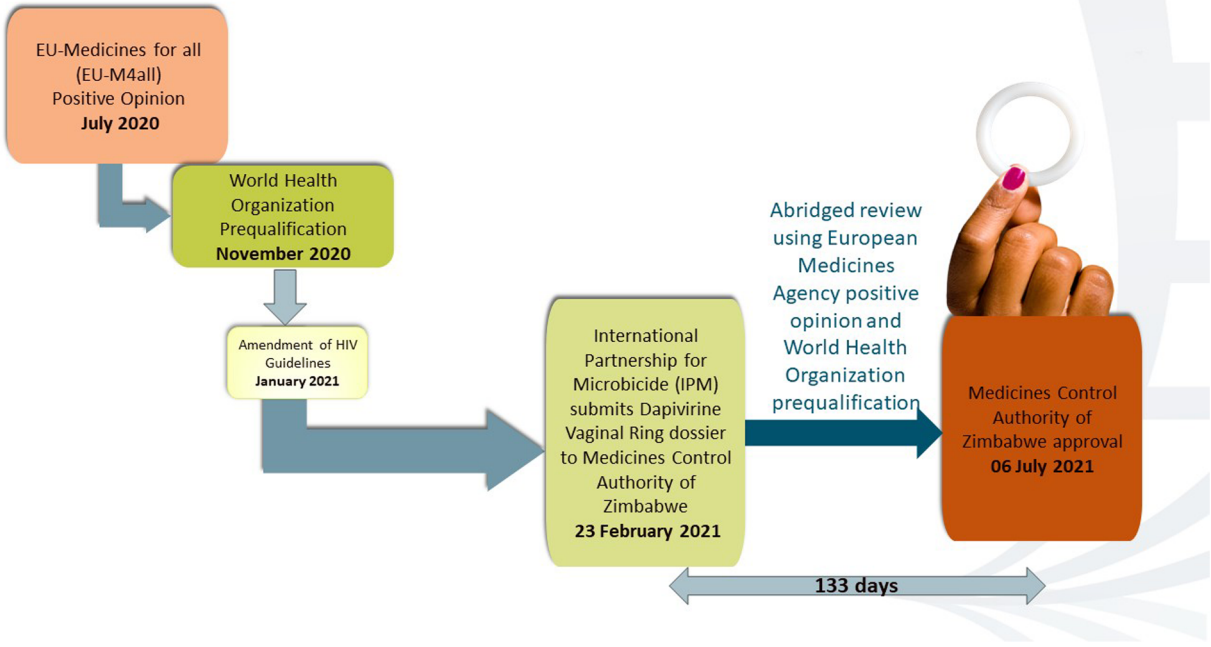

FIGURE 1
DVR regulatory pathway. Adapted from AIDS Vaccine Advocacy Coalition (AVAC) (12).

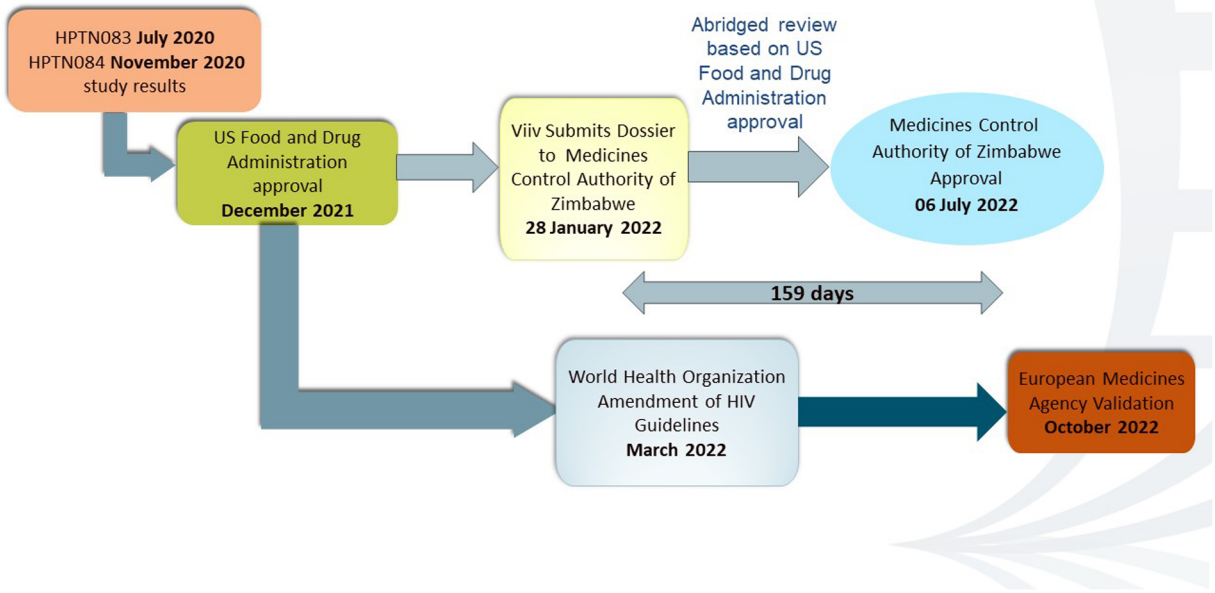

FIGURE 2
CAB-LA regulatory pathway.

Zimbabwe in 2009. In 2019, the median overall approval time was reduced to 473 days (15.8 months) for new active substances, which is comparable to mature and better-resourced regulatory agencies (21). Several strategies provided MCAZ with the capacity and expertise to approve DVR and CAB-LA for registration in a timely manner. The MCAZ used the abridged review to approve DVR and CAB-LA in Zimbabwe because the two products had been previously approved by at least one reference authority. MCAZ considers some SRAs as reference authorities because they have strict standards for safety, efficacy, and quality. These SRAs include the EMA, US FDA, Australian Therapeutic Goods Administration, Health Canada, and Japanese Pharmaceuticals and Medical Devices Agency (21, 22). Other processes utilized by the MCAZ are as follows:

(i) Full review for products not approved by any reference agencies
(ii) Verification review for WHO-prequalified products through the WHO Collaborative Medicines Registration Procedure (CRP)
(iii) Mutual Recognition
(iv) Joint assessment and work-sharing [ZaZiBoNa initiative of the Southern African Development Community (SADC) harmonization initiative]
(v) Unilateral recognition (14, 22)

3.1. Pharmacovigilance and Clinical Trials division and Evaluations and Registration division

A major strength of the MCAZ is the seamless collaboration between the Pharmacovigilance and Clinical Trials (PVCT) division, which regulates and monitors clinical trials conducted in Zimbabwe, and the Evaluations and Registration (EVR) division, which assesses applications for registration of medicines in Zimbabwe. Prior to implementation, MTN-020/ASPIRE, MTN-025-HOPE, and HPTN 084 were approved by MCAZ through the PVCT, which worked closely with the EVR division. The latter provided an expert review of the information on chemistry, manufacturing, and controls (CMC) for the DVR and CAB-LA. This is one of the strengths that enabled a faster review of the two products when they were eventually submitted for registration in Zimbabwe; some of the key aspects of the products had already been evaluated and approved by the MCAZ at the clinical trial stage. In addition, throughout trial implementation, the PVCT division regularly received and monitored adverse reaction reports from the three pivotal studies in Zimbabwe. A specialized committee of the PVCT routinely conducted a causality assessment of adverse reaction reports to determine if an event was related to the DVR or CAB-LA (14, 21). This ongoing assessment further expedited the approval process for the two products.

3.2. WHO prequalification

The WHO prequalification was instrumental in the expeditious review of DVR/CAB-LA in Zimbabwe. The WHO prequalification guaranteed the quality, safety, and efficacy of the two products, and this contributed to the approval of NMRA for registration. The WHO Prequalification Programme helped in the capacity building of MCAZ in regulatory processes and inspections.

MCAZ staff participated in dossier assessments and inspections conducted by the WHO (21, 23). The WHO Collaborative Registration Procedure pilot, which started in 2012 with Zimbabwe and nine other countries, provided capacity building that enabled faster registration of prequalified medicines and will avoid duplication of work in developing countries.

3.3. The European Medicines Agency

Since 2004, the EMA, working together with WHO, has been providing scientific opinions on essential human medicines that are planned for distribution in markets outside of the European Union (EU) (24). The purpose is to make access to essential medicines in low and low-middle-income countries (LMICs) with limited regulatory capacity much easier for patients. This procedure is called EU-Medicines for all (EU-M4all) and was previously known as the Article 58 procedure. The procedure is a combination of the scientific review capabilities of the EMA with the expertise of the WHO and national regulators in the target countries on the local epidemiology and disease. This provides a unique development and assessment pathway. Under this procedure, the Committee for Medicinal Products for Human Use (CHMP) of the EMA reviews medicines and vaccines to similar high standards to medicines intended for use in Europe. After the evaluation, the EMA publishes its scientific opinion of the benefit–risk balance of the product, which aims to facilitate prequalification of the medicine by the WHO and registration in the intended countries (24). The positive opinion of the EMA on the DVR enabled the IPM application to be reviewed under the abridged review process by MCAZ and resulted in approval within 133 days.

3.4. SPaRCS project in Southern African countries

MCAZ was also part of the strengthening pharmacovigilance and regulatory capacities in four Southern African countries (SPaRCS) project with Eswatini, Namibia, and South Africa from April 2020 to October 2023. The inclusion of MCAZ in the SPaRCS project strengthened the regulatory capacities of the authority through a participatory learning approach. The project will potentially pave the way for harmonization of requirements and reliance in the region in regulatory issues involving clinical trials and pharmacovigilance (25), making approval of future biomedical products even more expeditious.

3.5. ZaZiBoNa initiative

Zimbabwe is a founding member, alongside Zambia, Botswana, and Namibia, of the SADC collaborative medicine registration initiative, namely, the ZaZiBoNa initiative, which was established in 2013 (21, 22, 26, 27). The initiative has contributed to MCAZ capacity building by providing a program for training and enabling collaboration with other regulatory authorities. The initiative also strengthened the capacity of MCAZ by reducing workload and time to registration and developing mutual trust and confidence in regulatory collaboration (26, 27). Harmonization of registration requirements and joint reviews were also shown to have contributed to reduced workload for both the pharmaceutical industry and the regulatory authorities in the ZaZiBoNa countries (26).

4. Discussion

The Zimbabwean NMRA, i.e., MCAZ, is a member of several regulatory partnerships, such as the WHO Collaborative Registration Procedure and ZaZiBoNa initiative of the SADC. These collaborations have strengthened the regulatory capacity of MCAZ. MCAZ uses different models to approve medicines, including the abridged review, where review time is shortened when the product is already approved by one reference authority. This review type enabled Zimbabwe to register DVR and CAB-LA in a shorter time than other drug regulatory authorities. NMRAs in the region and other LMICs should emulate MCAZ by establishing similar collaborations in their geographical regions and with well-resourced authorities in other parts of the world.

The establishment of a SADC regional medicines authority has been suggested by previous researchers and is highly recommended to streamline the registration process across the region (26). A regional medicines authority, such as the EMA that regulates and monitors medicines for the entire European Union, would mean one approval would simultaneously accelerate access in many countries. Similarly, the establishment of the African Medicines Agency (AMA), whose treaty-signing process is currently ongoing, is expected to strengthen the capacity of African countries to regulate medicines and related products, provide regulatory guidance, and harmonize medical regulation efforts on a continental level (28, 29).

MCAZ was designated a Regional Centre of Regulatory Excellence (RCORE) under the African Medicines Regulatory Harmonization (AMRH) Initiative of the African Union and the New Partnership for Africa's Development (NEPAD) Agency in 2014. RCORE offers training services in medicine registration, PVCT, and laboratory testing of medicines for new and experienced regulators from NMRAs, regulatory affairs personnel from the pharmaceutical industry, and academia to increase the regulatory workforce in Africa (28). Regulators from other LMICs should participate in these courses to learn from the best practices of MCAZ in medicine registration and other regulatory aspects.

High staff turnover and poor skill retention have been reported at MCAZ and other NMRAs in the region for the ZaZiBoNa process (21, 26). Having a limited number of assessors with adequate skills leads to delayed timelines in medicine approval. There is a general scarcity of pharmaceutical professionals in most LMICs caused by low salaries, "brain drain," and lack of career structure (28). MCAZ has done well by participating in

several collaborative partnerships to capacitate its regulatory officers, but to retain them and have the maximum gain from all the training invested in its staff, MCAZ needs to ensure its staff is well renumerated to ensure the sustainability of these great partnerships.

Medicine approval is a complex process that is essential to ensure medicines registered in a country are of good quality, safe, and efficacious. The process can be time-consuming and result in delayed access to essential medicines for affected or at-risk populations. MCAZ has been able to register two HIV PrEP products, namely, DVR and CAB-LA, in a shorter time frame than other LMICs because of collaborations with other NMRAs and clinical researchers in the region and better-resourced medicine regulatory authorities from high-income countries. These collaborations have built the capacity of MCAZ regulatory officers and avoided duplication of effort, enabling them to efficiently review submissions promptly.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material; further inquiries can be directed to the corresponding author.

Author contributions

CM: Conceptualization, Writing – original draft, Writing – review & editing. LC: Writing – review & editing. GC: Writing – review & editing. ZC: Writing – review & editing, Conceptualization. NM: Writing – review & editing, Conceptualization, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Innovations in monoclonal antibody-based multipurpose prevention technology (MPT) for the prevention of sexually transmitted infections and unintended pregnancy

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Monoclonal antibodies (mAbs) are currently being produced for a number of clinical applications including contraception and the prevention of sexually transmitted infections (STIs). Combinations of contraceptive and anti-STI mAbs, including antibodies against HIV-1 and HSV-2, provide a powerful and flexible approach for highly potent and specific multipurpose prevention technology (MPT) products with desirable efficacy, safety and pharmacokinetic profiles. MAbs can be administered systemically by injection, or mucosally via topical products (e.g., films, gels, rings) which can be tailored for vaginal, penile or rectal administration to address the needs of different populations. The MPT field has faced challenges with safety, efficacy, production and cost. Here, we review the state-of-the-art of mAb MPTs that tackle these challenges with innovative strategies in mAb engineering, manufacturing, and delivery that could usher in a new generation of safe, efficacious, cost-effective, and scalable mAb MPTs.

KEYWORDS

multipurpose prevention technology, monoclonal antibodies, STI, HIV, contraception

The case for MAb MPTs

The global prevalence of STIs and unplanned pregnancies remains unacceptably high despite the availability of prevention strategies to curtail many such adverse reproductive health outcomes. Over 400 million new cases of STIs and 121 million unplanned pregnancies occur every year. Common bacterial and parasitic STIs (e.g., gonorrhea, syphilis, chlamydia, trichomoniasis) are curable with existing single dose regimens of antibiotics, yet these STIs continue to infect over 350 million people a year due to a large percentage of untreated, asymptomatic, and recurrent infections, and drug resistance. Effective vaccines have been approved for three viral STIs: Human Papilloma Virus (HPV), Hepatitis A and Hepatitis B, yet vaccine coverage remains suboptimal in many regions (1). No vaccines or cures exist yet for two other highly pathogenic viral STI's, herpes simplex virus (HSV) types-1 and -2 and the human immunodeficiency virus type 1 (HIV-1). Currently over 700 million people

worldwide are infected with genital HSV and 39 million people are living with HIV. Antiviral drugs can reduce viral load and transmission, but sexual transmission of these viruses is still common: 24 million new cases of genital HSV and 1.3 million cases of HIV are acquired annually (2, 3). Despite the availability of diverse contraceptive methods, many are unacceptable or unavailable to a large percentage of the world's population and as a consequence nearly 50% of pregnancies are unintended (4). MPTs are methods that provide dual protection against HIV, other STIs and/or unintended pregnancies. Recent surveys indicate a high level of user preference for MPT products (5), yet the only currently approved MPT product, the condom, is used by only a small percentage of sexually active adults (6). For these reasons, new more acceptable MPT methods are urgently needed to combat the current reproductive syndemic of STIs and unintended pregnancy.

In this review we advocate for the use of monoclonal antibodies (mAbs) as MPTs. MAbs have emerged in recent years as invaluable drugs for the treatment of a variety of clinical conditions. They are potent and highly specific, have an excellent safety profile, and can be used in various combinations to simultaneously recognize and inactivate STIs and contraceptive targets such as sperm. Advanced antibody engineering is being used to develop more effective mAbs, and new mAb production platforms are addressing cost and supply issues. Different delivery methods enable systemic or local applications, and short-term (on-demand) or long-term protection (Figure 1). The timing is right for the advancement of mAb-based MPTs.

Use of mAbs to prevent infectious diseases

Passive immunization, the administration of antibodies to people for the prevention and treatment of diseases, has been practiced for over a century (7). Early use of antisera was associated with severe side effects, but the invention of mAbs in 1975 and the introduction of enhanced human antibody cloning, screening and production techniques in the early 21st century gave rise to a new era of safer passive immunization. In 1986, the first mAb clinical product, muromonab-CD3 (OKT3), was approved for the treatment and prevention of acute rejection after solid organ transplantation (8). To date at least 137 mAbs have been approved by the FDA and/or EU for clinical use (9), and over 570 novel mAb products are in early commercial development (10). At present only two mAbs have been approved by the FDA for the treatment of infectious diseases, specifically anthrax and respiratory syncytial virus (RSV). Other mAbs targeting dangerous pathogens such as Ebola and SARS CoV-2 have received emergency use authorization (9). Several mAbs against STI pathogens (e.g., HIV-1 and HSV-2) are currently undergoing clinical trials. Academic centers and global

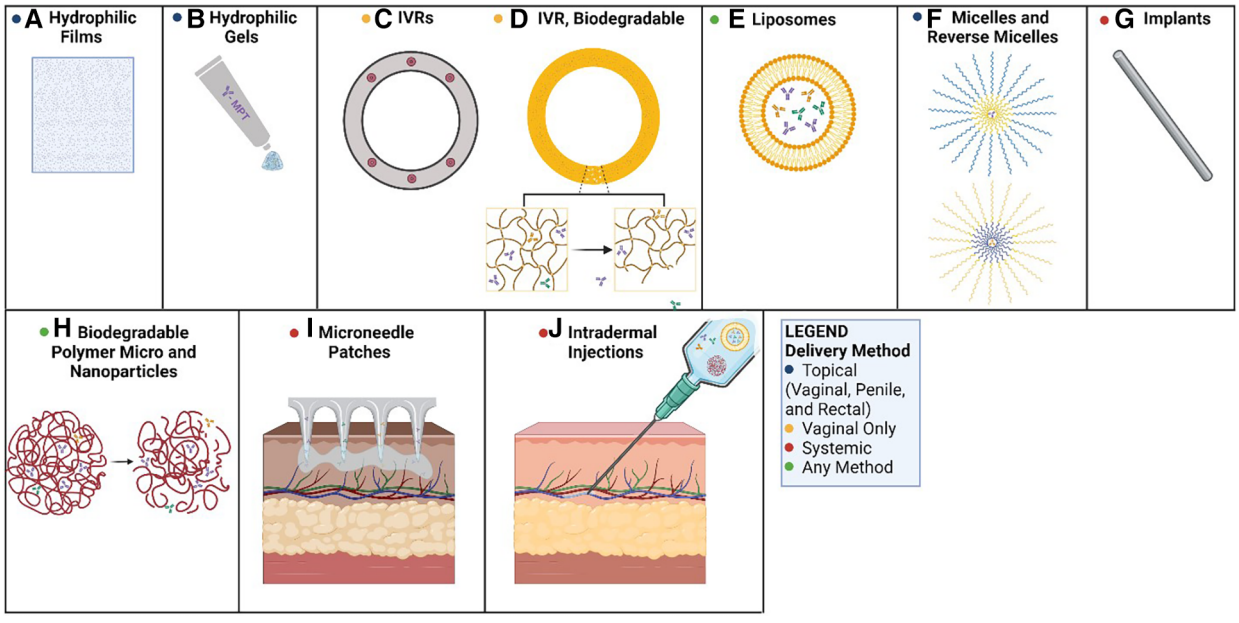

FIGURE 1
Methods of mAb-based MPT delivery. Potential routes for the delivery of mAb-based MPTs: (A) PVA-based films dissolve in the vagina, releasing mAbs; (B) hydrophilic gels can be applied to the penis, the rectum, or the vagina as a topical route of delivery; (C) PLGA or PCL pods erode releasing mAbs over time; (D) biodegradable polyurethane rings and implants erode, releasing antibodies over time; (E) liposomes can be delivered in hydrophilic suspensions or gels for topical applications or systemic delivery; (F) micelles can be used in hydrophilic solutions (reverse micelles in hydrophobic solutions) topically as creams; (G) biodegradable implants could deliver antibodies systemically as the matrix erodes; (H) biodegradable micro and nanoparticles erode allowing antibodies to diffuse from the matrix; (I) microneedle transdermal patches applied to the skin can systemically deliver mAbs over time; (J) intradermal injections can deliver a bolus dose of mAbs, or a solution of delivery vehicles for extended circulation time (e.g., nanoparticles, liposomes). Created with BioRender.com.

non-profit consortia have been leading the way in mAb discovery for infectious diseases.

MAbs against STI pathogens

Human immunodeficiency virus type 1 (HIV)

The WHO has identified mAbs as an important approach for HIV prevention (11). Anti-HIV mAbs are commonly derived from HIV-infected individuals that have developed "broadly neutralizing antibodies (bnAbs)", potent antibodies that are capable of neutralizing a wide variety of HIV strains. BnAbs develop over time from intense affinity maturation in the germinal centers. Over 500 monoclonal HIV bnAbs have been characterized to date (12). BnAbs primarily block HIV infection through viral neutralization; secondary mechanisms include complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cellular cytotoxicity (ADCC) (13). Many HIV bnAbs are currently undergoing testing in clinical trials for HIV treatment and prevention (Table 1A).

The first HIV mAbs to be tested in clinical trials were in a product containing three HIV bnAbs: 2F5, 4E10 and 2G12. Systemic intravenous infusion of the product and topical administration of a vaginal gel containing these antibodies (MABGEL) was determined to be safe (32, 33). The more potent HIV bnAb, VRC01, has undergone extensive investigation in clinical trials. The first studies demonstrated safety and pharmacokinetics following intravenous infusion (14). VRC01 was recently tested in two parallel phase 2b trials for HIV prevention involving thousands of patients (34). MAb infusions up to 30 μg/kg did not reduce the overall risk of acquiring an HIV infection due to the prevalence of VRC01-resistant strains where the trials were conducted. However, a subanalysis of the data revealed that VRC01 infusion provided a 75% prevention efficacy against HIV strains that were susceptible to the neutralizing effects of the antibody, providing proof of concept for the approach (34). VRC01 was administered in a topical vaginal film, MB66, to female volunteers. Single and multiple daily doses of the MB66 film were safe and vaginal lavages showed efficacy in ex vivo viral neutralization assays up to 24 h after dose administration (7). A series of new HIV mAbs that recognize diverse HIV epitopes have recently been tested in phase 1 clinical trials including: VRC07 and 3BNC117 (CD4 binding site), CAP256V2LS and PGDM1400 (V2 glycan), and PGT 121 and 10-1074 (V3 glycan) (35). Combinations of anti-HIV antibodies are better equipped than single antibodies to prevent the development of resistance by targeting non-overlapping epitopes. Thus, further trials involving two or three

TABLE 1 Published clinical trials of HIV and HSV mAbs.

Name	Description	Stage of development
A. HIV BnAbs		
VRC01 (7, 14–17)	CD4-binding site (CD4-BS)	Phase I and IIb clinical trials
VRC01LS (18)	LS variant-extended serum half-life	Phase 1 clinical trial
VRC07-523LS (19–21)	CD4-BS	Phase I clinical trials
3BNC117 (22, 23)	CD4-BS	Phase I clinical trials
PGT121 (24)	V3 Glycan	Phase I clinical trial
10-1074 (25)	V3 Glycan	Phase I clinical trial
CAP256V2LS (21)	V2 Glycan	Phase I clinical trial
PGDM1400 (26)	V2 Glycan	Phase I clinical trial
Combination mAbs		
3BNC117 10-1074 (27)	CD4-BS V3 Glycan	Phase Ib clinical trial
3BNC117 10-1074 (23, 28, 29)	CD4-BS V3 Glycan	Phase I clinical trial
VRC07-523LS PGT121 (20)	CD4-BS V3 Glycan	Phase I clinical trial
PGDM1400 PGT121 VRC07-523LS (26)	V2 Glycan V3 Glycan CD4-BS	Phase I clinical trial
CAP256V2LS VRC07-523LS (21)	V2 Glycan CD4-BS	Phase I clinical trial
B. HSV mAbs		
HDIT101 (30) (h2c)	Humanized mAb, recognizes conserved epitope in glycoprotein B present on HSV-1 and HSV-2 and virus-infected cells.	Phase 1 clinical trial
UB-621/E317 (31)	A gD-specific human IgG1 mAb that can neutralize HSV-1 and HSV-2. UB-621 is the clinical grade product of E317.	Phase 1 clinical trial
		Phase 2 clinical trial
		Phase 2 clinical trial
		Phase 2 clinical trial
HSV8 (7)	Glycoprotein D-specific human IgG1 with the capability of neutralizing HSV-1 and HSV-2.	Phase 1 clinical trial

bnAb combinations are underway. In addition, bi- and tri- specific antibodies that target multiple epitopes of HIV Env are being tested (36).

Herpes Simplex Virus (HSV)

At least 50 mAbs against HSV have been produced and shown to have antiviral effects *in vitro* and in animal HSV infection models [reviewed in Backes et al. (37)]. Three anti-HSV mAbs, 2C (HDIT101), E317 (UB-621) and HSV8, have progressed to human clinical trials (Table 1B).

2C is a humanized mAb that recognizes a conserved region of glycoprotein-B on the surface of HSV-1 and 2. It was determined to be safe after intravenous administration of escalating doses (maximum dose: 12,150 mg) to healthy volunteers (30). This antibody is currently being tested in phase 2 clinical trials for the treatment of orolabial HSV-1 lesions (NCT04539483), and anogenital HSV-2 lesions (NCT04165122).

E317 is an HSV glycoprotein-D specific human IgG1 mAb that can neutralize both HSV-1 and -2. The clinical grade of this mAb, UB-621, was recently determined to be safe and well tolerated in a phase 1 single dose (100 mg/ml) study in healthy volunteers; it is currently being tested in clinical trials for the prevention of orolabial and genital disease (37) (NCT02346760, NCT03595995, NCT04714060, NCT04979975). HSV8 is a human IgG1 mAb that recognizes HSV glycoprotein-D. A vaginal film, MB66, containing HSV8 and the anti-HIV mAb VRC01, was recently tested in a phase 1 clinical trial; no serious adverse events were reported, and antiviral neutralizing activity (both HIV and HSV) was detected in vaginal secretions from the women up to 24 h after treatment (7).

Other STIs

A large number of mAbs have been manufactured against other STI pathogens and are currently used for research and diagnostic applications. To our knowledge, none has been tested to date in clinical trials, although mAbs against *Neisseria gonorrhoeae* may be advanced into the clinical arena soon due to the emergence of multidrug-resistant strains of Neisseria. The mAb 2CT against *N. gonorrhoeae* appears poised to enter clinical trials (38).

MAbs as immunocontraception

The field of immunocontraception began in the early 1900s with the discovery that sperm can elicit immune responses in animals and humans, and observations that many infertile men and women have antisperm antibodies (39). International agencies including the World Health Organization (40) and the Population Council previously had contraceptive vaccine programs directed at eliciting immune responses to inhibit sperm, oocytes, placenta, and endocrine processes. In the 1980s and 90s, clinical trials were conducted to test the safety and efficacy of a β-HCG subunit contraceptive vaccine targeting human chorionic gonadotropin (hCG), a hormone secreted by the blastocyst early in pregnancy to ensure uterine receptivity. The hCG vaccine trials demonstrated safety, but antibody levels were highly variable indicating that some women would not be protected (41). Steps were underway to improve efficacy and to develop other contraceptive vaccines (e.g., against sperm), when the program was terminated in 1997 following concerns about safety, reversibility and potential for misuse (42).

Today, the immunocontraception approach is undergoing a renaissance due to breakthroughs in bioengineering and the ability to produce clinical grade human mAbs. Passive immunization bypasses the concerns raised with contraceptive vaccines which require active immunization: passive immunization is safe and reversible, and the dose and site of administration can be precisely controlled (43).

One promising immunocontraception candidate is an antisperm mAb, "Human Contraception Antibody (HCA)", that recognizes a sperm surface carbohydrate epitope, CD52g, and rapidly agglutinates and immobilizes sperm (44). Formulated into a vaginal film (ZB-06), HCA was recently tested in women in a phase I clinical trial. Not only was the antibody film safe, it effectively eliminated progressively motile sperm in cervical mucus in the post-coital test (45). Multivalent variants of HCA, which are 10–100 times more potent than the parent HCA IgG mAb, are currently being developed for potential use as second generation mAbs in contraceptive films and intravaginal rings (46). Mabs directed against other sperm antigens, originally identified as contraceptive vaccine candidates (47), are also in development.

Use of combinations of mAbs

A combination product incorporating mAbs against various STI pathogens and contraception targets such as sperm can take advantage of the specificity and safety profile of mAbs while maintaining the breadth required for a useful MPT. Mab combinations provide a suite of products that can be applied systemically or topically in fast- or extended-release formats to cover a gamut of delivery modalities and dosage regimes. For example, combining the film products from the MB66 and ZB-06 trials as a preventive for HIV, HSV and unintended pregnancy is an exciting avenue for the future of MPTs.

Reducing barriers to mAb MPTs

The barriers to widespread use of mAbs for infectious diseases and contraception include high cost, manufacturing challenges and limited delivery methods. Most mAbs are currently used in developed countries and current mAb production costs range between $95 and $200 /g (48). The WHO advises that costs need to decrease to <$10 /g to make mAbs feasible for use in developing countries. Advances in antibody engineering that increase antibody potency and extend serum half-life, and novel

mAb manufacturing platforms and delivery methods will reduce the cost and promote the feasibility of mAb MPTs. In addition, exploration of antibody features computationally can guide antibody engineering.

Advances in mAb engineering

Antibodies are well-studied molecules with many potential avenues for improvement. There are two main defined areas in which antibodies can be engineered: the antigen-binding fragment (Fab) and the crystallizable (constant) region (Fc) that interfaces with the immune system.

Engineering the Fab region

In the Fab region, antigen-binding sites on two Fab arms specifically recognize distinct areas (antigenic epitopes) on molecules or portions of molecules. The Fab region can be modified to increase the strength of the interaction between antibody and antigen (affinity and avidity), and/or to enable each Fab arm to bind to a different antigen (bi-specificity).

Increasing affinity with directed evolution

Engineering mAbs for greater affinity to antigen enables the use of lower mAb doses to achieve similar therapeutic effects, thereby lowering the cost. Protein engineering efforts to increase the affinity of natural antibodies have made great advances in the last decade, particularly as directed evolution platforms such as phage and yeast display increase screening capabilities. These automated platforms and systematized screens of millions of variants reduce the cost and labor involved with panning for higher affinity variants. Using these techniques, MedImmune improved an existing RSV monoclonal antibody known as palivizumab, resulting in a 70-fold higher affinity for antigen and 18-fold more potent neutralization of RSV *in vitro* (49). This improved mAb, called motavizumab, was compared to its parent antibody in a non-inferiority clinical trial, where it was deemed superior to its parent antibody with a 50% relative risk reduction in medically attended infections in children (50). Furthermore, the use of machine learning to inform variant selection even further reduces costs and labor associated with generating higher affinity antibodies from a parent sequence (51, 52). For example, a deep learning approach was recently used to select more potent variants of trastuzumab, a mAb used for cancer therapy (53). Applying such efforts to known STI and contraceptive mAbs could supercharge their affinities and reduce the doses required to observe therapeutic activity.

Increasing avidity with multivalent mAbs

While affinity describes the strength of a one-to-one molecular interaction, avidity describes the total binding strength between antigen and antibodies which have two or more antigen binding sites. The relationship between the number of binding sites on an antibody and its avidity is not a linear multiplier due to spatial effects from the first site of binding that affect subsequent binding events. The classic analogy for avidity is Velcro, where individual interactions can be weak, but many interactions together are much stronger than the sum of the individual interactions. Thus, the addition of more binding sites can supercharge the potency of a monoclonal antibody drug, and result in lower doses for the same therapeutic value. For example, the multimerization of the HIV mAb PGDM1400 showed a 40-fold improvement in neutralization (54). Avidity effects are also important for neutralization because the strength of bivalent or multivalent interaction between antigen and antibody are such that binding is irreversible on a biologically relevant timescale (55). In addition, many Fc effector functions are dependent on avid binding and clustering of antibody such as complement deposition, which is greatly enhanced by hexamerization of IgG (55).

Multivalent antibodies are developed in two different ways. The first is to mimic natural antibody isotypes that have more than two Fab arms, such as IgA (4 Fabs), and IgM (10 Fabs). The second is to engineer novel constructs with additional Fab regions on an IgG backbone. Using scaffolds that mimic nature enables a robust safety profile, and reasonable predictions of Fc functions, while using novel constructs requires more robust characterization of the immune response since there would be no natural analog molecule to guide predictions. Some novel scaffolds attach additional Fab arms to the Fc region, potentially inhibiting Fc function due to steric hindrance, while others add additional Fc regions to supercharge oligomerization of antibody to lead to enhanced Fc receptor crosslinking (56).

One such method, widely used to increase mAb valency, is the fusion of the IgM tailpiece to an IgG1 sequence, leading to multivalent structures that efficiently recruit complement binding (56), as well as an optimized C575S variant to reduce spontaneous hexamerization (57). Another method is the HexaBody method, where the IgG heavy chain is mutated to lead to concentration-dependent oligomerization on cell surfaces (56). Currently, 20 IgM-like antibodies are in clinical development (58). Many of these candidates have had limited regulatory success due to lack of specificity and binding strength because they have not been optimized beyond the germline sequence (58). To address these shortcomings, newer multivalent mAbs are built from optimized, potent IgG sequences. For example, 33C6-IgM, a class-switched version of an HIV antibody, was prophylactically administered to rhesus macaques and resulted in protection from high dose viral challenge (59). In addition, DH1017.IgM, a neutralizing IgM against Zika virus, demonstrated a 5-fold reduction in dose required for prophylaxis in mice than its IgG counterpart (60).

Increasing breadth and avidity with bi- and multi-specific mAbs

Increased avidity and breadth can be achieved with bi- and multi-specific antibodies that target multiple antigenic epitopes on the same protein. IgG mAbs typically have two Fab arms that bind to the same antigen. However, the natural IgG structure can be modified so that each Fab arm binds to a different epitope.

This can be a different epitope on the same protein, or an epitope on an entirely different protein. This modified structure can be helpful when targeting a single epitope does not lead to clinically efficacious antibody activity, or to increase the breadth of an antibody to achieve coverage of additional pathogen variants. In the MPT field, this can be helpful for prevention of genetically diverse pathogens, such as HIV or gonorrhea that historically have become resistant to antiviral and antibacterial drugs respectively.

These recombinant bispecific antibodies (bsAbs) are generated in two different classes—those lacking an Fc region and those containing an Fc region (61). BsAbs lacking an Fc region are often fusion proteins of antibody fragments (scFvs or Fabs) or single chain antibodies (VHHs). BsAbs containing an Fc region are more complex to synthesize, with many different possible structures. Some notable structures include a knob-into-hole structure, which looks like a typical IgG with two different Fab arms, a C terminal fusion, where a Fab region is fused onto each Fc chain, and an N terminal fusion, where there are two different antigen binding regions on each Fab arm (62). There is a significant overlap between increasing breadth and increasing multivalency because many bsAb constructs, including the N and C terminal fusions, have more than two Fab regions total. The targeting of multiple epitopes can enhance avidity, especially for sparse epitopes where binding multiple sites of the same epitope may not physically be possible. HIV is one such example, where it is estimated that only 14 HIV Env proteins are on each virion (63). In addition, the use of bsAb constructs in multivalent structures can enable a huge range of different ratios between the different Fab regions that can be tuned with transfection ratios in production.

Historically, a challenge in widespread adoption of bsAbs is quality control in production. Typical production platforms use co-transfection of two different heavy and light chains encoding two different Fab arms, but this can lead to variable expression because both the homodimer and the heterodimer can be produced, and because the expression of the four different antibody chains may not be equal (62). Purifying these mixed populations of antibody is difficult and adds additional costs to manufacturing. Fusion of antibody fragments that do not contain Fc regions partially addresses these manufacturing constraints, since a single continuous sequence can be transfected with no assembly required.

Currently, 85 bsAbs are in the clinical development pipeline, mostly for the treatment of cancer and autoimmune disease (61). An example of a potential bsAb that may be useful in an MPT product is bispecific HIV mAb, 10E8V2.0/iMab, which binds both CD4 and HIV-1 gp120. This bsAb demonstrated great breadth and potency, neutralizing 118 different pseudotyped HIV strains at an IC50 of 0.002 μg/ml (64).

Modeling antibody Fab parameters computationally

Biophysical models of antibodies use input parameters such as number of antibodies bound per cell, crosslinking rates, and surface antigen density to understand how binding of antibody can lead to downstream signaling (65). This modeling paradigm has been applied thoroughly in cancer immunotherapy to understand how best to deliver antibody drugs, and what affinity ranges are best for particular antigens. These insights can be extended to the fields of infectious disease and immunocontraception to understand how best to optimize antibodies for neutralization, mucus trapping, complement lysis, phagocytosis, and agglutination. Some of these methods have been applied in the field of mucus trapping, where it has been demonstrated that multiple antibodies binding to a single virion is required for trapping, and low affinity bonds between Fc and mucin are instrumental in trapping virus (66). Extending these analyses to other functions of antibodies could lead to a mechanistic understanding of what antibody parameters are important to design improved prophylactic antibodies.

Engineering the Fc region

The Fc region governs several antibody functions. Sequences in the antibody Fc region can: (1) bind to classical Fc receptors (FcR) on immune cells such as FcγR1, FcγRIIa/b and FcγRIIIa, enabling them to mediate antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC), mechanisms that inactivate and clear pathogens and infected cells; (2) bind to TRIM21, a cytosolic high-affinity FcR that functions to degrade antibody-bound viruses, a process called antibody-dependent intracellular neutralization (ADIN); (3) bind to the neonatal FcR (FcRn), a cytoplasmic receptor expressed by many cell types including mucosal epithelial cells and endothelial and placental cells, that plays a role in IgG transport and recycling; and (4) bind to C1q in serum and initiate the complement cascade which leads to the lysis and clearance of pathogens, infected cells and noninfected target cells, a mechanism called complement dependent cytotoxicity (CDC). In addition, the Fc region has been implicated in trapping of sperm and pathogens in mucus (67, 68). Thus, several functions and pharmacokinetic profiles of mAbs are dependent on distinct features in the Fc region and specific interactions with various receptors and proteins in tissues, mucus and serum. Many approaches including phage display, alanine scanning mutations and structure-based design have been successful in optimizing Fc functions of mAb-based biologics.

Increasing mAb serum half life

Increasing the half-life of mAbs is a major consideration for MPT products. The ideal mAb would have a predictable, consistent, and long half-life in serum or mucosal secretions. Currently, most mAbs are produced with similar human IgG1 backbones; point mutations of that backbone are explored for potential enhancement of pharmacokinetic properties. The site that has received the most attention is the region that interacts with FcRn. FcRn extends the half-life of IgG by reducing lysosomal degradation in endothelial cells and immune cells, and mutations that increase the stability of the Fc:FcRn interaction can increase the half life of mAbs in serum. An early

prototypical mutation to the FcRn binding site that extended IgG half-life nearly four-fold was the YTE mutation (M252Y/S254T/T256E). However, the YTE modification has lower thermal stability and lower ADCC potential compared to antibodies containing the native Fc domain. LS (Met428Leu Asn434Ser) is a currently popular Fc mutation that increases binding to FcRn and enhances circulating mAb half life several-fold (69). This mutation has been applied to many clinically relevant mAbs, including HIV bnAbs VRC01 and PGT121, where the LS mutation was found to increase half-life 4.7 and 2.9 fold, respectively (70, 71). Additional mutants, such as the quadruple mutant, Ser298Ala, Glu333Ala, lysine 334 alanine (Lys334Ala), and Asn434Ala, known as the AAAA mutant, have also been introduced to extend mAb half-life (61). For systemically delivered mAbs, these mutations can reduce the intervals between dosing and thus reduce cost. For mucosally delivered mAbs, additional characterization of pharmacokinetic profiles of these mutant Fc regions can inform variant selection, since the expressed Fc receptors may be in different proportions, and mucin-binding will also play a role in clearance of the mAb.

Modulating Fc receptor and C1q binding

Antibody engineering has introduced numerous strategies to optimize the ability of Fc to bind to FcRs and C1q. At least 27 Fc modifications have been described that enhance FcγR binding, and 10 modifications have been described that enhance CDC (69). The HIV prevention field is exploring the impact of such Fc modifications on HIV infection in animal models and clinical trials; it is possible that some of these modifications will boost the efficacy of mAb-based MPTs. In addition, Fc mutations that ablate Fc functions are also being explored for some applications to reduce the risk of inflammation and antigen presentation associated with ADCP and complement activation (69).

Cost-effective mAb manufacturing platforms

Big constraints on using monoclonal antibodies as MPTs are cost and manufacturability. The cost to the end-user needs to be affordable, and large quantities of the drug product need to be produced at clinical grade. It is estimated that global demand for a mucosal MPT based in mAbs would require 2 metric tons of antibody production annually (48). Innovations in mAb manufacturing in the last decade have contributed significantly to reducing costs and scaling production. Currently, mAbs can be produced in cell lines in bioreactors, and in transgenic plants.

Mammalian cells

Mammalian cell lines, including Chinese Hamster Ovary (CHO), murine myeloma NS0, and Human Embryonic Kidney-293 (HEK293) cells, have been used to produce mAbs for clinical use. These cells are grown in suspension, continuously stirred, and perfused with fresh media. Antibody is directly secreted into the culture media, which is collected and purified, typically about 1–10 grams/L (48). A potential pitfall of the CHO and NS0 cell lines includes aberrant glycosylation, and the lack of ability to produce α(2–6)-sialic acid residues on mAbs (72). These cell lines can be genetically modified to affect their glycosylation to modify effector function. For example, producing antibodies with afucosylated N-glycans by inactivating the Slc35c1 and FUT8 gene in CHO cells allows for enhanced interaction with Fc receptors (61). Human cell lines do not produce aberrant glycoforms but viral contamination is a concern. Costs are highly dependent on scale of production, varying from 26 to 134 dollars per gram (73).

Transgenic plants

Transgenic plants provide another platform for mAb production and have several advantages. These plants are transiently transfected with DNA encoding the mAb of choice, grown in green houses, then the leaves are collected and mAb is purified. Using RNAi or genome editing, the native glycosylases that encode fucosylation and xylosylation have been knocked out to obtain more human like glycoforms (74). These glycoengineered plants produce more functional mAbs, with higher ADCC activity and enhanced Fc receptor binding (74). They are quite cost-effective, reaching mg mAb per kg yields, require no cold chain, are highly scalable (48, 74). HIV mAbs have been produced at scale using plant platforms, in particular VRC01 and P2G12 (7, 75). Antibodies used in the MB66 and ZB-06 MPT clinical trials were produced in nicotiana plants and were deemed safe and effective (7, 45).

Other systems

Other production systems, including bacteria, yeast, and insect-derived cell lines have been explored for their utility in recombinant protein production. However, the mAb glycoforms that result are different from human glycans and likely immunogenic. Glycoengineered yeast, such as *P. pastoris,* result in a more human-like glycoform profile, while maintaining a high yield around 1.6 g/L of culture. Fungi have also been investigated as a potential production platform, with yields around 24.5 g/L of culture, though glycoengineering efforts remain ongoing for this species (48).

Optimizing mAb delivery

Systemic administration

Most clinical mAb therapies use parenteral administration [i.e., intravenous (IV) infusions or subcutaneous (SC) injections]. The recent Antibody Mediated Prevention (AMP) trials delivered 10 mg/kg or 30 mg/kg of anti-HIV mAbs by IV infusion every 8 weeks for a total of 10 doses for HIV prevention. The advantage of IV infusions is the rapid delivery of large amounts of antibody

into the systemic circulation. Pharmacokinetic studies indicated that the maximum antibody titer was achieved in blood within 8 h, and effective antibody titers persisted for 8 weeks. However, these trials also showed that only a fraction of the systemically infused antibody appeared in genital or rectal secretions where protection is needed (0.4% to 28% of serum levels) (76), indicating that systemic infusion may be too expensive and ineffective for the delivery of MPTs. Extravascular mAb injections [SC or intramuscular (IM)] are also used for some applications. Because of the limited solubility of IgG (about 100 mg/ml), and the fact that only small volumes of antibody solution can be administered via SC and IM routes (2.5 ml and 5 ml per injection site, respectively) these approaches are usually reserved for very potent antibodies. However, SC and IM administration is more convenient and less costly than IV infusions as they can be self-administered or administered by a healthcare professional and do not require hospital services.

Topical application

The MPT field has pioneered topical delivery of mAbs. This approach empowers women and men to deliver mAbs directly to the mucosal surfaces (e.g., vaginal, rectal, and penile mucosa) where they are needed and requires much lower antibody doses (e.g., 20 mg/dose for vaginal films vs. 1,000 mg/dose for systemic immunization) (7, 45). In this section, we review strategies to incorporate mAbs into gels, solid micro or nanoparticles, liposomes, micelles, or emulsions to improve their stability and release kinetics. Employing multiple strategies in tandem is also possible and can enable the delivery of multiple mAbs and antiviral drugs with different release rates and durations.

To deliver mAbs topically, the physiology of the vaginal, rectal, and penile mucosa must be considered. Broadly, mucosal surfaces protect and lubricate the underlying epithelial layer. Vaginal mucus is a constantly regenerating 50-micron layer mostly comprised of hydrated (around 95% water) negatively charged glycoproteins (cervical mucins) at a normal pH range of 4–5. This mucus composition and volume are affected by reproductive hormones and stage of the menstrual cycle (77, 78). In contrast, the colorectum contains a firmly adherent mucus layer and a thick, loosely adherent mucus layer at a pH of 7–8 with a different proportion of mucin glycoproteins with slightly different viscoelastic properties than cervical mucus (79). Additionally, gastrointestinal conditions like ulcerative colitis and Crohn's Disease lead to increased mucus secretion and decreased adherent mucus in the colorectum, causing difficulty in delivering drugs unless they can easily cross through the mucus layer (79, 80). The penis is covered in skin, but has mucosal surfaces at the opening of the urethra and the inner foreskin (81).

Dissolvable films and Gel formulations

There is already a precedent for using hydrogels and dissolvable polymer matrices to prevent HSV-2 and HIV transmission through the delivery of small-molecule antiviral drugs such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF) and elvitegravir (EVG) to the vagina or rectum (82–85). The first human clinical trial to topically deliver mAbs to the vagina was the MABGEL trial which delivered three HIV mAbs, 2F5, 4E10, and 2G12 in 2.5 ml of gel. The antibodies were well tolerated and persisted in vaginal secretions for up to 8 h. Recently, mAbs have been delivered topically via hydrophilic dissolvable films. Two relevant polyvinyl alcohol (PVA)-based dissolvable films containing mAbs have recently been tested in phase 1 clinical trials: MB66, a film, delivering mAbs against HIV-1 (VRC01-N) and HSV-1/2, (HSV8-N) (7, 45), and ZB-06, a film containing an antisperm antibody (HCA) for contraception (45). The mAbs delivered in film were also well tolerated and persisted in an active state in vaginal secretions for up to 24 h.

Biodegradable polymer matrices

To create an effective MPT, it may be important to extend the drug release time. One well-researched sustained release strategy involves incorporating drugs into biodegradable micro or nanoparticles. The gold standard material in this context is the copolymer PLGA, which has been used in the delivery of peptides like Leuprorelin (Lupron) (86). PLGA undergoes bulk erosion through hydrolytic degradation. Over time, the drug diffuses out as PLGA breaks down into its constituent glycolic and lactic acids. The ratio of these constituents and the copolymer structure (e.g., random, block, alternating) create regions of varying hydrophobicity, directly affecting the release profile of the encapsulated drug. For instance, a higher ratio of lactic acid enables longer degradation and release profiles due to its increased hydrophobicity. A new approach integrating nanomedicine and film technology for extended drug release was recently described. An HIV integrase strand transfer inhibitor, MK-2048, used for HIV prevention, was incorporated into poly(lactic-co-glycolic acid) (PLGA) nanoparticles, and the nanoparticles were delivered in a PVA—PEG (polyethylene glycol) film to female macaques. This new delivery system introduced more drug to the vaginal mucosa, and PK studies indicated sustained release for up to 3 weeks in vaginal secretions (87). This approach could potentially be used to extend the release of MPT mAbs at mucosal surfaces. However, it is important to consider the fabrication method of PLGA particles as it typically uses organic solvents, high salt concentrations, or high energy mixing. These harsh conditions could affect some drugs' stability and encapsulation efficiency (88). Rigorous planning, design, and validation must be employed to ensure post-encapsulation activity and release profile of mAbs.

For vaginal delivery, mucoadhesive nanoparticles (MHNP) are the most studied. MHNPs bind to the mucosa through electrostatic interactions, physical entrapment, or chemical binding. MHNPs can be coated with or natively consist of a variety of positively charged, hydrophilic polymers like chitosan, or stimuli-responsive polymers like poly(methacrylic acid-co-butyl methacrylate) or poly (4-vinylphenylboronic acid) (89). Although mucoadhesion is efficient at delivering a drug to the vagina, for

sustained release mucus-penetrating nanoparticles (MPNP) would be a better option due to high mucus clearance rates. Both surface charge and particle size influence the ability for particles to penetrate mucus. In contrast to mucoadhesives, nanoparticles in the range of 200–500 nm readily diffuse through major pores formed by mucins and glycoproteins in cervical vaginal mucus (CVM), whereas particles around 100 nm tend to become trapped in or slowed down by smaller channels (90).

Biodurable polymer matrices

A common method of delivering drugs is through physical encapsulation and diffusion through biocompatible non-degradable, or slowly biodegradable polymers. Contraceptive hormones are often delivered by intravaginal rings (IVRs), subdermal implants, and intrauterine devices (IUDs). The NuvaRing® (etonogestrel/ethinyl estradiol IVR, poly(dimethylsiloxane) (PDMS)), Nexplanon® (etonogestrel implant, poly(ethylene-vinyl acetate) (PEVA)), or Mirena® (levonorgestrel IUD, PDMS) are among the most popular and most effective contraceptive methods on the market today. Some HIV pre-exposure prophylaxis (PrEP) drugs are also delivered by IVRs made from thermoplastic polyurethane (TPU), PDMS, or ethylene-vinyl acetate (EVA) (63). Recently, more exotic materials like Poly(glycerol sebacate) urethane (PGSU) have been used to deliver both hydrophilic 4′-ethynyl-2-fluoro-2′-deoxyadenosine (EFdA) and hydrophobic levonorgestrel (LNG) at once (91) Translating these devices directly into an MPT, combining both contraceptives and anti-STI drugs, including mAb-based MPTs, might be more straightforward than any other methods, and research efforts are already underway (91–96).

Silicone elastomers (crosslinked PDMS, TPU, and PEVA) are the most commonly used biodurables in this field as they are bioinert, highly elastic, and have long therapeutic lifetimes. Though biodegradable options like poly(caprolactone) (PCL) or solid PLGA or PLA (poly-(lactic acid)) are also biocompatible and release drug, they do not have the same elastic properties (91, 94). Biodurable elastomer-based devices deliver drugs through diffusion out of the polymer matrix, instead of surface or bulk degradation. The degree of crosslinking in these elastomers is inversely proportional to their pore size, though, in general, more favorable mechanical properties (i.e., higher modulus of elasticity) occur in elastomers with a higher crosslinking ratio. Consequently, this tight mesh inhibits the diffusion of larger macromolecules like proteins or antibodies. Additionally, the delivery of hydrophilic drugs like mAbs is challenging as they do not readily diffuse through hydrophobic matrices like silicone and PEVA (96). These properties make creating a mAb delivery device from common IVR elastomers challenging. To remedy this, there has been research into hybrid silicone IVRs with biodegradable polymer "pods" or cores that deliver larger hydrophilic drugs, including mAbs, circumventing the pore size and hydrophobicity problems in single material elastomer IVRs (92–96).

Liposomes, micelles, and emulsions

Liposomes are vesicles made from a bilayer of amphiphilic molecules, typically phospholipids, with an aqueous core. In liposomal formulations, the drug payload can be encapsulated in the hydrophilic core, entrapped in the hydrophobic membrane, or attached to the surface. Micelles are formed from a monolayer of amphiphiles with a hydrophobic core. In contrast, reverse micelles contain a hydrophilic core and hydrophobic shell. Interestingly, reverse micelles can be packaged as a colloidal dispersion in non-polar solutions, like oils or silicone (PDMS) oils, and deliver hydrophilic drugs, like antibodies. The primary purpose of these systems is to extend drug release by protecting the encapsulated drug from degradation and from premature clearance in systemic delivery systems. Emulsions on the other hand are complex fluid suspensions constituting two or more immiscible phases, like oil and water or silicone and water, stabilized by surfactants. These surfactants are amphiphilic molecules that reduce interfacial and surface tension by adsorbing to the liquid interfaces (97).

Liposomal solutions are versatile pharmaceutical delivery systems used to deliver a wide range of drugs. In 2021, the FDA approved Pfizer-BioNTech's COVID-19 vaccine, the first liposomal mRNA vaccine (98). Liposomes are typically employed systemically to control the timing or targeting of drug release. Liposomes need to first be engulfed by cells and broken down to release their payload. Immunoliposomes are a type of liposome decorated with ligands, like antibodies, to target delivery of their encapsulated payload (98). Importantly, standard liposomes might not be appropriate for topical MPT applications unless there are stimuli-liable groups (e.g., pH, temperature) within the liposome membrane to destabilize and rupture them before being engulfed. Due to the commercial importance of liposomes in pharmaceuticals, utilizing them in the MPT space may be simpler than other options.

Common strategies for formulating liposomes are relatively simple and scalable. These amphiphilic systems self-assemble in water through agitation and evaporation of solvents, encapsulating aqueous drugs (98). There are no FDA-approved mAb-encapsulating liposomes, however. Traditional liposome fabrication methods can lead to the denaturation and instability of proteins and mAbs at hydrophobic interfaces or in organic solvents, like in nanoparticle synthesis. To improve on these problems, recent strategies like Supercritical Assisted Liposome Formation (SuperLip), utilize supercritical carbon dioxide to mix and expand a solution of ethanol and phospholipids before atomizing the solution into an aqueous antibody solution. This method precipitates uniform antibody-encapsulated liposomes, avoiding the high energy mixing used by other methods that cause antibody denaturation (99).

Micelles and emulsion-based systems offer a potential topical delivery mechanism through incorporating mAbs in creams or gels. As of now, there are no FDA-approved mAb-encapsulated micelle or emulsion-based systems, although there are FDA-approved emulsions containing peptides like cyclosporin (Gengraf and Sandimmune Neoral) which could serve as a template for incorporating mAbs instead (97). However, traditional top-down micelle and emulsion fabrication methods require high-energy mixing, which could disrupt and denature mAbs. To ensure stability, bottom-up strategies could be employed instead. Microfluidic mixing and hydrodynamic focusing or liquid antisolvent precipitation could be used to minimize the physical disruption of mAbs (100–102).

Use of DNA and RNA for delivery of mAbs to the female genital tract

DNA

DNA delivery systems induce durable mAb production that can reduce production costs. One approach, recombinant adeno-associated virus (rAAV)-mediated antibody gene delivery, provides an innovative means to achieve passive immunization. In this case, rAAV vectors can accommodate large sequence inserts such as a mAb sequence, and can infect a variety of tissues but do not have the viral elements necessary for replication. rAAV-based gene sequences in cells are long lived and do not integrate into nuclear DNA. This approach has recently been used in two clinical trials: (1) Genes encoding the PG9 broadly-neutralizing mAb were introduced by rAAV1 to human volunteers via intramuscular injection; the treatment was well tolerated and durable antibody production was detected (103). (2) Genes encoding the VRC01 bNab were introduced by rAAV8 vectors to adults living with HIV; this treatment was also well tolerated and bioactive antibodies were detected in some individuals up to three years after injection. The antibodies, however, had no effect on CD4 cell count or viral load (104). An earlier study showed that delivery of AAV-vectored HIV mAb genes to the vaginal mucosa of rhesus macaques produced antibodies in vaginal secretions out to 3 months (105). Another recent study used electroporation to deliver a gene encoding the 2C7 mAb against neisseria gonorrhea to mice, and observed 60 days of serum expression of the mAb, as well as complement engagement that cleared acute and re-challenge infections over a 9 week period (106). These studies provide encouraging indications that DNA-vectored antibodies might be used for mucosal delivery of MPT antibodies.

mRNA

mRNA delivery systems offer several advantages such as flexibility, rapid production and low cost, and the recent success of COVID-19 mRNA vaccines makes a strong case for mRNA safety and efficacy (107, 108). Direct delivery of mRNA encoded mAbs to vaginal and rectal mucosa may enable lower doses of antibody (107). When mRNA encoding bnHIV mAbs was delivered directly to the sheep vagina, doses of 750 μg mRNA led to an average of 40 μg/ml antibody in vaginal secretions over 28 days, with a maximum of 210 μg/ml (107). With mRNA delivery systems, the manufacturing challenges associated with IgA and IgM production are bypassed and the generation of bi- and tri-specific antibodies can be a question of co-delivery. This platform can be harnessed to combinatorically enhance protection. For example, an IgM hexamer that includes two separate antibodies against a pathogen could reduce the ability of a pathogen to escape by mutation of a surface protein. There are many exciting, as yet unknown, constructs that mRNA delivery can enable, exceeding the combinations possible with traditional mAb production techniques.

Self-amplifying RNA, mRNA sequences that include a viral RNA-dependent RNA polymerase complex, is further amplified after entering the cell (109). This enables lower dose vaccinations (0.01 μg for a SARS-CoV-2 vaccine candidate, compared to Moderna's conventional vaccine at 100 μg per dose) and can also enable lower doses for passive immunization efforts (109). With near thousand-fold lower doses needed, the multiplexing of antibody delivery could go extremely far, creating MPTs that include numerous antibodies per pathogen, covering multiple epitopes and variants, to avoid the development of resistant pathogens that are able to escape the antibodies. Such a product would be the ultimate mimic to nature's passive immunization via breast milk—harnessing the way genetic diversity in nature protects from infection with antibody repertoires instead of single mAbs (110).

Conclusions

MAb-based MPTs hold exceptional promise. Their advantages include safety, efficacy and combinatorial flexibility. Disadvantages include high production costs and limits to scalability which are being addressed by new production and delivery systems. Rapid developments in the MPT field have been fueled by extraordinary dedication of scientists and support from private foundations and government institutions, but the field awaits industry involvement to usher new MPT products to market.

Author contributions

SD: Writing – original draft, Writing – review & editing. MG: Writing – original draft, Writing – review & editing. JP: Writing – original draft, Writing – review & editing. DA: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Key programmatic and policy considerations for introducing multipurpose prevention (MPT) methods: reflections from healthcare providers and key stakeholders in South Africa

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Introduction: Multipurpose prevention technologies (MPTs) simultaneously prevent HIV, other sexually transmitted infections, and/or unintended pregnancy. Key gatekeepers, [healthcare providers (HCPs) and key stakeholders] require proactive engagement before product implementation. This manuscript identifies HCP demand creation strategies, key stakeholder considerations for the adoption of MPTs in South Africa.
Methods: Formative research was conducted in three districts in three South African provinces (July to November 2022). Nurses initiating oral PrEP at facility and mobile study sites participated in 4-hour participatory workshops, exploring HIV prevention, including MPTs, demand creation strategies, and preferred MPTs training packages. Activities were observed, transcribed, and thematically analysed. Five online in-depth interviews (IDIs) with Key informants (KIs) (National/district programme implementers and technical leads) and one in person, exploring key programmatic and policy considerations for MPT adoption. IDIs were approximately 40 min long, audio recorded, transcribed, and thematically analysed.
Results: Twenty-one Professional Nurses completed workshops: 19 female. Six IDIs were conducted with 4 Facility Managers, 1 NDoH representative and 1 DoH Provincial Deputy Director. All participants were females, aged 30–60+ years with >10 years' in SRH/HIV policy/advocacy/research. Community conversations and information at the clinic were the best MPT demand creation methods among HCPs. KIs identified five considerations for future MPT implementation: HCP training; demand creation and messaging; existing PrEP policy amendments; preparing users for additional choice; and sustaining MPT provision.
Conclusion: Contraceptive implant and oral PrEP implementation lessons learned should be proactively considered when preparing for MPT introduction. HCP training and demand creation are of particular importance before MPT introduction.

KEYWORDS

healthcare providers, multipurpose prevention methods, MPTs, South Africa, multipurpose prevention technologies, policy considerations, programmatic considerations

1 Introduction

In South Africa, HIV prevalence among young women in their early 20's is 9.1%, three times more than that of their male counterparts (1, 2). Adolescent girls and young women (AGYW) (15–24 years) have the highest HIV incidence (1.51%) (3). In addition to HIV, there is also a substantial burden of unintended pregnancy and sexually transmitted infections (STIs) in this population group. A Unitaid-funded PrEP Project working across four South African sites since 2018, led by Wits RHI, found that a third of AGYW were not using contraception at their first visit, when they were initiated on oral PrEP (4). In the same study, among a sub-set of PrEP clients tested for STIs, approximately a third had a curable STI (5).

Since 2017, oral Pre-Exposure Prophylaxis (PrEP) has been made available in South Africa seeking to prevent HIV infection (6). Integrated into sexual and reproductive health (SRH) services in 3034 primary healthcare public health facilities nationwide, 658 885 individuals had been initiated on PrEP, as of July 2022 (7). Effective use of oral PrEP has been proven to reduce HIV infections, however, maintaining adequate continued use remains a significant challenge for HIV prevention (8, 9). Barriers to effective PrEP use include fear of disclosing PrEP use to partners, daily pill fatigue, and stigma associated with pill taking when PrEP is misidentified as antiretroviral therapy (ART) (9–11).

PrEP programmes have shown an unmet need among AGYW, not only for HIV prevention but also for contraception (4, 12) and sexually transmitted infection (STI) diagnosis and management (13). In 2014, the subdermal contraceptive implant was introduced in South Africa, expanding the contraceptive method mix and availability of long-acting reversible methods in the public sector (14). However, data shows almost a 50% drop in insertions year on year (15), and the media reported that early implant removals were common and healthcare-provider resistance to women wanting to remove it was a challenge (16).

Multipurpose prevention technologies (MPTs) are products designed to simultaneously prevent HIV, other STIs, and/or unintended pregnancy (17–19). MPTs may address some of the barriers that currently exist around PrEP (20) and contraception use (2, 21). There are several MPTs in development, ranging from pre-clinical to clinical phase, each adopting a different delivery method (long acting injectables, oral pills, vaginal rings and films, implants, and transdermal compounds) (18). An implant has the potential to offer longer-term, reversible protection; however, noting that the contraceptive implant is not widely used in South Africa, and the challenges with its initial roll out in the country, early engagement with stakeholders is critical. The hypothetical MPTs of interest in this study were the one-year or two-year non-biodegradable, biodegradable and refillable subcutaneous implants, providing simultaneous prevention against HIV and pregnancy. These MPTs are not currently available.

Healthcare providers (HCPs) are key gatekeepers at various levels of health system governance and healthcare service provision (22). In South Africa, HCP attitudes are a known barrier to healthcare uptake (23) but evidence shows that actively engaging them when planning and implementing major health programmes improves both health outcomes and the health system (24, 25). Lanham et al. (2011) researched 113 HCPs at 36 public, private, and non-governmental health facilities in South Africa, Zimbabwe and Kenya that were offering PrEP. HCPs reported that it was challenging to deliver PrEP and SRH services to girls <18 years compared to those >18 because they had negative attitudes about adolescent girls being sexually active. In their review of uptake and early removals of the contraceptive implant in South Africa, Adeagbo et al. (26) found that contraceptive method preferences influenced HCP prescribing patterns for adolescents. Formative research with key stakeholders is key prior to product development and introduction to gain an informed understanding of local populations, socio-cultural norms and practices, and local perceptions, to ensure the introduction of the new products meets the needs and priorities of the end-users (22, 25).

This manuscript presents some of the results from formative research to determine HCP training needs and demand creation strategies to deliver and support the adoption of new MPT methods. We also sought to understand the policy and programmatic considerations for adopting alternative PrEP options from the perspective of key South African stakeholders (facility and district managers and technical leads). This research was part of a larger formative research project aiming to estimate the potential uptake of a hypothetical MPT implant to inform product development (23, 27).

2 Methods

2.1 Study design and setting

This component was a qualitative, descriptive study conducted between July and November 2022, through four workshops with 21 HCPs, and six in-depth interviews (IDIs) with six Key informants (KIs). Workshops were conducted using participatory action research (PAR). PAR emphasizes social change and transformation, active collaboration through participation between the researcher and members of the system, and iterative cycles of action and reflection to address practical concerns (28, 29). PAR is influenced by understanding that the culture, history, and local context of end-users is embedded in social relationships (30).

The study was carried out in three districts in three South African provinces (Tshwane District, Gauteng Province; OR Tambo District, Eastern Cape Province; and King Cetshwayo District, KwaZulu-Natal Province) leveraging the existing geographical footprint of Wits RHI implementation science projects, which are introducing oral PrEP. Each of the sites is in areas with a high HIV burden, with antenatal HIV prevalence ranging from 23% in Tshwane to 35% in OR Tambo (31). KIs were recruited from these three districts as well as from the National Department of Health.

2.2 Study population, recruitment, and sampling

The population for this component of the study comprised of HCPs and KIs.

2.2.1 Healthcare providers

HCPs included in the study workshops were nurses, providing oral PrEP, contraceptive, and SRH services at facility-based and community-based mobile study sites. HCPs were purposively recruited by trained fieldworkers. Those interested were provided with a study overview and what their participation entailed. Willing HCPs were then given the study information sheet and consent form, to review and bring to the workshop. HCPs provided fieldworkers with their contact details, to enable the study team to communicate the day, time, and venue, of the workshop.

2.2.2 Key informant IDIs

In-depth interviews were conducted with KIs, such as Facility Managers of selected study sites, district HIV and AIDS/STI/TB unit (HAST) managers, and PrEP and family planning technical leads at the National Department of Health (NDoH).

Purposive sampling was used to identify KIs, based on their roles in developing and implementing HIV prevention and SRH programmes. Eleven KIs were initially identified, three from each of the sites and two from a national level, seeking to include individuals working across various geographies and in various roles in the health system. Participants were approached via email and provided written, informed consent for participation and an audio recording of the interview.

2.3 Study procedures

2.3.1 Healthcare provider workshops

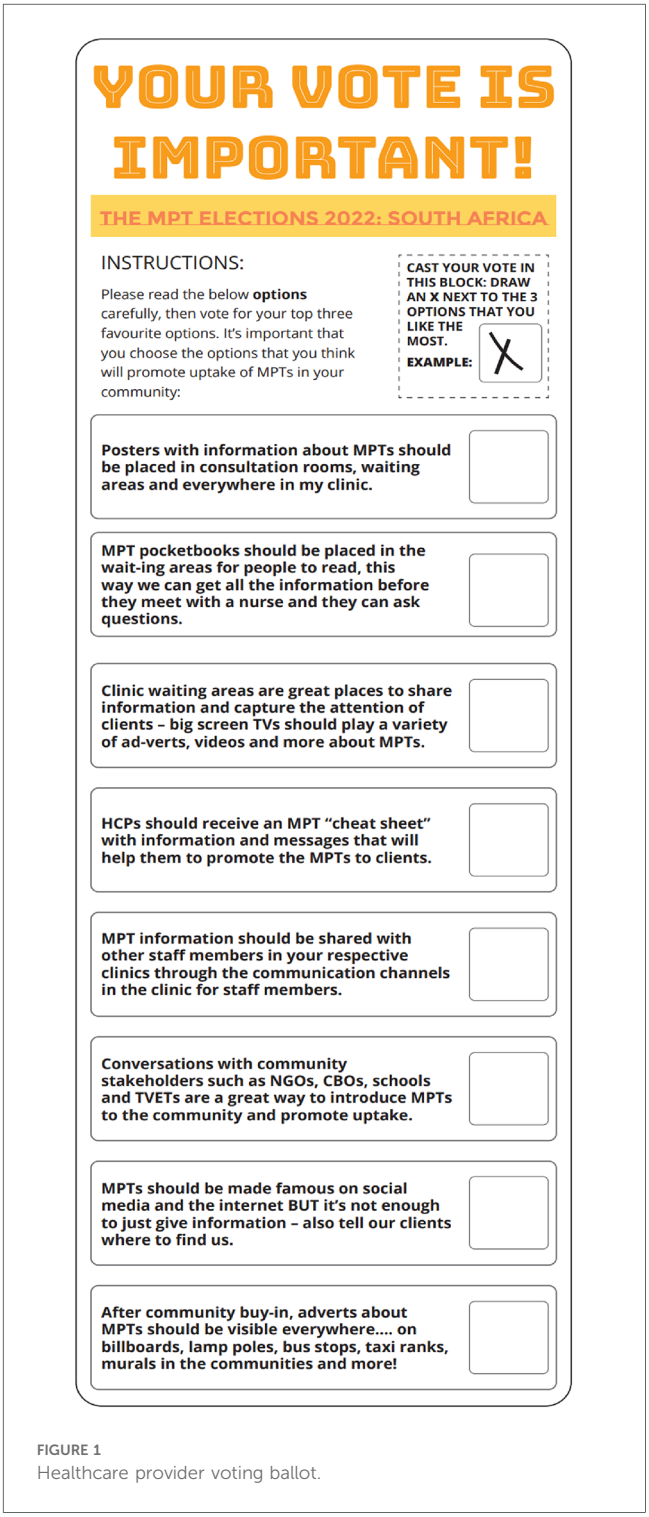
Participants were provided with information on new HIV prevention products and MPT implants. We sought to explore insights on suitable demand creation strategies and tactics to support the uptake of HIV prevention methods (including new MPTs) and to gather insights on the preferred packages for training clinicians on MPTs. One workshop of approximately 4 h was conducted per province with HCPs, with an average of 7 participants in each group. Workshops were held at a community-based site, convenient for participants. They were facilitated in English by the trained study team.

Each workshop was observed by at least two study team members, using an observation guide, which took the observers through a key set of questions for each activity of the workshop. The guide was used to capture the discussion points, participant questions, and reflections and to document the PAR activities. For example, when HCPs were developing their ideal training package, the observers documented participant responses to the facilitator about why they liked that specific training methodology. As partial participants (32), the observers took part in the interactions of the overall workshop but not in the specific PAR activities.

An overview of existing, and future HIV prevention methods as well as the various MPTs in clinical development was presented. Following this, HCPs participated in two PAR activities, demand creation elections and *izikhokho zegame* (skills & knowledge), which are outlined as follows:

2.3.1.1 Demand creation elections

The demand creation elections activity aimed to explore which demand creation tactics would best support end-user uptake of HIV prevention methods (including new MPTs), and to gather insights and build evidence for developing demand creation and social mobilization approaches for future MPTs. The room was set up to simulate a real voting experience, with a voting booth, a voting box and posters. Participants were given a voting ballot paper containing eight potential demand creation tactics for


YOUR VOTE IS IMPORTANT!

THE MPT ELECTIONS 2022: SOUTH AFRICA

INSTRUCTIONS:

Please read the below **options** carefully, then vote for your top three favourite options. It's important that you choose the options that you think will promote uptake of MPTs in your community:

CAST YOUR VOTE IN THIS BLOCK: DRAW AN X NEXT TO THE 3 OPTIONS THAT YOU LIKE THE MOST.

EXAMPLE: X

- Posters with information about MPTs should be placed in consultation rooms, waiting areas and everywhere in my clinic.
- MPT pocketbooks should be placed in the wait-ing areas for people to read, this way we can get all the information before they meet with a nurse and they can ask questions.
- Clinic waiting areas are great places to share information and capture the attention of clients – big screen TVs should play a variety of ad-verts, videos and more about MPTs.
- HCPs should receive an MPT "cheat sheet" with information and messages that will help them to promote the MPTs to clients.
- MPT information should be shared with other staff members in your respective clinics through the communication channels in the clinic for staff members.
- Conversations with community stakeholders such as NGOs, CBOs, schools and TVETs are a great way to introduce MPTs to the community and promote uptake.
- MPTs should be made famous on social media and the internet BUT it's not enough to just give information – also tell our clients where to find us.
- After community buy-in, adverts about MPTs should be visible everywhere.... on billboards, lamp poles, bus stops, taxi ranks, murals in the communities and more!

FIGURE 1
Healthcare provider voting ballot.

raising MPT awareness in their community (Figure 1) and invited to vote for their top three tactics on the ballot. Following the voting, the results were tallied, and each tactic was discussed, allowing participants to share what they liked about the tactic and what they would change.

2.3.1.2 Izikhokho zegame (skills & knowledge)

This activity aimed to establish the training needs of HCPs in relation to a potential MPT, including the resources needed and their preference for receiving training, skills building, and ongoing mentoring. Each HCP was given the opportunity to develop their ideal training package made up of five broad thematic areas (theory, assessment, practical, training others, and mentoring) using a card-sort activity. The training themes were divided into specific elements to illustrate self-learning, in-person learning, different assessment formats, different approaches to skills building and knowledge acquisition, and mentoring approaches.

Each participant was given five colour block cards with the five thematic areas written on them and four sub-element cards for each theme. On their own, participants read through each card and could choose one sub-element for each thematic area. At the end of the activity, each participant was left with a potential training package for MPT introduction that reflected their own needs. The facilitator then led a discussion based on the packages that they built. Figure 2 outlines an example of an ideal training package.

2.3.2 Key informant IDIs

IDIs were conducted and audio recorded via MS Teams by one of the study team members (AK, PM, NM or JM) with master's degrees and trained in qualitative data collection methodologies, the study protocol and research ethics. A structured interview guide was used to guide the discussion, exploring key considerations in adopting new MPT methods, and reflecting on the 2014 contraceptive implant implementation process (14). Each IDI was up to 40 min in duration.

2.4 Data management and analysis

To ensure anonymity of the participants, each participant was allocated a unique identification number. All hard copies of completed data collection instruments were kept in locked storage cabinets, only accessible to the study team. Electronic data were stored on password-protected computers of the study

FIGURE 2
An example of *izikhokho zegame* (skills & knowledge) activity in action, a participants ideal training package.

team. Research activities were conducted predominantly in English however, sometimes, local languages were used by the participants.

2.4.1 Healthcare provider workshops

The two or three observation guides from each workshop were transcribed by each observer and consolidated by either the Researcher (PM) or Associate Researcher (NM), to produce one consolidated observation guide per workshop for analysis. Data were double coded to ensure reliability of coding. Facilitated using NVivo software (33), data from the observation guides were coded deductively to describe and explore preferences for the different demand creation tactics and the training package sub-elements. The different demand creation tactics guided the coding for the demand creation elections. Content analysis (34) was used to analyse the data.

2.4.2 Key informant IDIs

IDIs were transcribed by a fieldworker and then cross-checked for accuracy by the Associate Researcher (NM) and Research Intern (JM). One analysis workshop was held where four study team members (PM, NM, JM, and AK) reviewed the transcripts thematically, identified emerging themes and coded facilitated by the NVivo (33) software. The first round of codes was created through the open coding of one transcript during a workshop, to ensure reliability of coding. Then, using axial coding, these codes were organized into 13 codes. The remaining five transcripts were coded by two study team members (AK and NM). Once all the transcripts were coded, the 13 codes were further grouped into five major themes, namely: "*HCP training*", "*messaging and demand creation*", "*policy considerations*", "*preparing for choice*", and "*sustainability of MPT provision*".

2.5 Ethical approvals and considerations

Ethical approval for the study was granted by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (M220305). Relevant provincial research approval was also granted. Written informed consent was obtained from participants before the workshop began and prior to the IDI. Participants received a signed copy of the informed consent form. HCPs were reimbursed ZAR50 ($2.75) for transport and ZAR200 ($10.95) for participating in the half-day workshop.

3 Results

3.1 Study sample

Twenty-one HCPs from across three provinces participated in PAR workshops (9 in OR Tambo, 8 in King Cetshwayo and 4 in Tshwane). All participants were Professional Nurses working at primary healthcare facilities and 90% ($n = 19$) were female.

Six IDIs were conducted with KIs: 4 Facility Managers, 1 NDoH representative, and 1 DoH Provincial Deputy Director. Participants were all females, ranging from 30 to 60+ years of age. All KIs had more than 10 years of experience in the field of SRH/HIV policy/advocacy/research.

3.2 HCP demand creation elections

The most voted for demand creation tactic for the MPT introduction was to have conversations with community stakeholders (including non-governmental organisations (NGOs), community-based organisations (CBOs), schools, and Technical and Vocational Education and Training (TVET colleges)) (22%, $n = 14$), followed by having MPT information in the clinic waiting areas (19%, $n = 12$) (Table 1). sixteen percent ($n = 10$) of HCPs thought that posters in the consultation rooms, waiting areas and walls of the clinic would be a good MPT demand creation tactic. Only 4 HCP participants (6%) liked the idea of MPT adverts visible everywhere, on billboards, lamp posts, taxi ranks or on murals in the community. None of the HCPs liked the idea of HCPs having a cheat sheet[1] with MPT information and messaging on.

3.2.1 HCP training requirements for the MPT introduction

Table 2 presents the results of the *Izikhokho zegame* activity, as voted by the 21 HCPs.

3.2.1.1 Theory

Over half preferred attending once-a-week in-person training ($n = 11$), with 29% ($n = 6$) indicating they preferred an online theoretical MPT course. The benefits of in-person training included the opportunity to engage with the course instructor and ask clarifying questions, which they felt would be harder online. Those that preferred completing a course online liked the convenience to complete the course in their own time. However, a few challenges were anticipated, these included access to internet data, internet connection challenges, and lack of time to do the training at home after hours. A one-day training was preferred over attending a session weekly. The HCPs' busy schedules meant working through the training alone would be hard.

3.2.1.2 Assessment

Most workshop participants agreed (66%, $n = 14$) that an average of 65%–70% was an appropriate, and attainable, pass mark for the first assessment before doing further training, rather than a pass mark of 85% or writing an open-book exam. Participants indicated that an 85% pass mark was considered high for a new subject and felt that their workload would hamper them from achieving this mark. However, some mentioned that 85% was an appropriate score, using it as a good measure of HCPs understanding of the training content and capability to insert

[1]Also known as a crib sheet, with a concise set of notes, used for quick reference

TABLE 1 Demand creation election results.

Demand generation tactic	Total	
	N	%
Conversations with community stakeholders (NGOs, CBOs, schools and TVETs) are a great way to introduce MPTs to the community and promote uptake.	14	22%
Clinic waiting areas are great places to share information and capture client attention—big screen TVs should play a variety of adverts, videos and more about MPTs.	12	19%
MPT posters should be placed in consultation rooms, waiting areas and everywhere in my clinic.	10	16%
MPTs should be made famous on social media and the internet but also tell our clients where to find us.	8	13%
MPT pocketbooks should be placed in the waiting areas, so patients can get all the information before they meet with a nurse and ask questions.	8	13%
MPT information should be shared with other staff members in the clinics through the communication channels in the clinic for staff members.	7	11%
After community buy-in, MPT adverts should be visible everywhere…. on billboards, lamp poles, bus stops, taxi ranks, murals in the communities and more!	4	6%
HCPs should receive an MPT "cheat sheet" with information and messages that will help them to promote the MPTs to clients.	0	0%
Total number of votes	63	100%

TABLE 2 The ideal MPT training package, as voted by HCPs.

Theme	Sub-element	Total votes	
		N	%
Theory	**HCWs will attend ONE in-person training in their district comprising of theoretical and practical sessions. A training manual with all MPT in-formation will be couriered to selected clinics.**	**11**	**52%**
	Complete an online theoretical course on the MPT. The course concludes with an assessment and if passed will secure your place for further training	6	29%
	An HCW will be required to attend a once-a-week (full day) session facilitated by an MPT specialist at a local college for one month.	2	10%
	HCWs are expected to work through this within a given time frame before completing an assessment.	2	10%
Assessment	**A 65% pass rate is required for the first assessment to move ahead with further training.**	**7**	**33%**
	A 70% pass rate is required for the first assessment to move ahead with further training.	**7**	**33%**
	A formal open book exam will be required as the first assessment with a time limit. The Clinic Manager will oversee the exam at the clinic and send the completed exam sheet to the organizers for formal marking.	4	19%
	An 85% pass rate is required for the first assessment to move ahead with further training.	3	14%
Practical	**HCWs that pass the speed test will receive a certificate of compliance. Thereafter invited to a week-long "on the job training" of how to insert and remove an implant**	**9**	**43%**
	An MPT nurse will visit your clinic once a month to guide you on MPT insertions and removals. As an HCW you will be expected to mobilize at least 4 MPT clients on the day that the MPT nurse visits your clinic.	5	24%
	Pass the minimum score and advance to attend an in-person workshop. The workshop will be a theoretical refresher of the training and focused on practical application. The training will be completed with an exam.	4	19%
	HCW will have to complete an assessment after completing the in-person training.	3	14%
Mentoring	**While studying and applying your knowledge at the clinic, you will have a dedicated mentor who will assist you with clinical enquiries. Submit daily reports to your mentor.**	**7**	**33%**
	The more you report your successes & challenges to your mentor, the better your chances of becoming a national trainer.	6	29%
	HCWs commit to in person check-in meetings with a designated district mentor and will perform an insertion or removal in the presence of the mentor.	6	29%
	HCWs commit to mentoring calls via WhatsApp at least once a month with a clinical mentor.	2	10%
Training others	**HCWs will be expected to use the training manual for training and provide mentorship to other HCWs on how to become fully fledged MPT nurses.**	**10**	**48%**
	HCWs who complete their training and meet their targets will have the honour of recruiting, training and mentoring 2 or more HCWs from their clinic on an ongoing basis.	5	24%
	HCWs who adhere to the training and mentoring requirements will receive an award for exceptional service delivery.	3	14%
	I really don't want to train others.	3	14%

and remove the MPT implants. The open-book exam was viewed as time-consuming, as HCPs were preoccupied with work. Practically, they also mentioned that Clinic Managers would not be able to oversee an exam because they are busy.

3.2.1.3 Practical

After passing the first assessment, most preferred a one-week, on-the-job training on insertion and removal of an MPT (43%, $n = 9$), compared to an exam, an additional assessment, or a monthly visit from an MPT nurse. Participants said that receiving certificates is personally important, providing proof that they are trained on MPT's, allowing them to advance in their careers. Generally, HCPs felt that attending practical training would help them become proficient at MPT implant insertion and removal, however, some HCPs were not in support of a week-long training.

3.2.1.4 Mentoring

A third of participants (33%, $n = 7$) preferred having a dedicated mentor to assist with clinical enquiries, with daily reports to their mentor compared to monthly mentoring calls via

WhatsApp with a clinical mentor, a designated district MPT mentor or frequent reporting to a mentor about the successes and challenges of MPT insertion. HCPs said that reporting daily to mentors would allow them to report strengths and weaknesses, helping them stay accountable and provide better MPT services. Where they struggled, the mentor could provide guidance and strategies for improvement. Other HCPs thought that daily reporting to a mentor would be demanding; they suggested reporting weekly, bi-weekly, or once a month. Some HCPs liked the idea of performing insertions and removals in the presence of their designated district MPT mentor, with the mentor correcting any mistakes, thereby improving their skills and confidence. Almost a third of HCPs ($n = 6$), liked the idea of becoming a national MPT trainer, as it allowed for career growth and recognition.

3.2.1.5 Training others

Almost half of the HCPs (48%, $n = 10$) chose the option that required them to provide training with a training manual so others could also be capacitated to provide MPTs, once the products become available. Task sharing, by training and mentoring other nurses, was seen as important, avoiding tasks becoming one person's responsibility, providing cover when someone is on leave, and providing opportunity for training of new nurses. This could be done by an MPT champion in each clinic. A few HCPs mentioned that they would want recognition for adhering to training, mentoring, and providing exceptional service delivery. Only 3 HCPs did not want to train others, noting they didn't like training, and that it would be a huge responsibility.

3.3 Key considerations for future MPT implementation

The following five themes emerged during the KI IDIs as considerations for future MPT implementation: healthcare provider training, messaging, and demand creation, policy considerations, preparing for choice, and sustainability of MPT provision. Table 3 outlines the themes and sub-themes that were identified: the related quotes are embedded in the text.

TABLE 3 Key informant interview themes and sub-themes.

Theme	Sub-themes
Provider training	Provider training
Messaging & demand creation	Correct understanding
	Myths
	Peer educators
Policy considerations	Age of consent
	Distribution of condoms
	Priority populations & areas
	Safety and efficacy across a wide group of populations
Preparing for choice	Acceptability
	Choice
	Combination prevention
Sustainability	Few healthcare visits

3.3.1 Healthcare provider training

All KIs indicated that training for HCPs is crucial because MPTs are new products and there is noted anxiety around new interventions. While there are many similarities between the MPT and contraceptive implant and some basic implant knowledge base, one KI noted that provider training should occur well ahead of MPT implementation, ensuring that providers feel well prepared for MPT insertion and removal, especially due to the novel aspects of the biodegradable and refillable MPT implants:

> "*we'll have to provide sort of training because uhh it will be a new uh thing for the providers … something that has never been done before. Obviously, … they do perform similar processes like you've just mentioned that the Implanon. So, … it will be easier for them to sort of uh shift, their knowledge of how to insert, insert the implant eh with the biodegradable and the non-bio because then even to remove the non-bio, they might just need to be orientated, …we know health care providers they get very anxious when new things come and they start having attitude it's because we don't prepare them enough. We need to make enough sessions for them to be prepared.*" (Female, 42)

> "*Some of the professional nurses …were trained on inserting [Implanon], but the removal were not trained and they've got to ask, ask for the doctor or [tell] the client to go to other facilities for the removal… If you train the professional nurses on insertion [of the MPT implant], also train them removal*" (Female, 55)

Some noted that training manuals and the new products should be available at the training and that time should be allocated for practical demonstrations.

3.3.2 Messaging and demand creation

Under this theme, participants discussed ensuring accurate knowledge and understanding about PrEP and the new MPT methods, including dispelling myths and preferred dissemination platforms.

3.3.2.1 Accurate knowledge and understanding

KIs highlighted that accurate knowledge and understanding of any new method is crucial to ensure that potential end users can make an informed choice and use the method effectively.

> "*enhance the capability of young people to broaden…their understanding of different methods so that they can choose based on their own … preferences and …what's convenient for them and what would work best for them as opposed to what my grandmother or my mother took.*" (Female, 60+)

Reflecting on the implementation of the contraceptive implant, some KIs noted that addressing local myths, especially those around side effects, with end users, families, and the local

communities is a crucial step to ensure accurate product understanding. Furthermore, there must be timeous messaging to enable understanding and prevent myths.

> "*If you don't reassure people around … the side effects and … what to expect, you know if it does come it's when you speaking to your neighbour speaking, to your mother is speaking to your colleagues or speaking to your friends and you getting all kinds of…information that may not be accurate.*" (Female, 60+)

> "*the* [contraceptive] *implant is not likeable, people don't like it …if something new is coming you need to do a lot of grounds work of orientating people towards it because Implanon just came and people were inserted and then the myths started where they went home, and somebody told them, they're getting more fat.*" (Female, 42)

3.3.2.2 Dissemination platforms

Information, education, and communication (IEC) materials need to be tailored for different age groups, ensuring that the community, as well as potential end users, are educated on these new products.

> "*when you bring on new innovations…we don't take much time eh making them understand what is the benefits of…the [product] and how is it different from what has been there historically. So, we need to focus on that so that we can get the buy-in from both the providers and the beneficiaries*" (Female, 42)

Traditional IEC materials such as posters and pamphlets were mentioned as platforms for dissemination as well as video recordings and community radio. One KI noted that the National Department of Health should play a role in the dissemination of accurate information but noted that that online platforms like Tik Tok must be active and accurate. Another KI noted that the use of peer educators was a good strategy to reach young people.

> "*I don't understand the language of the youth… we put the younger generation there so that when they talk, they talk one in the same language isn't it?*" (Female, 52)

3.3.3 Policy considerations

When reflecting on the policy considerations of adding a new MPT method to the SRH prevention package, one KI (NDoH representative) outlined the following processes that would need to be followed: regulatory approval for the product, followed by a review from an expert committee in terms of cost-effectiveness. The South African Health Product Regulatory Authority (SAHPRA) reviews the safety profile, while National Essential Medicines List Committee conducts cost effectiveness, comparing what's available in the market. The guidelines then need to be amended or addenda added, including the specific initiation processes and standard operating procedures for that new product.

The age of consent and inclusion of specific population groups in the research were other policy considerations that were mentioned. This is to ensure that when the product is available, it is safe and effective for a wide range of population groups, specifically those who are under 18 years and pregnant women.

> "*under 18s are excluded from the rings at the moment and …for CAB-LA* [long acting cabotegravir] *pregnant women are not included … and I think those … things became a barrier and …the product is already coming in with a shortcoming.*" (Female, 60+)

A few KIs noted that priority populations and geographic areas should be targeted when these products are provided. As with oral PrEP, the suggestion was to start in areas with the highest burden of HIV and unmet need for contraception and then expand to a wider areas/population.

> "*we know kuthi [that] even the 11-year-old are sexually active. So, if you cannot give them PrEP, what [can you give*?]." (Female, 49)

> "*we need to think through that carefully … using our population and incidence data. So, if we bringing in an MPT … that is … a combination of HIV prevention as well as contraceptives, we then need look at where is the greatest need.*" (Female, 60+)

3.3.4 Preparing for choice

Among the KIs there was overall acceptability for the inclusion of MPT methods into the package of HIV and pregnancy prevention services, with an emphasis that new options provide greater choice:

> "*We actually have multiple different options that people could choose uh as a contraceptive choice, uhm I think for … HIV prevention the more options we have the better and … the reason for that is that … we know that one size doesn't fit all. You know, we need to think about what the different preferences are… What people find convenient or what they find uh easy to use, or easy-to-access, will influence their choices.*" (Female, 60+)

> "*There was a condom only for HIV prevention, but PrEP came then we were able to give people choice. So, it's always best if … people have a choice to different methods.*" (Female, 49)

Two KIs noted that these new products provide potential end users with additional choices for combination prevention, allowing us to "win" two battles, both unintended pregnancy and HIV.

> "*Once we use … combination prevention methods and then eh we look into institutions of higher learning …and do activations in schools and…we get the injectables going we*

> *know that we have won, we might just go there … saying we are winning some kinds of battles*" (Female, 42)

However, one KI cautioned that the social context need to be considered when providing people with new contraception and HIV prevention methods, taking time to sensitize people on the new methods and how they differ from other methods, as historical choices impact future choices.

3.3.5 Sustainability of MPT provision

Two KIs highlighted the need for proper planning, budgeting, monitoring and evaluation by the Government and partners to ensure sustained access to such methods. Product affordability, availability, and access were also noted as key components of sustainability, both linked to continued use.

> "*We need to think of ways to sustain because what I often find is that a new project started and then falls off because we haven't explored to say what we'll what could cause uh uh the government not to afford, maybe affordability or maybe uhm what could but what would cause the program to fall….Systems must be in place, proper budget, proper planning, monitoring and evaluation.*" (Female, 42)

> "*The availability of the stock will also increase sustainability.*" (Female, 55)

Furthermore, four KIs noted the long-acting benefit of the MPT resulting in fewer healthcare visits, would be an enabler to the continued use and reduced patient load in clinics, thereby increasing acceptability of the method among clients and providers, and improving its ongoing availability, uptake, and use.

> "*people will always forget at some point … to take the treatment on a daily basis. So, … if there is a long-acting uhm like the CAB one and the other ones it is … like that might improve … uptake and also just improve their adherence because then the client doesn't have to come to the facility like often to get the treatment.*" (Female, 42)

> " *Even if they move to another location at least they are moving with the Implanon. We are trying … to reduce the number of people coming* [to the facility] *because …we're having shortages of staff. So, if they just put it for a year and then come back …for another year, I think we'll be able to … reach them once, and also reduce the number of people coming to the facilities.*" (Female, 49)

4 Discussion

This study aimed to determine HCP needs and gather key policy and programmatic considerations for the introduction of new MPTs into the SRH package in South Africa. HCP training, messaging and demand creation, policy considerations, preparing for choice, and sustainability of MPT provision are the five key programmatic implications to consider. These can be grouped into policy level, facility level and individual level considerations.

At a policy level, policy amendments and sustainability of MPT provision need to be considered. As policy leaders, the NDoH will be responsible for amendments to the existing PrEP policy and guidelines (35). The priority populations, geographic target areas and inclusion/exclusion criteria will be important considerations for the introduction of new MPT methods.

KIs highlighted the need for proper planning, budgeting, monitoring and evaluation, prior to the introduction of new products to improve the sustainability of these interventions and the continued provision of and access to MPTs. Creating and maintaining a sustainable intervention is a challenge faced by all health systems stakeholders, including politicians, funders, providers, insurers, policymakers, taxpayers and patients (36). Product affordability, availability and accessibility are key elements of sustainability, both linked to continued and effective use. A meeting with key policy makers could be set up, to share these research findings.

At a facility level, HCP training need to be considered. Insights into HCP training needs, and preferred training methods were unpacked during HCP workshops. The ideal training package provides theoretical content through a face-to-face district level training, followed by a short assessment with a pass rate between 65%–70%. Those that pass, will then participate in a week of on-the-job training on how to insert and remove an MPT implant. A dedicated mentor would support clinical enquiries, while the HCP applies their knowledge in the clinic. Training and capacitating other HCPs would be a part of their role. KIs reinforced that HCP training needs to be ongoing and must include training on the removal of the implant, a finding supported by Adeagbo et al. (26). When reflecting on the lessons learned from the contraceptive implant implementation, Pleaner et al. (14) and Humphries et al. (37) both recommended capacity building for HCPs, including training on insertion and removal of implants: our research supports this finding. Due to the similarities between the contraceptive implant and the MPT implant, many HCPs will have existing knowledge as a basis for the MPT introduction. Reflections from oral PrEP implementation, suggest the training of various levels of HCP, not only those who are trained to provide anti-retroviral therapy (ART), to broaden access and relieve the existing burden on HCPs in the delivery of PrEP (38). Our research suggests alternative training strategies which were appealing to HCPs (certificate of compliance, dedicated mentor and fully fledged MPT nurse status). These research findings provide considerations for innovative approaches to HCP training, ensuring that we learn from previous implant introductions, to proactively address any pitfalls. Closer to the new MPT introduction, careful consideration is required by the NDoH, to ensure that there is adequate HCP training, planning, and preparation. Particular attention should be paid to HCP attitudes towards the new methods, given the bias of HCPs for specific methods (39). At the right time, engagements with HCPs and their representatives are key to building on our research findings.

At an individual level, messaging, demand creation and preparing for product choice need to be considered. The accurate knowledge and understanding of new MPT methods, through messaging and demand creation is crucial, particularly with stakeholders at a community level. A variety of demand creation methods (in-person, IEC materials, billboards and radio as well as online platforms) should be employed, seeking to reach as many people as possible. This is supported by Mataboge et al. (23). HCPs recognise that young people would like information in a language appealing to them, from someone who understands their needs, like a peer educator (40, 41). Myths and misconceptions, especially those that exist from the contraceptive implant implementation process (42–44) need to be addressed, as they may be a barrier to MPT implant introduction. In their research in Cape Town, Krogstad et al. (45) found that the uptake of contraceptive implants was declining, due in part to real experiences or myths about women being assaulted by robbers who physically remove the implants to smoke as drugs. In another study in the Western Cape and Gauteng, adolescent girls also mentioned this myth during focus group discussions (46). This reinforces the need for accurate information sharing and demand creation, especially about the composition of the implant. Mataboge et al. (23), presenting findings from another objective of this research study, highlights the various demand creation tactics and messages that were appealing to potential end users when MPT methods are closer to implementation. Further engagements with potential end users, local community groups and key stakeholders should be held to build on our research findings.

In 2023, South Africa welcomed the Dapivirine Vaginal Ring (47) into the package of PrEP options at specific demonstration sites (48) and anticipates the arrival of long acting cabotegravir (49). As part of this, work is underway, preparing people for a choice of methods. Counselling for choice, ensuring that people use their voice and agency to make the choices that meet their contraceptive needs (50), becomes increasingly important as the choices for contraception and HIV prevention expand.

4.1 Strengths and limitations

This study included participants from three South African provinces, and different cadres within the DoH, enabling a variety of perspectives to be represented. However, the KI response was low, resulting in a smaller IDI sample size is smaller than originally planned. Although the majority of participants were females, this sex-skew is representative of the country's HCP population, who are mostly female. We adopted novel methodologies in this study, allowing for triangulation of data.

Observations conducted during the workshops rely on the purposive selection of what information is important to note down. Each observation already contains an element of interpretation of what is important, therefore introducing bias (33). While valuable insights were provided, the HCP workshops relied on a small sample size and therefore the results may not be nationally representative but provide insight to HCPs perceptions across different areas. Also, our research only included HCPs who were professional nurses, however many other cadres are involved in provision of SRH services, and they may hold different opinions on appropriate training methods and their perceptions on demand creation and messaging.

5 Conclusion

There are many lessons to be learned from the contraception implant and oral PrEP implementation that can be proactively considered when preparing for MPT introduction. HCP training and messaging and demand creation are of particular importance, ahead of MPT introduction. Providing this feedback to policy makers is key to ensure these lessons are learned and proactively addressing them will improve the success of the new MPT introductions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Ethics statement

The studies involving humans were approved by Human Research Ethics Committee (HREC) of the University of the Witwatersrand. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AK, PM, NMt, VB and SM contributed to conception and design of the study. MM and NMt organised the database. PM, NMt, MM, NMa and KK conducted data collection. AK, PM, NMt and CM conducted data analysis with support from LM. AK led the write up of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Estimating the costs and perceived benefits of oral pre-exposure prophylaxis (PrEP) delivery in ten counties of Kenya: a costing and a contingent valuation study

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Background: Kenya included oral PrEP in the national guidelines as part of combination HIV prevention, and subsequently began providing PrEP to individuals who are at elevated risk of HIV infection in 2017. However, as scale-up continued, there was a recognized gap in knowledge on the cost of delivering oral PrEP. This gap limited the ability of the Government of Kenya to budget for its PrEP scale-up and to evaluate PrEP relative to other HIV prevention strategies. The following study calculated the actual costs of oral PrEP scale-up as it was being delivered in ten counties in Kenya. This costing also allowed for a comparison of various models of service delivery in different geographic regions from the perspective of service providers in Kenya. In addition, the analysis was also conducted to understand factors that indicate why some individuals place a greater value on PrEP than others, using a contingent valuation technique.

Methods: Data collection was completed between November 2017 and September 2018. Costing data was collected from 44 Kenyan health facilities, consisting of 23 public facilities, 5 private facilities and 16 drop-in centers (DICEs) through a cross-sectional survey in ten counties. Financial and programmatic data were collected from financial and asset records and through interviewer administered questionnaires. The costs associated with PrEP provision were calculated using an ingredients-based costing approach which involved identification and costing of all the economic inputs (both direct and indirect) used in PrEP service delivery. In addition, a contingent valuation study was conducted at the same 44 facilities to understand factors that reveal why some individuals place a greater value on PrEP than others. Interviews were conducted with 2,258 individuals (1,940 current PrEP clients and 318 non-PrEP clients). A contingent valuation method using a "payment card approach" was used to determine the maximum willingness to pay (WTP) of respondents regarding obtaining access to oral PrEP services.

Results: The weighted cost of providing PrEP was $253 per person year, ranging from $217 at health centers to $283 at dispensaries. Drop-in centers (DICEs), which served about two-thirds of the client volume at surveyed facilities, had a unit cost of $276. The unit cost was highest for facilities targeting MSM ($355), while it was lowest for those targeting FSW ($248). The unit cost for

facilities targeting AGYW was $323 per person year. The largest percentage of costs were attributable to personnel (58.5%), followed by the cost of drugs, which represented 25% of all costs. The median WTP for PrEP was $2 per month (mean was $4.07 per month). This covers only one-third of the monthly cost of the medication (approximately $6 per month) and less than 10% of the full cost of delivering PrEP ($21 per month). A sizable proportion of current clients (27%) were unwilling to pay anything for PrEP. Certain populations put a higher value on PrEP services, including: FSW and MSM, Muslims, individuals with higher education, persons between the ages of 20 and 35, and households with a higher income and expenditures.

Discussion: This is the most recent and comprehensive study on the cost of PrEP delivery in Kenya. These results will be used in determining resource requirements and for resource mobilization to facilitate sustainable PrEP scale-up in Kenya and beyond. This contingent valuation study does have important implications for Kenya's PrEP program. First, it indicates that some populations are more motivated to adopt oral PrEP, as indicated by their higher WTP for the service. MSM and FSW, for example, placed a higher value on PrEP than AGYW. Higher educated individuals, in turn, put a much higher value on PrEP than those with less education (which may also reflect the higher "ability to pay" among those with more education). This suggests that any attempt to increase demand or improve PrEP continuation should consider these differences in client populations. Cost recovery from existing PrEP clients would have potentially negative consequences for uptake and continuation.

KEYWORDS

HIV, contingent valuation (CV), pre-exposure prophylaxis (or PrEP), Kenya, costing

Introduction

Recent evidence suggests that the use of oral pre-exposure prophylaxis (PrEP) is highly effective at lowering the risk of HIV infection (1–4). Several clinical trials reported high efficacy of oral PrEP among individuals at high risk of HIV acquisition, ranging from 99% among men who have sex with men (MSM) to 94% among female sex workers (FSW) (1, 2, 5, 6). Earlier randomized clinical trials reported efficacy ranging from 44%–75% among high-risk individuals in heterosexual relationships, while demonstration projects reported effectiveness greater than 80% (4, 7–9).

In 2015, the World Health Organization recommended that PrEP be offered "as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (10)." However, WHO also noted that "PrEP costs are substantial, and include costs for clinic staff, medications, laboratory testing, pharmacy services, community education, provider education and monitoring and evaluation." They noted that PrEP can be cost saving when the incidence of HIV is greater than 3 per 100 person-years and may still be cost-effective at lower levels of incidence. Kenya included PrEP as part of its combination HIV prevention interventions and subsequently developed guidelines on the use of PrEP (11) in 2017. However, there has been limited information on the cost of scaling up the use of oral PrEP across various populations in the country.

A key component of PrEP adherence relates to how individuals value their medication. Is the medication perceived as being effective, for example? Do individuals have preference for using other prevention methods rather than PrEP (e.g., condoms)? Do certain populations view PrEP as being more valuable than other populations? Understanding how individuals value a good or service, and which service they prefer, can be determined based on their "stated preference." Stated preferences are frequently utilized when a competitive marketplace does not exist, but there is still a need to understand the magnitude of the benefits that are accrued, as well as the preferences of the consumers. The stated preference approach is most widely used where there is no clear competitive market. In the WTP approach, consumers are asked to state their maximum WTP for a good or service.

For this study, WTP was utilized to understand the perceived benefits of PrEP among members of key populations and adolescent girls and young women (AGYW) in Kenya, as well as to assess the factors that influence a client's strength of preference for PrEP. One objective of this study was to estimate the costs of delivering oral PrEP to various populations through integrated platforms and in different geographic regions of Kenya. A second objective was to determine the preference and strength of preferences for oral PrEP by clients and potential clients in Kenya.

Methodology

Source data

A total of 4 data collectors were assigned responsibility for collecting data at each of 44 facilities where PrEP services were

available. Each 2-person team then split responsibility between conducting a costing of individual facilities and interviewing individual clients to assess their WTP. Data collection was completed between November 2017 and September 2018.

Costing

The *Jilinde* (translated "protect yourself") project (12) was implemented in ten out of the forty-seven counties in Kenya. These counties are classified into three clusters based on geographic proximity: Coast (Mombasa, Kilifi, Kwale and Taita Taveta counties), Nairobi (Nairobi, Kiambu and Machakos counties) and Lake cluster (Kisumu, Kisii and Migori counties). The costed facilities included all facilities where PrEP was being offered by Jilinde, including 23 public health facilities, 16 drop-in-centers and 5 private facilities.

A semi-structured, interviewer-administered questionnaire was used to obtain retrospective cost information from 44 facility managers on the costs of resources used in delivering PrEP services. The data collected included personnel, equipment, medications, consumables, lab tests and reagents, test kits, utility, maintenance, and utilities for each visit (initial visit or first contact, refill visits and quarterly visits) and for each stage of client flow in a facility: (i) Reception, (ii) Triage, (iii) Health education, (iv) HTS and STI testing, (v) Prescription of drugs and (vi) Dispensing drugs client).

Contingent valuation

The contingent valuation survey was administered to 1,940 PrEP clients and 318 non-PrEP clients. Respondents were interviewed about their personal and household characteristics (age, religion, marital status, individual income, household income, level of education, employment status, etc.). Respondents were asked to self-identify as to whether they were MSM, FSW or AGYW. All participants in the WTP study were asked to sign a consent form noting that they had been explained the purpose of the study, understood that they would not be compensated for participating, and were voluntarily choosing to participate.

Participants were enrolled during their routine visits to these facilities for PrEP and other services. PrEP clients were selected based on their availability during the data collection process and their willingness to be interviewed. Non-PrEP clients were selected based on their utilization of health services at the identified facilities. In some cases, non-PrEP clients were individuals who had been offered PrEP services but had not yet adopted the intervention.

Data from PrEP clients were collected during initial visits (screening visits), refill visits and quarterly visits (13). The initial visits describe the first screening visit, the refill visits describe the Month 2, 4, 5, 7, 8, 10 and 11 where PrEP clients visited the facilities to only refill their PrEP. Quarterly visits were conducted at 3, 6, 9 and 12 months and included an HIV test, clinical assessment, and PrEP refills.

As for the WTP surveys, respondents were reminded that PrEP was being offered for free but asked, "if it was necessary to pay a small amount to participate in this program, would you be willing to do so?" Understanding the factors that influence a person's decision not to pay for a service is critical in assessing if the decision is based on the value of the service ("true zero"), or if it is based on a protest against the idea of paying for any service ("protest zero") (14). The two most common reasons given for not being willing to pay for PrEP were: (1) since other HIV services are free, PrEP should be free or (2) I have insufficient funds to pay for PrEP. Respondents who indicated that "PrEP services should be free because other prevention methods are free" were categorized as "protest zeros" because the response did not necessarily indicate how they valued PrEP. On the other hand, if a respondent indicated that they did not have enough money to pay for PrEP, it was assumed to be a true reflection of value given their lack of resources and they were thus categorized as a "true zero." If a respondent did not provide a reason they would be unwilling to pay for PrEP, they were assumed to be a "true zero." The analysis then focused only on those who indicated a willingness to pay and those who indicated that their unwillingness to pay represented a "true zero."

If a respondent did indicate a WTP, they were then shown 14 payment cards (including an "other" card), randomly distributed in front of the respondent, with various amounts in Kenyan Shillings. This "payment card approach" has been widely used as it tends to produce high response rates that are closely aligned with an individual's ability to pay, while at the same time avoiding anchoring bias (15). The amounts varied from Kshs 0–Kshs 10,000 (US$100). Respondents were then asked to indicate which card represented the highest amount they would be willing to pay monthly for PrEP services. Once an amount was selected, they were then shown the card with the next highest amount and asked if they would pay that amount. If the respondent indicated "no," then the original amount selected would be identified as the maximum WTP. If the respondent indicated "yes," then the next highest card was selected, and they were again asked if they would be willing to pay this amount. In this way, the respondent is "bid up" until they confirm that the amount indicated is truly the maximum WTP. After two attempts to "bid up" the respondent, the bidding process ended, and the highest amount was confirmed.

Ethical considerations

A protocol was submitted to Kenya Medical Research Institute (KEMRI) in Kenya and the Johns Hopkins School of Public Health (JHSPH) in the US. Approval for the study was received from KEMRI (No. 0583) on October 9, 2017. Institutional review board (IRB) approval was also received from JHSPH (IRB No. 00007657) on January 17th, 2018.

Statistical analyses

Independence between the WTP and categorical and continuous variables were analyzed, in bivariate analysis, using Fisher exact test, since WTP is discrete by design.

A multivariate polytomous logistic regression model was used to determine the characteristics that are associated with the willingness to pay variable for which we considered the categories 0-to-0.5, 1, 2, and 4-to-100. All variables that were believed to be relevant for the analysis were included in the regression. Stepwise procedure was then used for model selection. Data were analyzed with R version 3.5.1 (16).

Results

Cost analysis

The total number of PrEP clients (initial, refill and quarterly visits) for a six-month period preceding data collection (April–September 2017 (phase 1), and from October 2017–March 2018 (phase 2) was 8,256. The Nairobi cluster accounted for 47% of all clients, while the Lake and Coast clusters accounted for 31% and 22% of clients, respectively. The largest number of PrEP clients were FSW (66%), followed by MSM (15%) and then serodiscordant couples (SDC) (13%). General population (GP) and AGYW accounted for 5% and 1%, respectively.

The cost per person year (CPPY) is the cost of providing one client with PrEP services including (generic TDF/FTC) for 12 months. The overall weighted unit CPPY across all the 44 facilities was $253 ranging from $217 at health centres to $283 at dispensaries. The unit cost for DICEs, which served about two-thirds of the client volume at surveyed facilities, was $276. The weighted unit cost of PrEP at the dispensaries was the highest, with a unit cost of $283. These are depicted in Figure 1.

Examining the unit cost components, the largest was personnel which represented 58.5% of all costs, followed by drugs (generic TDF/FTC), which represented 25% of all costs. The other cost components are illustrated in Figure 2.

Regarding the target populations for PrEP, the weighted unit cost per person year on PrEP varied widely from a low of $224 for GP to a high of $355 for MSM. The unit costs per person year for each of the target populations is shown in Figure 3.

Across the three cluster regions, the average weighted cost of PrEP varied marginally. The unit costs of PrEP were higher in the Coast cluster than in the Lake cluster: $269 vs. $267, respectively. Nairobi cluster had the lowest unit cost, estimated at $263. Differences in the unit cost of PrEP by cluster were not statistically significant (Nairobi cluster vs. Lake cluster, $p = 0.57$; Nairobi cluster vs. Coast cluster, $p = 0.65$ and Coast cluster vs. Lake cluster, $p = 0.59$).

Cost of PrEP per visit

The estimated unit cost for the initial visit varied across service delivery models and by population type. For FSW, the unit cost for the initial visit ranged from $44 in the DICEs to $62 in hospitals. The estimated unit cost for refills was highest at the DICEs ($21 per visit) and lowest at health centers ($12 per visit). The average costs during quarterly visits varied between $34 for the private facilities to $20 for the hospitals. MSM were only served in DICEs and the unit cost was $62 for the initial visit, $22 for the refills and $40 for quarterly visits. For AGYW, the unit cost for the initial visit was higher in private facilities, at $100 compared to $52 in hospitals. The lowest unit cost for refills was in the hospitals ($17) and highest in private facilities ($26). For quarterly visits, the cost per visit was estimated at $32 and $76 in the hospitals and private facilities, respectively. The costs for the various populations for each type of visit are summarized in Table 1.

By altering the frequency of HIV testing to every six months instead of every three months, the CPPY estimates dropped by between 0%–19%. This varied by population type and service delivery model as depicted in Table 2.

To better understand the costs associated with integrating PrEP services into public health facilities, we conducted an incremental unit cost analysis. Whereas full economic costing analyses all resources used in the delivery of PrEP, the incremental costing analysis considered the cost of drugs (generic TDF/FTC), medical supplies (HIV test kit, gloves, dry and wet swabs), non-medical supplies (client files) and the cost of provider training in

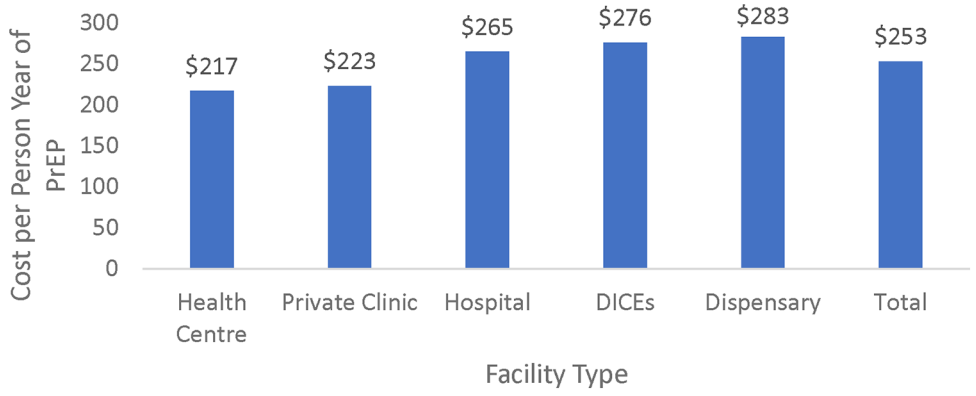

FIGURE 1
Weighted unit cost—total and by type of facility.

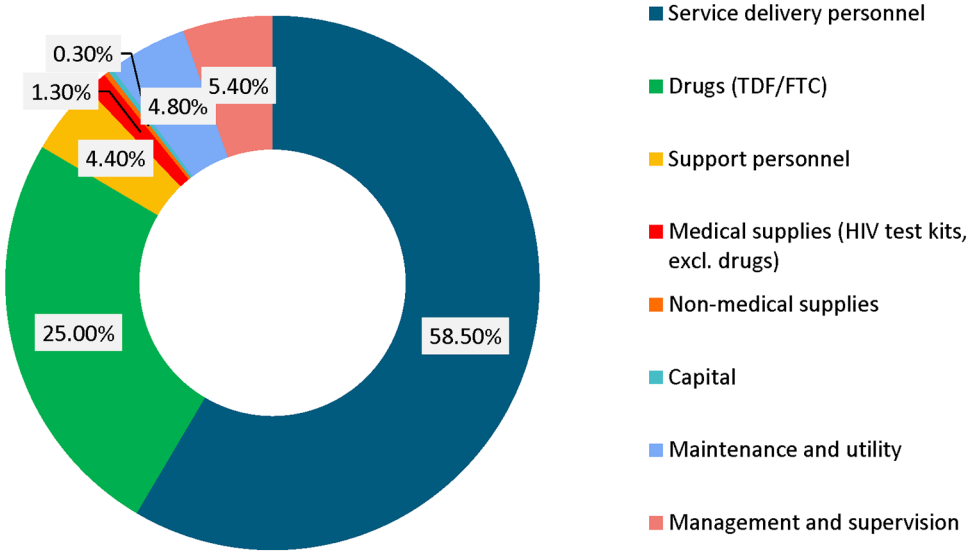

FIGURE 2
Unit cost by major cost categories.

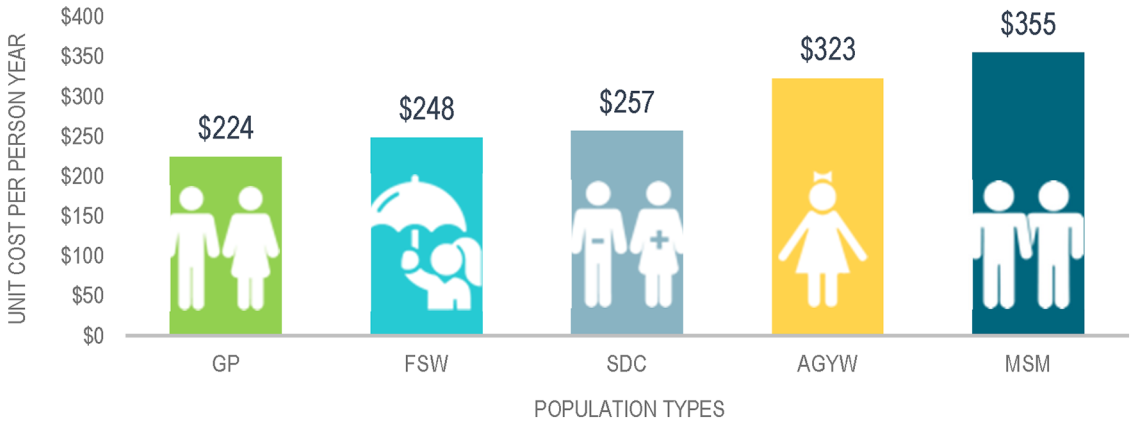

FIGURE 3
Weighted unit cost per person year by target population.

the analysis. Given that PrEP is provided as an additional service for clients in public health facilities, a facility may not require additional staff but rather may undertake training for clinical staff on PrEP delivery.

The average annual incremental cost of delivering PrEP across the different public health facilities was $84 per person per year. The variation of the incremental cost of PrEP delivery between public health facilities was small: $84.80 vs. $83.56 for health centers and hospitals, respectively. The incremental cost in the dispensaries was $83.64 per person per year.

The largest component of the incremental costs was drugs (generic TDF/FTC), at $ 75.24 (88% of all the costs), followed by training, at $5.55 (6%) and medical supplies, $3.81 (4%). These are depicted in Figure 4.

Contingent valuation analysis

A total of 2,258 individuals participated in the survey and reported their WTP for PrEP in Kenya. The characteristics of these respondents are included in Table 3. This included 1,683 female sex workers (74.5%), 308 men who have sex with men (13.6%), 264 adolescent girls and young women (11.7%) and 3 who were not classified (0.1%). Of the respondents, 989 were in the Lake cluster (43.8%), 764 were in the Nairobi cluster (33.8%) and 505 were in the Coast cluster (22.4%). Respondents tended to be young, with the majority (51.8%) being under the age of 25. Most individuals were single and had never been married (61.3%). Most of the respondents have had at least some high school education (64%), with 13% having at least some tertiary

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TABLE 1 Unit costs per visit and per person-year for PrEP (2018 US dollars).

Population	Service delivery	Initial visit	Refills	Quarterly visits	CPPY
FSW	DICEs	$44	$21	$32	$305
	Health center	$48	$12	$28	$229
	Hospital	$62	$20	$20	$324
	Private	$39	$16	$34	$272
	Dispensary				
MSM	DICEs	$62	$22	$40	$349
	Health center				
	Hospital				
	Private				
	Dispensary				
AGYW	DICEs				
	Health center				
	Hospital	$52	$17	$32	$287
	Private	$100	$26	$76	$538
	Dispensary				
GP	DICEs				
	Health center	$51	$17	$37	$271
	Hospital				
	Private				
	Dispensary				
SDC	DICEs				
	Health center	$43	$17	$28	$265
	Hospital	$45	$16	$32	$260
	Private	$34	$15	$26	$233
	Dispensary	$52	$18	$29	$283

TABLE 2 Variation of CPPY by reducing frequency of HIV testing by population type and service delivery model.

Population	Service delivery model	CPPY (HIV testing every 3 months)	CPPY (HIV testing every 6 months)	% Decrease with 6 m vs. 3 m testing
FSW	DICEs	$308	$286	7.1%
	Health center	$228	$196	14.0%
	Hospital	$282	$282	0.0%
	Private	$269	$233	13.4%
	Dispensary			
MSM	DICEs	$358	$322	10.1%
	Health center			
	Hospital			
	Private			
	Dispensary			
AGYW	DICEs			
	Health center			
	Hospital	$284	$254	10.6%
	Private	$536	$436	18.7%
	Dispensary			
GP	DICEs			
	Health center	$274	$228	16.8%
	Hospital			
	Private			
	Dispensary			
SDC	DICEs			
	Health center	$263	$241	8.4%
	Hospital	$269	$237	11.9%
	Private	$232	$210	9.5%
	Dispensary	$283	$261	7.8%

education. The most common religion reported by respondents was Protestant Christians, who represented 60% of the sample size. Of the total population of respondents, 86% were current PrEP clients, while the remaining 14% were members of a key population or AGYW but were not currently PrEP clients.

Of the total population of respondents, 43% indicated that they would not be willing to pay for PrEP. This differed between current PrEP clients (41%) and non-PrEP clients (50%) ($p < 0.01$). This higher willingness to pay for PrEP by current clients is not surprising, since PrEP clients are already motivated to take PrEP and therefore would be expected to be more incentivized to pay something for PrEP than those who are not already a part of the intervention.

Among existing PrEP clients, respondents were asked if they would pay anything for PrEP. A total of 1,563 respondents indicated either that they had some willingness to pay for PrEP or, if they were unwilling to pay anything, this represented a true valuation of the service.

The median WTP (including those categorized as "true zeros" but excluding those who were "protest zeros") was US$2 per month. In other words, about half (49%) of all current PrEP clients were willing to pay $2 per month or more for PrEP, while the other half were not willing to pay this much. The mean WTP was $4.07.

The cost to the government of Kenya for a 30-day supply of generic Truvada was approximately $6 per month. As the willingness to pay for PrEP drops off rapidly as the proposed price increases, only about 17% of all clients indicated they would be willing and able to pay this price for PrEP monthly.

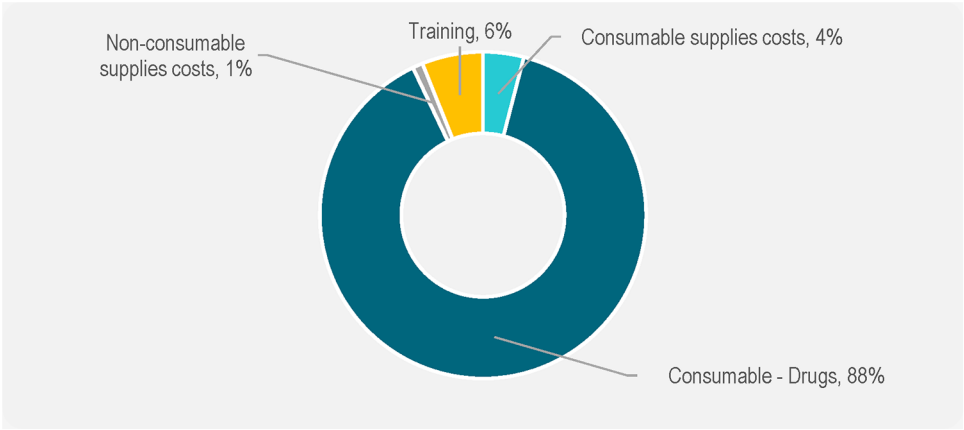

FIGURE 4
Components of incremental cost of PrEP (%).

Only about 5% of all clients were willing to pay $20 per month, which would represent full cost recovery (including the medication, labor, lab tests, etc.).

Table 4 indicates that several categorical variables were associated with willingness to pay. By client population, MSM had the highest mean WTP, at $8.26 per month. This was followed by FSW, who indicated a mean WTP of $3.79 per month. The lowest mean WTP was among AGYW, who indicated a WTP of only $1.36 per month. This is also consistent with data on monthly household income, which indicated that MSM had the highest income ($300 per month), followed by FSW ($255 per month), and AGYW ($90 per month).

Breaking down the mean monthly WTP by cluster, respondents in the Lake cluster were willing to pay much less ($2.02) than in either Coast ($6.55) or Nairobi ($2.52) clusters. This is consistent with data regarding household income, which indicates that monthly household income in the Lake Cluster ($176 per month) is much lower than in either the Coast ($305 per month) or Nairobi ($307 per month) clusters.

Based on the location where PrEP clients receive services, clients at dispensaries had the highest WTP ($5.78 per month). This was then followed by DICES ($4.41 per month), Health Centers ($2.99 per month), Hospitals ($2.96 per month) and clinics ($1.48 per month). This result might either be an indication that those who attend DICEs or Dispensaries (mostly FSW and MSM) are the most motivated to obtain PrEP, or alternatively it may mean that those who attend DICEs or dispensaries are the most satisfied with the services they are receiving and therefore are willing to pay more for the services they receive.

WTP also varied by the relationship status of the individuals. The highest mean WTP was for those who were living together but not married ($9.58 per month). This was followed by those who were never married/single ($4.18 per month) and those who were widowed/separated/divorced ($3.66 per month). Those with the lowest willingness to pay were those who were married/in-union ($3.28 per month).

In terms of age, willingness to pay was highest among those 25–34 years old ($4.50 per month). Those who were younger or older than this age range were willing to pay less, with mean WTP varying between $2.51 and $4.27 per month.

In addition, several other variables were also found to be correlated to WTP. These include total monthly income, size of household and total expenditures. As expected, there was a positive relationship between WTP and household monthly income. Individuals who had a higher household income also had a higher willingness to pay. On average, respondents indicated that they would be willing to pay 1.5% of their household income for PrEP. MSM were willing to pay 2.0%, AGYW were willing to pay 2.1% and FSW were willing to pay 1.2%. Thus, relative to their income, AGYW were willing to pay the most while FSW were willing to pay the least.

Several other variables were not found to be statistically significant in terms of WTP. This includes the number of days that the respondent worked in a typical week.

Next, a multivariate regression analysis was performed to determine the variables that are most likely to be associated to an individual's WTP for PrEP. The key variables in the multivariate analysis included the 12 variables that were statistically significant in the univariate analysis:

- The population type of the respondent (MSM, FSW, AGYW)
- The location of the respondent (Lake, Nairobi and Central, Coast)
- The age of the respondent
- The marital status of the respondent
- The education level of the respondent
- The religion of the respondent
- The insurance status of the respondent
- The type of facility where respondent received PrEP
- The size of the household
- The number of days worked in a week
- The income of the respondent
- The total expenditure of the respondent

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TABLE 3 Descriptive characteristics of the full sample.

Variable		% (*N* = 2,258)
Population		
	AGYW	11.69%
	FSW	74.53%
	MSM	13.64%
	Missing	0.13%
Cluster		
	Central Region	28.57%
	Coastal Region	22.36%
	Lake Region	43.80%
	Nairobi	5.27%
Age		
	15–19	11.65%
	20–24	33.75%
	25–34	41.14%
	35+	13.42%
	Missing	0.04%
Marital status		
	Living together	1.77%
	Married/in union	7.71%
	Never married/Single	61.20%
	Widowed/separated/divorced	29.23%
	Missing	0.09%
Level of education		
	College/Higher/Tertiary(completed)	8.59%
	College/Higher/Tertiary(not completed)	4.47%
	No Grade completed(none)	1.51%
	Primary complete	20.24%
	Primary incomplete	13.86%
	Secondary complete	24.93%
	Secondary incomplete	26.35%
	Missing	0.04%
Religion		
	Muslim	7.79%
	No Religion	3.32%
	Protestant/Other Christian	60.14%
	Roman Catholic	28.48%
	Missing	0.27%
Agreed to join PrEP		
	No	13.99%
	Yes	85.92%
	Missing	0.09%
Health insurance		
	No	78.65%
	Yes	17.23%
	Missing	4.12%

In assessing the association between variables and then performing a stepwise multinomial regression, only the location, the population type, age, level of education, and total income of the respondent were included. The highest WTP was among MSM and FSWs, those in the Coastal cluster, between the ages of 25 and 34, and those with a higher income and education.

Discussion

The analysis showed that overall, it costs $253 per person year on PrEP in Kenya, with variability between the different service

TABLE 4 Bivariate analysis of willingness to pay.

Variable		Mean amount WTP (Sd)	*P* value of Fisher's exact test[a]
Population			$P < 0.01$
	AGYW	1.36 (1.12)	
	FSW	3.79 (5.7)	
	MSM	8.26 (16.69)	
	No response	20.5 (27.58)	
Cluster			$P < 0.01$
	Central Region	5.9 (11.8)	
	Coastal Region	6.55 (8.22)	
	Lake Region	2.02 (2.1)	
	Nairobi	2.52 (1.8)	
Age			$P < 0.01$
	15–19	2.51 (3.48)	
	20–24	4.27 (8.42)	
	25–34	4.5 (8.44)	
	35+	3.26 (5.31)	
Marital status			$P = 0.01$
	Living together	9.58 (23.01)	
	Married/in union	3.28 (7.7)	
	Never married/Single	4.18 (7.86)	
	Widowed/separated/divorced	3.66 (5.12)	
	Others	6. (.)	
Level of education			$P < 0.01$
	None/Some Primary/Primary Complete	3.65 (7.64)	
	Some Secondary/Secondary Complete	4.11 (7.99)	
	Some Tertiary/Tertiary Complete	4.97 (7.08)	
	No response	6. (.)	
Religion			$P < 0.01$
	Muslim	7.96 (13.86)	
	No Religion	3.67 (3.09)	
	Protestant/Other Christian	3.55 (6.42)	
	Roman Catholic	4.14 (8.09)	
	No response	4. (.)	
Health insurance			$P < 0.01$
	No	3.7 (6.22)	
	Yes	5.67 (10.65)	
	No response	3.99 (16.72)	
Facility category			$P < 0.01$
	Clinic	1.48 (1.36)	
	DICES	4.41 (8.36)	
	Dispensary	5.78 (9.39)	
	Health center	2.99 (4.43)	
	Hospital	2.96 (4.62)	
Size of the HH			$P < 0.01$
	Q1: 1.0–2.0	4.91 (9.09)	
	Q2: 2.0–3.0	4.2 (8.14)	
	Q3: 3.0–4.0	3.19 (4.87)	
	Q4: 4.0–12.0	2.59 (3.24)	
	No response	11.75 (8.8)	
#Working days/week			$P < 0.01$
	Q1: 0.5–4.0	5.57 (8.51)	
	Q2: 4.0–6.0	4.17 (8.02)	
	Q3: 6.0–7.0	2.68 (3.45)	
	No response	4.5 (13.31)	

(*Continued*)

TABLE 4 Continued

Variable		Mean amount WTP (Sd)	*P* value of Fisher's exact test[a]
Total income			$P < 0.01$
	Q1: 8.0–137.0	3.23 (7.49)	
	Q2: 137.0–200.0	2.86 (4.46)	
	Q3: 200.0–300.0	4.66 (6.79)	
	Q4: 300.0–1,950.0	6.31 (9.93)	
	No Response	3.07 (10.38)	
Total expenditure			$P < 0.01$
	Q1: 2.0–104.8	3.43 (7.72)	
	Q2: 104.8–165.0	3.22 (4.73)	
	Q3: 165.0–252.1	3.81 (6.13)	
	Q4: 252.1–1,244.5	6.32 (9.71)	
	No Response	3.07 (10.27)	

Statistics of the test are not available for Fisher test; simulations with 10,000 samples were used to estimate its *p*-values.
[a]Continuous variables were discretized following their quartiles, and WTP is discrete by design.

delivery models and the populations served. The variability in the cost estimates could be explained by the delivery approach (whether it was through outreach or through static facilities), the volume of PrEP clients, and the number of personnel involved in the delivery pathway. As the scale-up continues, the unit costs are likely to be reduced due to economies of scale and increased efficiencies in delivery.

This contingent valuation study does have important implications for Kenya's PrEP program. First, it indicates that some populations are more motivated to adopt oral PrEP, as indicated by their higher WTP for the service. MSM and FSW, for example, placed a higher value on PrEP than AGYW. Higher educated individuals, in turn, put a much higher value on PrEP than those with less education (which may also reflect the higher "ability to pay" among those with more education). This suggests that any attempt to increase demand or improve PrEP continuation should consider these differences in client populations. Cost recovery from existing PrEP clients would have potentially negative consequences for uptake and continuation.

Cost

The key cost drivers across all service delivery models were personnel and drug costs (generic TDF/FTC) which accounted for over 80% of the weighted unit costs. This is consistent with earlier studies, which found that the two primary cost drivers associated with providing PrEP are personnel and drugs (17–19). Other noticeable cost drivers were management and supervision, and support personnel. These findings suggest that any effort to reduce PrEP costs should focus on leveraging the existing personnel by integrating PrEP into routine services. This is supported by results from this study which show that the incremental cost of layering PrEP into the existing Ministry of Health facilities would be $84 per person per year, assuming the facility staff absorbs Prep responsibilities. These results show that the additional cost required to offer PrEP in public health facilities is almost a third the full economic costs. These findings are comparable with a study on integrating PrEP into routine maternal and child health and family planning in Western Kenya which found that drugs accounted for 25% of the total programme costs (19). Based on these results, sustainability could be guaranteed by ensuring consistency in supply of PrEP commodities, complemented with minimal resources for provider training, medical supplies, and management and supervision.

The study found differences in the unit cost depending on the type of visit, with the highest costs estimated for the initial visit, followed by the quarterly visit and then the refill visit. There was variability in the cost for the three visits across service delivery models and population type. These variations could be accounted for by the explanations on the overall unit cost, and our findings are consistent with other studies conducted in Africa (20–22). The unit cost for the initial visit is much higher compared to the unit costs for refills and quarterly visits. This difference is because clients spend more time with providers during initiation and quarterly visits on HIV testing, adherence counselling and eligibility assessment, compared to refills, where most of the time is spent at the dispensing points. This is supported by time and motion studies (18) which found the time taken to conduct activities related to PrEP and ART for discordant couples was 42 min during screening/initial visits and 36 min during follow-up visits.

Our analysis suggests that performing HIV testing once every six months could reduce the cost per person per year by up to 19%. While mathematical modelling suggests reducing the frequency of HIV testing could lead to more HIV drug resistance from PrEP implementation (23), a modelling study in South Africa found that quarterly and biannual HIV testing would have a similar health impact and resistance consequences (24). Other innovative approaches that could reduce costs by reducing frequency of clinic visits and increasing efficiency include differentiated PrEP delivery models. For instance, dispensing intervals can be increased by using multi-month dispensing for clients who have demonstrated good adherence, to reduce the number of refill visits. Additionally, group refills and counselling which have been successfully applied in antiretroviral therapy and antenatal care settings, can also be explored (25). Further research is warranted on the feasibility of using HIV self-testing to empower clients to monitor their HIV status while on PrEP and reduce the intensity of clinic-based monitoring.

Contingent valuation

The contingent valuation study determined that the average willingness to pay was insufficient to cover the cost of the medications, not to mention the full cost of delivering PrEP in Kenya. Any attempt to achieve cost recovery from the existing populations would likely result in significantly reduced demand and reduced continuation rates among those who have adopted PrEP. On the other hand, the results may

suggest an opportunity to use financial incentives to encourage greater use of PrEP. Additional experimental research may establish the impact on uptake and continuation if small incentives were introduced.

While contingent valuation studies are useful for assessing if cost recovery is or is not feasible, they also provide critical information about how different populations value goods and services. In this case, the study found that certain populations place a higher value on PrEP than others, as indicated by their higher willingness to pay. AGYW, for example, placed a lower value on PrEP than MSM or FSW, but had a higher WTP relative to their income. Higher educated individuals and higher income individuals, in turn, put a much higher value on PrEP. Individuals from Nairobi and Coast clusters placed a higher value on PrEP than individuals from the Lake cluster. In terms of age, the highest valuation peaked among those who were 25–34 years old. Those who received PrEP at dispensaries had a higher WTP. This suggests that any attempt to increase demand or improve PrEP continuation should consider these differences in client populations.

There are various potential explanations for why certain populations have a higher WTP than others. The lower WTP in the Lake cluster may reflect existing intensive and free HIV prevention programming in the region, which might cause the respondents to indicate a lower WTP than those in the other two clusters where access to free services might be more limited. The data on WTP among AGYW relative to income may be an indication that adolescents have fewer other financial burdens (e.g., rent and food might already be paid by parents or other relatives), and therefore they are willing to pay a greater percentage of their income on services such as PrEP. The fact that WTP peaks at 25–34 years of age may reflect either higher income at that age, or higher risk.

Contingent valuation is one tool that is available that assists researchers and policymakers to examine the motivations of consumers as they value a health service such as PrEP. Understanding what motivates PrEP clients requires more than an understanding of personal costs, gains, and risk. As indicated in previous research, factors such as social capital are also critical in understanding how individuals can be recruited into PrEP programs and enabled to remain on PrEP (26).

In conclusion, the two components of this study found useful findings. The costing study confirmed the cost of oral PrEP in Kenya, while also noting how costs may vary from site to site. The contingent valuation study found that there are a range of factors that influence the value placed on PrEP by clients.

Study limitations

There are various limitations, which should be considered as part of this study. First, the cost analysis was based on sites located in certain counties in Kenya. These sites may not necessarily be representative of other counties throughout the country.

In addition, the costing exercise was based on interviews with providers and did not entail following clients. Therefore, the time spent with clients was based on the responses detailed by the providers and not based on actual observed provision of services. This may entail some bias, as providers may either underestimate over overestimate the actual time spent with clients.

Next, the costing categorized sites based on the primary target population of each site and not based on individual clients. This may also introduce bias, as the total cost at facilities may not be driven by the targeted clients, but rather may be influenced by other populations that are reached.

In terms of the contingent valuation study, this requires an accurate assessment of valuation by PrEP clients. However, there are several reasons why individuals may not reveal their true maximum WTP. On one end, respondents may understate their WTP, to avoid providing any information that might lead to a higher price being charged for the service being discussed. On the other hand, respondents may overstate their WTP. Respondents, for example, might want to indicate that they are enthusiastic about continuing with the intervention, even if they are not truly capable of paying the indicated amount monthly.

Another limitation to this study concerns the "protest zero" responses. The authors attempted, to the best of their ability, to distinguish between: (1) those who indicated truly that they were unwilling or unable to pay for PrEP, and (2) those who responded that they were unwilling to pay for PrEP based on a protest towards the idea of having to pay for PrEP. Distinguishing between these two types of responses was problematic. If some of the responses categorized as "protest zeros" (and therefore excluded from the analysis) were "true zeros," then the average WTP estimates may be overestimated. Conversely, if some of the "true zeros" really represented protests to the idea of having to pay (and therefore should have been excluded), then the average WTP may have been underestimated.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

A protocol was submitted to Kenya Medical Research Institute (KEMRI) in Kenya and the Johns Hopkins School of Public Health (JHSPH) in the US. Approval for the study was received from KEMRI (Non KEMRI 583). Institutional review board (IRB) approval was also received from JHSPH (IRB No. 00007657).

Author contributions

SF: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing –

original draft, Writing – review & editing. UK: Data curation, Formal Analysis, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. GM: Data curation, Formal Analysis, Methodology, Validation, Writing – review & editing. RG: Data curation, Formal Analysis, Methodology, Validation, Writing – review & editing. AM: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. AG: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing. JR: Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. DW: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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End-user research into understanding perceptions of and reactions to a microarray patch (MAP) for contraception among women in Ghana, Kenya and Uganda

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Introduction: Many organizations are developing new contraceptive products and approaches that promote self-care including a microarray patch (MAP) that has the potential for self-administration with appropriate training. We studied women's perceptions of the MAP technology with the primary goal of providing feedback on product attributes to inform early technical design decisions regarding various MAP contraceptive products in development by MAP developers.

Methods: Our study consisted of a qualitative phase with in-person In-Depth Interviews (IDIs) with a total of 60 women of reproductive age (WRA) and quantitative surveys, via face-to-face computer-assisted interviews of a total of 927 women in Ghana, Kenya and Uganda. Women's perceptions on 12 attributes of the MAP were assessed through written descriptions, a profile, and visual stimuli such as graphics and images.

Results: Overall, the most widely preferred attribute set included: a hand-applied MAP, utilizing one circular patch, with a sticky backing, no larger than 2 cm diameter in size, applied by self, to the arm, offering sensory feedback (clicking sound and/or color change signals) to confirm enough pressure, successful application and removal, lasting 6 months with up to 12 months return to natural state of fertility. There is space to allow for variation in MAP designs (including the use of an applicator or provider administered MAP) if the design promotes and reflects the needs and expectations of users and providers.

Discussion: The contraceptive MAP had a high and broad level of appeal amongst all groups of women who participated in the study and has a strong value proposition around important contraceptive needs such as ease of use, convenience, and discretion.

KEYWORDS

family planning, Africa, social behavioural research, microneedles, acceptability, products in development, MAP developers, MAP attributes

1 Introduction

The Sustainable Development Goals call for universal access to sexual and reproductive health care services including increasing the proportion of women of reproductive age (WRA) (15–49 years) who have their family planning needs satisfied by use of a modern contraceptive method (1). Despite progress to meet this goal, just over half (56%) of WRA who wanted to avoid pregnancy in sub-Saharan Africa were using a modern method in 2021 (2). The World Health Organization (WHO) recommends self-care, or "the ability of individuals, families and communities to promote their own health, prevent disease, maintain health, and to cope with illness and disability with or without the support of a health worker" as an innovative way to increase access to primary health care while minimizing strain on the health care facilities and workers (3). Self-care has the potential to increase access to modern contraception and support women's empowerment by allowing discreet access and use in preferred locations like a pharmacy or private home, as well as to start and stop using contraception when they want to do so (4).

Many organizations are developing new contraceptive products and approaches that promote self-care including microarray patches (MAPs) that have the potential for self-administration with appropriate training. The MAP technology comprises microneedles, or micro-sized tips, attached to a backing material and applied to the skin using a finger or applicator allowing for transdermal drug delivery (5) (Supplementary Figure S1). The MAP technology is being studied for use in several indications including vaccines, HIV prevention drugs and long-acting contraception (5–15).

Research to understand end-user perspectives is important to incorporate early and often in the development of new products, but has not always been practiced in the sexual and reproductive health field (16–20). Product characteristics such as duration of action, form (e.g., pill, injection), presence and magnitude of side effects, user- vs. provider-administration and many other factors like risk perception, social and cultural norms and costs influence whether someone will use and continue a method (16, 17, 20, 21). Over the past decade, there has been an effort to study and incorporate end-user preferences into the design of new contraceptives, HIV prevention products and multi-purpose prevention technologies (MPTs) (16–18, 20–25). The results of these studies indicate several areas of overlap including preferences for discretion, longer duration, and ease of use and are relevant when considering use of a MAP platform for contraception, HIV prevention or a combination of both (24–31).

Our study's primary objective was to provide feedback to MAP developers on MAPs' product-based attributes to inform early technical design. The secondary objective was to understand what respondents thought about MAPs and what they saw as its value from the various stimuli, the Consumer Target Product Profile (CTPP), and product attributes respondents were shown. The third objective was to understand interest and intent to try, as well as whether respondents thought MAPs was a better contraceptive option than those they knew of. Given the proprietary nature of product development, this publication does not include specific information on any one product but provides overall suggestions for researchers and practitioners to consider when developing a contraceptive MAP.

The study was conducted in Ghana, Kenya, and Uganda and included qualitative and quantitative methodologies to triangulate the findings and generate insights. These three countries were selected to represent voices from both East and West Africa with varying rates of contraceptive use and method mix, wherein the depot medroxyprogesterone acetate (DMPA) contraceptive injection is one of the most used methods (32).

2 Methods

2.1 Overview of project

Figure 1 shows the flow of the research study results and findings. The results of the research will follow the objectives laid out in the methodology of this paper, with the inclusion of an upfront section based on results which illustrate the environment and context of the respondents who took part in this study.

Our study consisted of two phases: a qualitative phase with in-person In-Depth Interviews (IDIs), followed by a quantitative phase upon the completion of the qualitative research and analysis, via face-to-face computer-assisted interviews (CAPI). Respondents that participated in the qualitative component did not participate in the quantitative component. All interviews were conducted at a place of the respondent's choosing, often in their home, or a space they felt they could talk openly. The primary objective sought to gauge women's perceptions on 12 attributes of the MAP were assessed through written descriptions, a profile, and visual stimuli such as graphics and images. The secondary objective of this research naturally overlaps with the first objective. A value proposition is how a product or product attributes can fill relevant end-user needs. Therefore, the value of a product naturally builds on and from the product attributes themselves.

2.2 Qualitative phase

2.2.1 Sample and data collection

Data were collected via in-person IDIs with a total of 60 women in Ghana, Kenya and Uganda. The target population consisted of WRA, who self-reported as being sexually active (with a man in the last 3 months), not currently pregnant and not planning to conceive in the next year, open to using contraceptives/family planning, and in Socio Economic Class (SEC) C-D. This research utilized the EquityTool which is a short, country-specific questionnaire to measure relative wealth (34). SEC strata C and D were selected for this research as they encompass the broadest and largest section of the population, and are critical target populations for contraceptive programs. Eighteen to 40 was selected as the age range for the qualitative sample as an upper limit of 40 was considered to be able to provide an adequate representation of the older age range among childbearing women in qualitative work. Aside from the

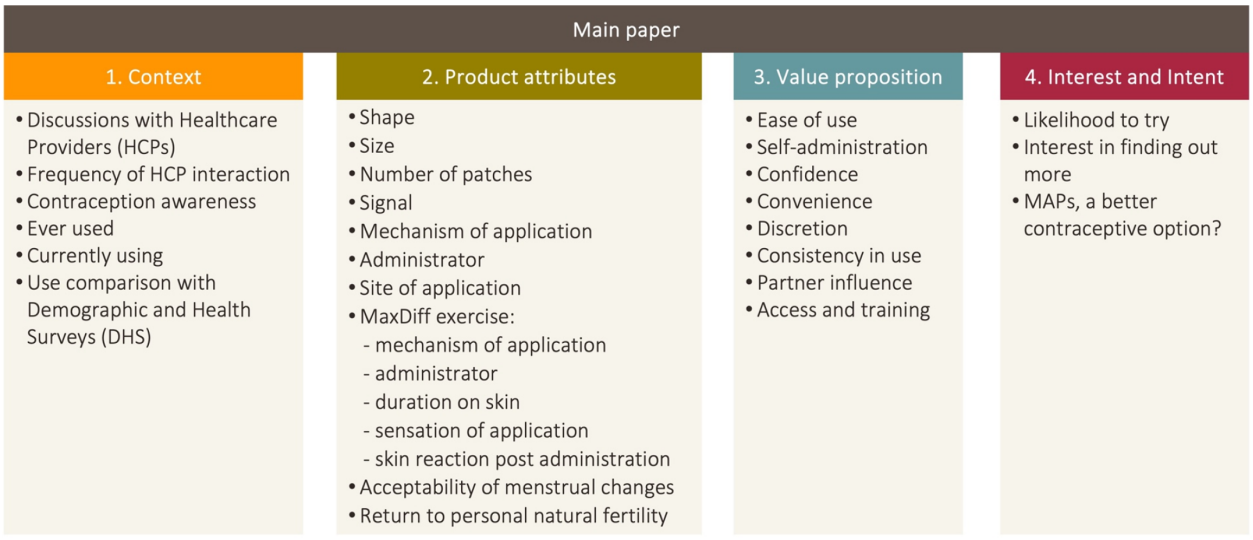

FIGURE 1
Research study results and findings flow.

eligibility criteria detailed above, there were no quotas to subdivide the sample, and characteristics of the sample depended on the natural fallout following recruitment. For the qualitative component, discussions lasted between 40 and 60 minutes with the consent of respondents in face-to-face one-on-one IDIs. For data collection, interviews were audio-recorded, transcribed, and, where necessary, translated prior to analysis.

2.2.2 Data analysis

For the qualitative data, a coding framework was developed by the study team following a primary round of reviews of the first set of transcripts. This initial framework was then used to code all remaining transcripts fully, with scope to broaden and clarify the initial code frame as more transcripts were reviewed and analyzed. The third round of analysis identified key themes that emerged from the data, as well as points of difference. An iterative and systematic process of content and pattern analysis was carried out. The study team used the analytical categories developed as part of the coding framework to derive meaning from the various pieces of evidence to answer the research questions.

2.3 Quantitative phase

2.3.1 Sample and data collection

The quantitative phase took place subsequently to the qualitative phase. Data were collected via face-to-face CAPI of a total of 927 women in Ghana, Kenya and Uganda. The target population for the quantitative phase mirrored that of the qualitative phase; the age range, however, of 18–49 was chosen, to reflect recommendations by the WHO for survey research among WRA (35). Other demographic information was captured during the interviews (Table 1); however, this did not determine eligibility.

For the quantitative phase, women were surveyed via face-to-face computer-assisted 30-minute interviews. For data collection, mobile phones/tablets with offline data storage capability were used and data were automatically uploaded when an internet connection was available.

2.3.2 MaxDiff

For the quantitative research study, a MaxDiff exercise was co-created through consultations with MAP product developers, product development experts, and contraception experts and researchers. A pre-defined set of product attributes were selected, and within each attribute a number of variables (on how it would perform or act) were developed. These attributes were considered important to inform product development in aspects where variation was possible and where end-users' perceptions were unknown. The exercise was approximately halfway through the interview after respondents had read and thought about the CTPP.

The MaxDiff methodology is a useful tool to extract least and most motivating attributes. Respondents were shown a series of six screens, where each screen presented one set of two options and respondents indicated which was more and which was less motivating. Scoring was then calculated based on the number of times an option was shown *and* selected as less motivating and more motivating.

2.3.3 Data analysis

The closed-ended quantitative data were analyzed initially by total base size including an examination of data at a total respondent level and at a country level. Following this, quantitative data were analyzed by key groups such as marital status, across age groups, and urban vs. rural.

In accordance with the conventional acceptance of statistical significance at a *P*-value of 0.05 or 5%, confidence intervals (CI) are frequently calculated at a confidence level of 95%. Tests used in

TABLE 1 Demographic and motherhood-related data, self-reported at quantitative phase of this study (%).

Demographics	Total ($n = 927$)	Ghana ($n = 315$)	Kenya ($n = 303$)	Uganda ($n = 309$)
Age (%)				
18–23 years old	23.9	27.9	23.1	20.7
24–30 years old	40.1	37.5	39.3	43.7
31–35 years old	18.2	17.8	18.8	18.1
36–48 years old	17.7	16.8	18.8	17.5
Mean (years)	28.95	28.46	29.32	29.06
Education level (%)				
Primary + below	16.1	14.0	18.8	15.5
Junior secondary	17.8	27.3[b]	7.9	17.8
Senior secondary	41.4	43.5	51.2	29.8[a]
Higher education	23.8	14	23	36
Religion (%)				
Practicing	87.1	91.4	90.1	79.6[a]
Non-practicing	12.5	8.3	9.2	20.1[b]
Christian	34.0	47.0	46.5	8.4[a]
Protestant	21.1	4.1[a]	24.1	35.6
Catholic	16.5	5.4	12.2	32.0[b]
Pentecostal	16.2	31.7[b]	8.3	8.1
Muslim	11.5	10.8	8.3	15.5
Other	0.3	0.6	2	0.3
No religion	0.3	0.3	0.7	–
Relationship status (%)				
Married live*	53.6	37.1	70.3[b]	54.0
Single + BFs***	17.0	23.5[b]	13.9	13.6
Not living together	10.4	12.7	7.3	11.0
Living together	9.6	15.6[b]	3.3	9.7
Married not live**	4.6	3.5	2.0	8.4[b]
Single + BF(s)***	17.0	23.5[b]	13.9	13.6
Single no BF(s)***	3.6	7.0[b]	2.0	1.6
Widowed	0.9	0.6	1.0	1.0
Divorced	0.3	–	0.3	0.6
Motherhood				
	Total ($n = 927$)	Ghana ($n = 315$)	Kenya ($n = 303$)	Uganda ($n = 309$)
Number of pregnancies (%)				
None	18.3	27.6[b]	13.9	13.3
1	24.8	21.3	27.4	25.9
2	24.5	21.3	24.8	27.5
3	17.8	16.5	20.1	16.8
4	8.3	6.3	6.6	12.0[b]
5	4.4	5.1	5.0	3.2
6	1.8	1.9	2.3	1.3
Mean	1.95	1.75[a]	2.05	2.06
Number of children (%)				
None	20.9	32.1[b]	15.2	15.2
1	26.3	21.0[a]	28.7	29.4
2	25.4	20.3[a]	28.4	27.5
3	16.3	15.2	17.2	16.5
4+	11.1	11.4	10.6	11.3
Mean	1.76	1.60	1.85	1.83
Pregnancy desire (%)				
Yes, next 2 years.	28.4	27.9	22.8	34.3
Yes, >2 years.	53.1	59.4	47.9	51.8
I don't want any	18.6	12.7	29.4	13.9

(*Continued*)

TABLE 1 Continued

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.
*Married living with partner.
**Married not living with partner.
***Boy Friend(s).

analysis included paired/overlap *T*-Test for means and paired/overlap *Z*-Test for percentages. In general, if an observed result is statistically significant at a *P*-value of 0.05, then the null hypothesis should not fall within the 95% CI. Statistical significance ($P < 0.05$) is observed when data in one country is different from findings in the other that are not due to chance. There were, however, no significant differences between sample groups (demographics such as age, setting, contraceptive use etc.,) which were relevant to the objectives. Results from the qualitative research are given to provide context to the quantitative results.

Perceived ease of administration, interest, intent and whether respondents felt the MAP was an improvement on current contraception they were aware of, will be presented including Top 2 Box scores (T2B or "positive" scoring) and Bottom 2 Box (B2B or "negative" scoring) scores as a way of looking at the Likert scale questions. The Top 2 Box score is a method utilized within the market research industry of summarizing the positive responses (the two most positive options in a Likert scale question), and the Bottom 2 Box scores are a way of summarizing the negative responses (the two most negative options in a Likert scale question). This paper does not wholly rely on Top 2 Box or Bottom 2 Box scoring, and will also present each score for every rating statement within the overall scale.

Where predefined lists of reasons were provided in the quantitative questionnaire, these were written based on answers from the qualitative phase, with an "Other—specify" option also included.

Open-ended data within the quantitative interviews were also analyzed. The process began with review of verbatim responses for each question. Common themes were identified, as well as factors associated with each theme. This represented a code frame. Each verbatim response was then analyzed and assigned to its appropriate code.

2.4 Shared methodology

2.4.1 Recruitment methods

For each country, specific urban and rural locations were selected with three key locations in each market (Table 2). These locations were selected to provide cultural and social variances and geographical diversity. Within each of these locations, the research was conducted in the main urban area and also

TABLE 2 Sample across qualitative and quantitative phases of this study (n = 987).

	Total	Ghana	Kenya	Uganda
Overall sample				
Total	60	20	20	20
Region 1: Abokobi (Ghana), Ndumberi (Kenya), Kiyindi (Uganda)	30	10	10	10
Region 2: Juaben (Ghana), Muhoroni (Kenya), Masese (Uganda)	30	10	10	10
Quantitative sample across regions				
Total	927	315	303	309
Region 1: Accra (Ghana), Nairobi (Kenya), Kampala (Uganda)	303	100	100	103
Region 2: Akokobi (Ghana), Kisumu (Kenya), Jinja Uganda)	185	100	42	43
Region 3: Takoradi (Ghana), Muhoroni (Kenya), Mbarara (Uganda)	134	51	41	42
Region 4: Juabeb (Ghana), Mombasa (Kenya), Kyanja (Uganda)	112	31	40	41
Region 5: Kumasi (Ghana), Ndumberi (Kenya), Masese (Uganda)	107	27	40	40
Region 6: Ukunda (Uganda only)	40	–	40	–

surrounding rural regions. A 50-50 split between urban and rural was achieved with the aim of providing an urban and rural view of each country.

The recruitment process was consistent across all three countries and all regions. The target population was recruited using screening questionnaires (programmed and conducted on CAPI devices), which set out eligibility to take part in the research. All recruitment teams were female-led, and respondents were recruited from low-income areas. Specific households were selected through a random walk process (from a landmark such as a school, hospital or similar) whereby the teams attempt door-to-door screening with skips between houses (three dwellings in a rural area and five in an urban area).

2.4.2 Stimuli

Participants in both parts of the study were shown the same stimuli: an overview of the MAP based on five showcards and moderator script (Supplementary Figure S1); an end-user-friendly profile (CTPP) read alongside the moderator/interviewer who would check in on understanding throughout (Supplementary Figure S2); images depicting potential patch appearance: shape (Supplementary Figure S3), size (Supplementary Figure S4), application site (Supplementary Figure S5), applicator types (due to intellectual property rights, applicator type images cannot be reproduced in this article) and a show-card presenting options of duration of pregnancy prevention against time to potential return to personal natural fertility (RTF) (Supplementary Figure S6). All stimuli were translated, and translations were offered throughout the interview to ensure optimal understanding of the research questions, and maximize ease of conversation for the respondent. Stimuli were always shown to all participants in the same order.

2.4.3 Translations

All informed consent forms, stimuli and research tools were translated into the main languages spoken in the areas where fieldwork was conducted (Twi in Ghana, Kiswahili in Kenya, Luganda in Uganda). Respondents were able to choose languages for written materials and discussion, and to switch if preferred.

2.4.4 Data collection

All interviews were conducted by interviewers from Ask Afrika and their in-country offices who were trained in market research methodologies and were native speakers. The research teams (comprising female interviewers and recruiters and mixed-sex supervisors) were briefed and trained, and pilot interviews were observed across all countries ensuring adherence to objectives, processes and ethical considerations.

2.4.5 COVID-19

Due to the COVID-19 pandemic, precautions were put in place to minimize risk of viral transmission. Inter-country travel was minimized; the study team briefed the in-country fieldwork teams remotely using video meeting technology. Fieldwork was conducted only when there were no government restrictions in place which would be contravened by carrying out this work. Guidelines were developed based on those provided for face-to-face interviewing by the European Society for Opinion and Marketing Research (ESOMAR) (35). Provision was made for the use of alternative formats for completing the research such as telephone or video conferencing tools, if needed, to comply with government restrictions; in the event, however, it was possible to conduct all research face-to-face.

3 Results

3.1 Context

Table 1 illustrates the demographic make-up, including age, education level, religion, relationship status, number of pregnancies, children, and desire for more children in the next two years from the quantitative survey. Table 2 illustrates the achieved sample for qualitative and quantitative phases of this study across the regions per country.

3.2 Interaction with healthcare practitioner (HCP) about/accessing contraception

3.2.1 Quantitative

Table 3 respondents were asked whether they have ever talked to an HCP about contraceptives. HCPs were described to respondents as including a doctor, a nurse, a nurse-midwife or community healthcare worker in a clinic or elsewhere. In Ghana more than half (59.4%, significantly high) of respondents reported not having any discussions with HCPs, compared to just under a quarter in Kenya and Uganda (24.1% and 23.6% respectively). Of those that reported having discussions with HCPs, these mostly happened in a clinic setting [Ghana 31.7%; Kenya 70.0% (significantly high); Uganda 48.2%]. Respondents in Uganda reported having a much higher frequency of interaction with HCPs (7.5 times on average in the last 12 months, significantly high), compared to 2.1 times (Ghana) and 1.5 times (Kenya).

In Kenya and Uganda, most obtained their current contraceptives in a healthcare facility (66% and 74% respectively), and there was a split in Ghana between healthcare facility and pharmacy (41% vs. 36% respectively). The majority of healthcare facilities accessed were in a public setting across all three countries, at 71.9% overall (Ghana 78.6%, Kenya 78.0%, Uganda 63.9%) whereas 28.1% overall accessed contraceptives from a private facility (28.1% in Ghana, 21.4% in Kenya and 36.1% Uganda).

TABLE 3 Interaction with HCPs—conversations about contraception, frequency and where most recent contraceptive was obtained (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
Interaction with HCPs—conversations about contraceptives (%)				
Yes, in a clinic	49.7	31.7	70.0[b]	48.2
No, never spoken to HCP	35.9	59.4[b]	24.1	23.6
Yes, elsewhere, not in a clinic	14.3	8.9	5.9	28.2[b]
Frequency of conversations with HCPs in past 12 months—about contraceptives (#) mean/median number of discussions in the past 12 months				
Sample (*n*=)	461	100	212	149
In a clinic (mean)	2.36	2.1	1.5	7.5[b]
Sample (*n*=)	133	28	18	87
Elsewhere, not in a clinic (median)	2.0	2.0	1.0	2.0
Where most recent contraceptive was obtained (%) of women that named a recent contraceptive				
Sample (*n*=)	478	102	196	180
Healthcare facility	62.3	41.2	64.8	73.9
Pharmacy/drug store	26.6	36.3	27.0	20.6
Do not know/no answer	6.3	12.7	6.1	2.5
In the community	4.0	9.8	2.0	2.8
Setting: public or private for location of most recently obtained contraceptive (%)				
Public	71.9	78.6	78.0	75.4
Private	28.1	21.4	22.0	36.1

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

3.3 Contraceptive awareness

Male condoms had the highest level of awareness across all countries (Table 4) (83.2% in Ghana, 96.0% in Kenya and 75.4% in Uganda). This was followed by the oral contraceptive pill (70.5% in Ghana, 94.7% in Kenya and 85.8% in Uganda). The third most selected method was the contraceptive injection (68.6% Ghana, 96.0% in Kenya and 87.1% in Uganda). Kenya generally had significantly higher awareness levels than Ghana and Uganda across nearly all (10 out of 15) methods, except the Contraceptive Vaginal Ring (CVR) DMPA and DMPA sub cutaneous (DMPA-SC) injectables. Conversely, Ghana had significantly lower percentages of respondents reporting awareness of listed methods (7 out of 15).

3.4 Contraceptive use

A third (30.7% in Kenya and 30.0% Uganda) to just under half (47.3% in Ghana (significantly high) were not currently using a contraceptive (Table 5). Overall, 12.3% stated they had discontinued their contraceptive use. Ghana had a significantly higher proportion of respondents (20.3%) who had discontinued their contraceptive compared to Kenya and Uganda (5.3% and 11.0% respectively). Male condom was the most ever used method by 60.5% of respondents overall (52.9% in Ghana, 64.7% in Kenya and 64.1% in Uganda). The next most ever used contraceptive was the contraceptive injection which was selected by 43.1% of respondents overall [26.8% in Ghana (significantly low), 55.8% in Kenya and

TABLE 4 Aided awareness of contraception/methods to prevent pregnancy/family planning (%).

	Total	Ghana	Kenya	Uganda
Aided awareness of contraceptive methods (%)				
Sample (*n*=)	927	315	303	309
Male condom	84.8	83.2	96.0[b]	75.4
Oral daily contraceptive pill	83.5	70.5[a]	94.7[b]	85.8
Contraceptive injection	83.7	68.6[a]	96.0[b]	87.1
Oral emergency contraceptive pill	65.9	62.9	83.5[b]	51.8[a]
Contraceptive implant/rod	69.9	48.9[a]	88.4[b]	73.1
Female condom	58.0	50.2	80.5[b]	44.0
Intrauterine device (IUD)	48.8	25.1[a]	65.3[b]	56.6
Counting days	30.9	26.7	42.2[b]	23.9
Hormonal IUD	28.5	15.6[a]	38.9[b]	31.4
Contraceptive vaginal ring (CVR)	25.6	14.9[a]	26.7	35.3[b]
Withdrawal	23.7	22.9	27.1	21.4
Contraceptive patch	14.9	12.7	19.8[b]	12.3
Depot medroxyprogesterone acetate sub cutaneous (DMPA-SC)	13.5	5.7[a]	13.9	21.0[b]
Diaphragm/cap	11.4	11.1	13.2	10.0
Spermicide	10.0	7.3	9.2	13.6
Other methods	1.6	0.3	1.3	3.2
None — I have never heard of any methods	0.1	0.3	–	–

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

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TABLE 5 Ever and current use of contraception.

	Total	Ghana	Kenya	Uganda
Total Sample (*n*=)	927	315	303	309
Ever used contraceptive (%) [methods used by over 2% of sample listed]				
Male condom	60.5	52.9	64.7	64.1
Contraceptive injection	43.1	26.8[a]	55.8	47.2
Oral daily contraceptive pill	35.4	27.1[a]	40.3	39.2
Oral emergency contraceptive pill	33.3	26.8[a]	55.8	47.2
Contraceptive implant	25.1	15.0[a]	34.7[b]	25.9
Counting days	23.7	24.8	27.4	18.8
Withdrawal	17.8	19.4	19.5	14.6
IUD	6.8	2.5[a]	8.3	9.7
Female condom	5.1	4.8	7.3	3.2
None	3.7	7.6[b]	1.3	1.9
DMPA-SC	2.6	1.0	1.3	5.5[b]
Hormonal IUD	2.4	1.6	3.3	2.3
CVR	2.3	1.0	1.0	4.9[b]
Currently used contraceptive (%) [methods used by over 2% of sample listed]				
Demographic Data (DHS)*	–	DHS 2014	DHS 2020	DHS 2016
Modern contraceptive use by all women[†], DHS %				
		18.2	42.0	27.3
Total R2R**		DHS / R2R	DHS / R2R	DHS / R2R
Contraceptive injection	18.0	6.0 / 12.7[a]	13.6 / 20.8	13.9 / 20.7
Contraceptive implant	12.6	3.7 / 6.7[a]	13.2 / 18.5	4.7 / 12.9
Male condom	9.9	2.0 / 11.4	3.8 / 9.6	3.1 / 8.7
Oral daily contraceptive pill	9.6	3.9 / 6.7	5.3 / 10.6	1.5 / 11.7
Oral emergency contraceptive pill	5.4	[‡] / 10.3[b]	0.6 / 3.0	0.1 / 2.9
Counting days	4.4	3.1 / 6.7	3.7 / 4.6	1.2 / 1.9
Withdrawal	3.6	1.4 / 4.1	1.1 / 3.6	1.9 / 2.9
I am not currently using	36.1	77.2 / 47.3[b]	53.4 / 30.0	69.7 / 30.7

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.
*DHS data refers to USAID's Demographic and Health Surveys Program data.
**R2R stands for Routes2Results, data from this study.
[†]DHS data relates to women from 15 to 49 years, whereas R2R data collected included women from the age of 18 to 49 years, and participants in the R2R study were screened into the research on the basis that they were sexually active, and open to using contraceptives.
[‡]No data available.

47.2% in Uganda]. Over a third of the overall sample reported ever use of the oral daily pill and oral emergency pill (35.4% and 33.3% respectively).

Current use for any specific contraceptive method was low. The injection was the most currently used method by 18.0% of respondents overall [12.7% in Ghana (significantly low) and 20.8% in Kenya and 20.7% in Uganda], with the vast majority (72.7% overall) using DMPA Intramuscular (DMPA-IM) three-monthly injection. Between a third (Kenya and Uganda) or nearly half (Ghana) of the respondents in this study were not currently using anything to prevent an unwanted pregnancy. However, Demographic and Health Survey (DHS) data from all countries shows higher percentages of women not currently using from 53.5% (Kenya) to 77.2% (Ghana) (36–38).

3.5 Primary objective

3.5.1 MAP attributes

Women's perceptions on 12 attributes of the MAP were assessed. These were: shape of the patch, size of the patch, the number of patches, sensory feedback mechanisms/signals to confirm correct usage, mechanism of application, preferred administrator, site of application, duration on skin, sensation of application, administration site reactions, menstrual changes and return to personal natural fertility level.

3.5.2 Shape

In both phases, respondents were shown two possible MAP shapes: a circle and a rectangle (Supplementary Figure S3).

3.5.2.1 Qualitative

In the qualitative component of the study, views on shape were mixed. Respondents were asked about whether they had any preferences on shape, and around half indicated that they did; even among those who specified a preferred shape, there was a moderately common view that it was not of great importance. Reasons for shape preference were similar across the actual shape options preferred: a perception that certain shapes (particularly the circle) were smaller, and easier to use. Some respondents mentioned that the shape was not important as compared to the functionality of the MAP.

3.5.2.2 Quantitative

The quantitative results indicated that respondents had a strong preference for a circular patch (74.2% overall). This preference was present in all countries, but was more prevalent in Ghana and Kenya [85.7% (significantly high) and 73.9% of respondents respectively] than in Uganda (62.8% of respondents). Overall, 18.2% of respondents selected rectangle, which was driven by Uganda and Kenya (25.9% and 17.8% respectively), whereas a small percentage of respondents from Ghana selected rectangle (11.1%). Respondents were also given the answer option of "no preference", which was selected by 7.65% overall [3.2% in Ghana (significantly low), 8.3% in Kenya and 11.3% in Uganda].

3.5.3 Size

Respondents were shown in both the qualitative and quantitative phases three visual graphics representing the three possible sizes for a square MAP: 2 × 2 cm, 3 × 3 cm and 5 × 5 cm (Supplementary Figure S4).

3.5.3.1 Qualitative

Respondents in all three countries expressed a preference for the smallest patch size; the main reasons given for this were discretion, both in terms of perceived discreet application (for example, potential irritation left post application would cover a smaller area) and fear of worse side effects with a larger patch size. It is of note, however, that almost all respondents indicated, when asked, that if the biggest patch were to be the only available option, they would still be willing to try the MAP on the grounds that it would fulfill the same function.

3.5.3.2 Quantitative

In general, a smaller size was preferable. Three quarters of respondents in all countries (75.0% overall) preferred the smallest given option of 2 × 2 cm (76.8% in Ghana, 75.6% in Kenya and 72.5% in Uganda); the next smallest size, 3 × 3 cm, was preferred by around a quarter (26.3% overall) of respondents (25.1% in Ghana, 26.1% in Kenya and 27.8% in Uganda). The largest size, 5 × 5 cm, was preferred by a small minority (5.5% overall) of respondents [3.5% in Ghana, 2.0% in Kenya and 11.0% in Uganda (significantly high)].

3.5.4 Number of patches and duration of protection

Across the quantitative and qualitative results, respondents reacted negatively to the idea of using multiple patches to achieve the same duration of protection (6 months) which had been proposed as being achieved by one patch, and to the idea of multiple patches in general.

3.5.4.1 Qualitative

The majority of respondents indicated that multiple patches (2, 3, or 4) would not be acceptable, and the already limited acceptability declined as the number of patches increased, regardless of patch size. As with the idea of larger patches, respondents were concerned about the potential of increased side effects and possible discomfort at application, alongside the corresponding potential impact on discretion. The idea of multiple patches was felt to undermine the product's appeal of 6 months' continuous protection, its perceived simplicity with regard to ease of use, and the ability to maintain discretion around its usage.

3.5.4.2 Quantitative

Respondents were asked whether three duration sets of pregnancy prevention (1 month, 3 months and 6 months) and three patch number options (one, two or three patches) were acceptable. Acceptability was discussed for each option set provided (Table 6). The most acceptable set, selected by 89.4% overall, was one patch to achieve 6 months of pregnancy prevention [87.6% in Ghana, 93.7% in Kenya (Significantly high), 87.1% in Uganda]. There was openness to one patch to achieve 3 months of pregnancy prevention which was the second most acceptable set, selected by 40.9% overall, (44.1% in Ghana, 42.6% in Kenya and 35.9% in Uganda). The remaining duration sets did not garner much acceptability support, however one patch to achieve 1 month of pregnancy prevention was selected as acceptable by a quarter (25.1%) overall, which was driven by Uganda (30.4% significantly high).

TABLE 6 Acceptability of number of patches (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
1 patch to achieve 6 months of pregnancy prevention	89.4	87.6	93.7[b]	87.1
1 patch to achieve 3 months of pregnancy prevention	40.9	44.1	42.6	35.9
1 patch to achieve 1 month of pregnancy prevention	25.1	22.9	22.1	30.4[b]
2 patches to achieve 6 months of pregnancy prevention	22.2	11.4	37.3[b]	18.4
3 patches to achieve 6 months	13.3	5.4[a]	18.5	16.2

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

3.5.5 Sensory feedback mechanisms

Respondents were asked to choose whether they would want sensory feedback mechanisms or signals at any of the following three stages: to indicate that the patch had been successfully applied to the body, whether enough pressure had been applied, and whether the patch could be removed.

3.5.5.1 Qualitative

The clicking sound or color change was most preferred by respondents, depending on whether there is greater preference for associating correct application with sight (color change) or sound (click). The clicking sound was strongly associated with having applied enough pressure. It was perceived as useful in terms of alerting the user if they were to become distracted during the process of application, but there was a caveat from a minority of users around it not being acceptable if it were loud enough that it could potentially be overheard, risking the application being noticed by others. The color change was perceived to be discreet because of its lack of audibility. Concerns around the color change related to the potential of missing the signal if it were to appear and disappear rapidly. An image appearing on patch was viewed as being similar to color change and was less preferred as it did not serve any additional purpose.

3.5.5.2 Quantitative

The signal choice set comprised color change, clicking sound, an image appearing on the patch or applicator and temporary dye appearing on the skin. Respondents were also able to choose all signals or no signal for any point; these options, however, were selected by a small minority of respondents (Table 7).

As Table 7 demonstrates, it is important to provide some feedback mechanism at any stage, color change and a clicking sound were the two most preferred signals to indicate successful application of the MAP across all stages. There was a slight preference for color change at application (43.4% overall, which was significant different in Ghana and Uganda) and a slight preference for a clicking sound to indicate that enough pressure had been applied (40.0% overall, and significantly different in Ghana). There is a split preference overall towards color change and a clicking sound for the final stage, readiness for removal (33.5% and 30.6% overall, respectively).

3.5.6 Mechanism of application

Respondents were presented with the choice of applying the MAP using an adhesive-backed patch which would be applied by hand and removed from the application site following the application process, or using an applicator (reusable or disposable) to apply the MAP.

3.5.6.1 Qualitative

Reasons for wanting an adhesive-backed patch were related to its familiarity (in terms of its similarity to a sticking plaster), that it appeared less intimidating than an applicator, and that it was

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TABLE 7 Signal preference per application stage (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
Successfully applied to the body				
Color change	43.4	45.1	42.6	42.1
Clicking sound	34.3	35.2	34.3	33.3
Images appears on skin	6.7	8.9	4.3	6.8
A dye appears on skin	4.3	4.8	5.9	2.3
All signals	5.4	2.9	7.6	5.8
No signal	4.3	1.0[a]	4.3	7.8
No preference	1.7	2.2	1.0	1.9
Enough pressure applied				
Color change	31.4	29.2	37.6[b]	27.5
Clicking sound	40.0	47.3	39.6	33.0[a]
Images appears on skin	12.0	11.7	7.9	16.2
A dye appears on skin	5.8	3.8	5.3	8.4
All signals	4.1	2.2	5.0	5.2
No signal	4.2	3.2	2.6	6.8
No preference	2.5	2.5	2.0	2.0
All steps complete—OK to remove				
Color change	33.5	40.0	36.0	24.6
Clicking sound	30.6	33.0	29.0	29.8
Images appears on skin	8.7	10.2	7.6	8.4
A dye appears on skin	5.6	3.6	10.2[b]	3.2
All signals	8.4	3.2	9.2	12.9
No signal	9.4	6.7	6.3	15.2[b]
No preference	3.7	3.5	1.7	5.8

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

considered more discreet than an applicator. There was, however, a concern raised by some respondents regarding the adhesive-backed patch, relating to the challenge of applying the correct amount of pressure evenly across the surface of the patch.

The applicator was seen to address the concern around consistency of action, pressure and correct application. It was also considered to be faster than the patch, and by a minority of respondents, more hygienic. Concerns relating to the applicator were that it might be forceful and that it was seen to be potentially painful.

3.5.6.2 Quantitative

(Table 8) most respondents (60.3%) preferred the adhesive-backed patch, with 34.1% preferring the applicator, and 5.6% having no preference. There were country differences, most respondents in Ghana and Kenya preferred the adhesive-backed patch [78.1% (significantly high) and 65.0% respectively; 37.5% in Uganda (significantly low)], with most respondents in Uganda preferring the applicator [52.1% (significantly high); 19.7% in Ghana (significantly low), 30.7% in Kenya].

TABLE 8 Preferred device type (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
Adhesive ("sticky") backed patch	60.3	78.1[b]	65.0	37.5[a]
Applicator	34.1	19.7[a]	30.7	52.1[b]
No preference	5.6	2.2	4.3	10.4[b]

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

3.6 Administration/administrator

3.6.1 Most preferred

3.6.1.1 Qualitative

Self-application was most preferred, followed closely by HCP application—particularly at the initial application, as HCPs were perceived as being able to educate and enable women to self-administer the MAP with confidence in the future. Respondents perceived self-application as discreet, because they could select when and where they chose to apply the MAP, without the involvement of anyone else. It was also perceived as convenient for the same reason; that no one else's assistance or involvement is required.

3.6.1.2 Quantitative

A pre-defined list comprising self, partner, family member, friend and two sets of three HCP options (physician or nurse; community healthcare worker; pharmacist, either every time or HCP first or self thereafter) and an "Other—specify" option; HCP responses were grouped. Overall, 49.1% of respondents preferred self-administration (Table 9), which was driven by respondents in Ghana (81.1% significantly high) compared to respondents in Kenya 36.4% and Uganda 27.9% (significantly low). For respondents in Kenya, the same percentage, 36.0% (significantly high), selected self-administration after initial administration by a physician or a nurse, compared to Ghana (4.2% significantly low) and Uganda (10.3%). For respondents in Uganda, over a third preferred administration by a physician or a nurse (33.1% significantly high), whereas under a third preferred self-administration (27.9%).

TABLE 9 Preferred administrator of MAP (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
I would administer it myself	49.1	81.1[b]	36.4	27.9[a]
A physician or nurse administers it the first time and then I would administer it to myself thereafter	16.4	4.2[a]	36.0[b]	10.3
A physician or nurse	16.0	2.5[a]	12.9	33.1[b]
My partner	5.6	8.1	3.0	5.5
A Community Healthcare Worker (CHW)	5.0	1.4	1.1	12.5[b]
A CHW administers it the first time and then I would administer it to myself thereafter	2.6	0.4[a]	2.7	4.8
A pharmacist	1.8	1.1	2.7	1.8
A pharmacist administers it the first time and then I would administer it to myself thereafter	1.5	–	3.8[b]	0.7
A friend	1.2	1.1	1.1	1.5
A family member	0.5	0.4	–	1.1
Other	0.4	–	0.4	0.7

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

3.6.2 Least preferred

3.6.2.1 Qualitative

Partners, family members and friends received the lowest preference. For partners, the reasons for this were that the partners may not have a high level of awareness of contraception and were not felt to be knowledgeable or reliable in terms of correct application, and that partners may not approve of using contraception. Family members and friends were felt not to be trustworthy in terms of confidentiality, in stark contrast to the view of HCPs; furthermore, respondents noted that family and friends may not support family planning, and as with partners, respondents were not confident that they would be able to apply the MAP better than they would themselves.

3.6.2.2 Quantitative

Family was selected the least often (0.4% in Ghana, 0.0% Kenya, 0.7% in Uganda); friend was selected by 1.2% in all three countries; partner was selected by 5.6% overall (8.1% in Ghana, 3.0% in Kenya and 5.5% in Uganda).

3.6.3 Site of application

Respondents were offered a pre-defined selection of potential application sites on the body and were asked to determine which sites were acceptable or unacceptable. Respondents were shown a women's body map designed specifically for this research (Supplementary Figure S5).

3.6.3.1 Qualitative

Upper arms (with inner more preferred than outer, but both accepted) and thighs were the preferred application sites. Figure 2 illustrates the level of preference across the body map according to the person administering the MAP. Respondents noted that they felt confident that they could apply the MAP in these areas themselves with sufficient pressure, and that they were easy to reach, and the MAP could be applied sitting down to both areas. Furthermore, these areas are not frequently touched, not too sensitive and have the lowest perceived risk of post-application skin irritation. There was a split in opinion regarding the shoulder, in terms of whether it was perceived as an accessible area. The calf and back were perceived as hard to reach. A minority of respondents perceived that certain areas would create risk either to the MAP's efficacy or to the health of the respondent; the kneecap was seen as bony and uncomfortable, and there was concern that friction would impact the MAP, and the abdomen was viewed as delicate and close to important organs, leading to concern about how the medication would affect this area.

In terms of application by someone else, shoulder and knee were not preferred. As with self-administration, upper arms and thighs were preferred, with the addition of back and calf; for these areas, preference depended on privacy (in terms of coverage with clothing and how much clothing would need to be removed to allow access). For partner application, which was preferred by a minority of respondents, all areas were considered acceptable apart from knee and calf, with thigh and arms most preferred; the abdomen was acceptable only for partners, on the grounds that it is an area which the partner already sees.

3.6.3.2 Quantitative

Respondents were asked to select which sites were acceptable for self-administration (Table 10); only self-administration was considered because the results from the qualitative phase indicated that self-administration was strongly preferred. Upper arms were the overall most preferred location. Upper outer arm was selected by 31.0% of respondents (24.8% in Ghana, 31.7% in Kenya and 36.6% in Uganda). Upper inner arm was selected by 29.1% of respondents (30.8% in Ghana, 30.4% in Kenya and 26.2% in Uganda).

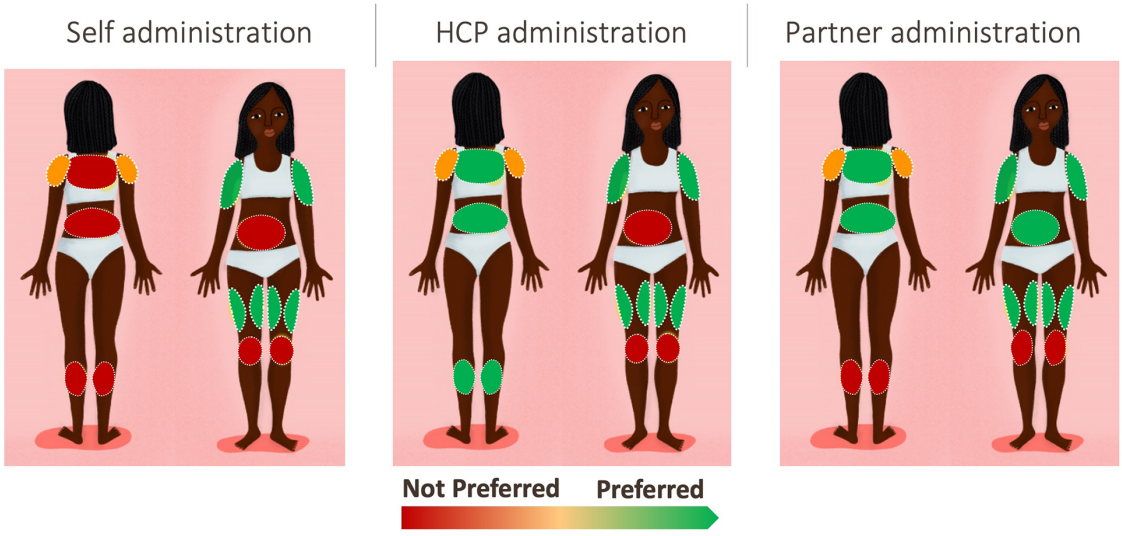

FIGURE 2
Preferred areas for administration, qualitative results.

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TABLE 10 Preferred location for MAP application (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
Upper arm (outside)	31.0	24.8	31.7	36.6
Upper arm (inside)	29.1	30.8	30.4	26.2
Upper inner thigh	10.7	12.4	10.2	9.4
Stomach (left or right)	9.3	10.5	11.6	5.8[a]
Upper outer thigh	9.1	5.4	8.3	13.6[b]
Shoulder	3.6	6.0	0.7	3.9
Knee	2.0	1.6	2.6	1.9
Upper back	1.9	2.5	1.7	1.6
Lower back (left or right)	1.8	4.4[b]	0.7	0.3
Calf	1.5	1.6	2.3	0.6

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

3.6.4 MaxDiff exercise: mechanism of application, administrator, duration on skin, sensation of application and skin affect post administration

3.6.4.1 Quantitative only

The results of the MaxDiff exercise are shown in Table 11. Among those tested, the most motivating attributes averaged across all countries were: a patch alone (47.8%), self-administered (56.0% overall), seconds on the skin (52.0%), causing a sensation of bristles or prickles against the skin, leaving small welts or scarring which disappears after a period of one day and with no visible skin irritation (65.7%). The least motivating attributes were overall: an applicator (44.2%), applied by a friend or family member (49.2%), staying on the skin for more than five minutes (59.7%), causing a pinching sensation (55.3%), visible grid of dots (52.4%) and redness, swelling that disappears after 3–4 days (51.9%).

In terms of differences between countries, the patch being selected as the most motivating option was driven by Ghana (55.6%) and Kenya (55.8%). In Uganda, while the patch was preferred (32.0%), relatively fewer respondents selected it as most motivating compared to the other two countries, and nearly a quarter (24.3%) selected most motivating for applicator variable. With regard to skin irritation and sensation, Ugandan respondents had significantly lower most motivating scores for bristles/prickles (54.7%) than Ghana (76.8%) and Kenya (75.9%). Self-administration is a clear motivating factor in Ghana (74.3%) and strong motivating factor in Kenya (59.1%). Although a motivator in Uganda (34.3%), respondents in Uganda also indicated that application by trained HCPs was also a motivating factor (32.4%).

Some product attributes were not included in the MaxDiff exercise and asked outside and after the exercise because, product

TABLE 11 Most and least motivating attribute (%).

	Total		Ghana		Kenya		Uganda	
Total sample (*n*=)	927		315		303		309	
The MAP is administered with a(n) …								
	Most	Least	Most	Least	Most	Least	Most	Least
Patch (alone)	47.8	14.1	55.6	17.5	55.8	12.9	32.0[a]	12.0
Reusable applicator and patch	22.3	17.0	21.6	11.7	18.5	21.8	26.9	17.8
One-time applicator and patch	15.4	24.6	14.3	19.0	15.2	28.7	16.8	26.2
Applicator (no patch)	14.5	44.2	8.6	51.7	10.6	36.6	24.3[b]	44.0
Who administers the MAP								
Myself	56.0	12.9	74.3[b]	13.3	59.1[a]	7.3	34.3[a]	18.1
Trained provider (pharmacist and CHW*)	23.7	16.8	11.7[a]	21.6	27.4	16.2	32.4	12.6
My partner	10.4	21.0	6.0	18.7	6.6	20.8	18.4[b]	23.6
Chosen family/friend	9.9	49.2	7.9	46.3	6.9	55.8[b]	14.9[b]	45.6
How long the MAP stays on the skin …								
Matter of seconds	52.0	14.6	52.1	21.3	54.5	16.5	49.5	5.8[a]
<1 min	16.8	10.7	22.2[b]	7.6	14.9	7.3	13.3	17.2
1–5 min	17.8	15.1	13.0[a]	14.0	18.8	13.2	21.7	18.1
>5 min	13.4	59.7	13.0	57.1	11.9	63.0	15.5	58.9
Sensation of applying MAP is like …								
Prickles against your skin; briefly uncomfortable, but it can be ignored	69.1	14.0	76.8	17.1	75.9	12.9	54.7[a]	12.0
A group of pin pricks/scratches; cannot be ignored, may interfere with concentration	15.4	30.6	11.1	23.2	11.9	32.3	23.3[b]	36.6
A pinching sensation; cannot be ignored and may interfere with concentration	15.4	55.3	12.1	59.9[b]	12.2	54.8	22.0[b]	51.5
Post administration skin affect could be …								
There is no visible skin irritation after	65.7	11.2	70.8	15.9	69.3	7.9	57.0[a]	9.7
Small welts/scarring, disappears after 1 day	51.0	19.0	62.5[b]	21.0	50.2	22.1	40.1[a]	13.9
There may be a visible "grid of dots" after; no discomfort, disappear 1 h. −1 day	31.0	52.4	29.8	53.3	33.3	52.1	29.8	51.8
Small fluid droplets under the skin, but will disappear after 1 day	18.0	28.6	7.6	25.7	16.5	25.7	30.1[b]	34.3[b]
Redness, swelling, itching, discoloration, or pain immediately, disappears after 1 h	14.7	17.2	14.0	12.4	15.5	19.8	14.6	19.4
Redness, swelling … dis. after 3–4 days	9.9	51.9	7.0	50.5	5.0	57.4	17.8[b]	47.9
Redness, swelling … dis. after 1 day	9.7	19.7	8.3	21.3	10.2	14.9	10.7	23.0

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

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attributes like side effects, menstrual changes, fertility, duration can overshadow other attributes. These attributes were either too early in development to understand variables, or the attribute/variable list were binary or unlikely to change.

3.6.5 Acceptability of menstrual changes

3.6.5.1 Quantitative

An inherent feature of giving a progestin continuously for 6 months is the possibility of changes to menstrual cycle and experience. Respondents were asked to assess the acceptability of pre-defined potential changes to their menstrual cycle from using the MAP, as follows: "It is possible that the microarray patch/MAP could cause changes to your monthly bleed/period. Would you find these changes acceptable or unacceptable, if they lasted beyond the first few months of use?". The changes asked about were *No monthly bleed/period at all* and *Irregular periods*. Overall, having no bleed and irregular periods were unacceptable for many women (78.7% and 52.0% respectively; Table 12).

3.6.6 Duration of pregnancy prevention (PP) and return to fertility (RTF)

Respondents in both the qualitative and quantitative research phases were shown the same figure (Supplementary Figure S6) and were asked to assess options of duration of pregnancy prevention against potential return to personal natural fertility (RTF).

3.6.6.1 Qualitative

Views on acceptable duration of protection and return to natural fertility time were similar across the three countries. Generally, acceptability decreased along with the duration set options; equal length of PP and RTF was also important. However, views differed and there was not one overarching consistent opinion. The main perceived advantage of contraceptive protection was expressed across the range of options: the ability to space births as needed or wanted and to have time to prepare for pregnancy. However, the preferred spacing/time differed between respondents—some wanted as long a time as possible, others wanted a shorter time. The most acceptable option was 6 months' PP with a 12-month RTF time. However, this was not acceptable to around a third of respondents. There were some respondents who felt that the RTF was too short, and for some too long, for most options. Despite the variance in opinions, some disadvantages emerged from shorter durations: affordability concerns, getting pregnant sooner than wanted, and the potential of forgetting to renew the contraceptive. The same duration sets were considered too short or too long, depending on women's current need for spacing. The question on most preferred option was added to the quantitative study after the qualitative responses were analyzed to provide more clarity regarding this complex topic.

3.6.6.2 Quantitative

Respondents in the quantitative study were asked to assess whether each pregnancy prevention and RTF duration set options (Supplementary Figure 6) was acceptable or not; they were then asked to select one of the options they had previously indicated to be acceptable as their preferred option. Respondents were also able to indicate that they had no preferred option. Table 13 shows that the three most acceptable options were 2 (6 + 6), 4 (3 + 3) and 1 (6 + 12). Overall, option 2 (6 + 6) was the option most rated as acceptable, with 57.5% of respondents indicating this (55.9% in Ghana, 61.7% in Kenya, 55.0% in Uganda). Option 4 (3 + 3) was indicated as acceptable by 46.4% of respondents [41.3% in Ghana, 54.1% in Kenya (significantly high), 44.0% in Uganda]. Option 1 (6 + 12) was rated as acceptable by 42.5% of respondents (41.0% in Ghana, 46.2% in Kenya, 40.5% in Uganda).

Respondents were then asked to select their most preferred duration set or select no preference (those who selected no

TABLE 12 Acceptability of menstrual changes (%).

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
No monthly bleed/period at all				
Unacceptable	78.7	91.4[b]	60.7[a]	83.5
Acceptable	21.3	8.6	39.3[b]	16.5
Irregular periods				
Unacceptable	52.0	45.4	51.2	59.5[b]
Acceptable	48.0	54.6	48.4	40.5[a]

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

TABLE 13 Acceptability and preference of pregnancy prevention (PP) and potential return to personal natural level of fertility (RTF) duration sets, %.

	Total	Ghana	Kenya	Uganda
Total sample (*n*=)	927	315	303	309
6 months PP + 6 months RTF (6 + 6)				
Acceptable	57.5	55.9	61.7	55.0
Unacceptable	42.5	44.1	38.3	45.0
Preference	20.2	21.9	18.2	20.4
3 months PP + 3 months RTF (3 + 3)				
Acceptable	46.4	41.3	54.1[b]	44.0
Unacceptable	53.6	58.7	45.9[a]	56.0
Preference	4.7	6.0	3.0	5.2
6 months PP + 12 months RTF (6 + 12)				
Acceptable	42.5	41.0	46.2	40.5
Unacceptable	57.5	59.0	53.8	59.5
Preference	29.2	32.1	33.0	22.7[a]
1 month PP + 1 month RTF (1 + 1)				
Acceptable	41.3	32.4	40.9	50.8[b]
Unacceptable	58.7	67.6[b]	59.1	49.2
Preference	6.7	2.5[a]	6.3	11.3[b]
3 months PP + 6 months RTF (3 + 6)				
Acceptable	34.4	28.6	37.3	37.5
Unacceptable	65.6	71.4[b]	62.7	62.5
Preference	6.4	7.0	5.6	6.5
1 month PP + 3 months RTF (1 + 3)				
Acceptable	31.8	24.1[a]	31.7	39.8[b]
Unacceptable	68.2	75.9[b]	68.3	60.2[a]
Preference	1.0	2.2	1.0	2.6
No preference	28.0	27.9	28.1	28.2

[a]Significantly lower than the 2 other countries.
[b]Significantly higher than the 2 other countries.

option was acceptable are also included in Table 13 for preference selection data). Option 1 (6 + 12) was most selected, with 29.2% of the overall sample choosing this option [32.1% in Ghana, 33.0% in Kenya, 22.7% in Uganda (significantly low)]. The next most selected options were no preference, at 28.0% overall (27.9 in Ghana, 28.1 in Kenya and 28.2 in Uganda). Option 2 (6 + 6) was preferred by 20.2% overall (21.9% in Ghana, 18.2% in Kenya, 20.4% in Uganda).

3.7 Secondary objective

3.7.1 Value proposition

The qualitative component of this study revealed a consistently held set of value propositions. There were three central value propositions for a MAP: ease of use, convenience and discretion. Qualitative discussions illustrated that they were not mutually exclusive and interact with one another. For example, respondents explained that some factors such as self-administration double up as ease of use and convenience value propositions. Furthermore, respondents also stated that something that can be self-administered also means less reliance on the healthcare system and having to spend time accessing HCPs, which was described as the convenience value proposition. Respondents described self-administration as also feeding into a very important value proposition—discretion.

3.7.2 Perceived ease of administration

3.7.2.1 Quantitative

Respondents in the quantitative phase were asked: "Based on the description and picture of the microarray patch/MAP, how easy do you think it will be to administer yourself?" Answer options were given as a 1–5 scale, with 1 being *Very difficult*, 2 being *Somewhat difficult*, 3 being *Neither easy nor difficult,* 4 being *Somewhat easy* and 5 being *Very easy*. 84.6% of the overall sample selected T2B, whereas 6.1% selected B2B. The mean score overall was high, at 4.36 out of 5.0.

Those who thought that it would be difficult to administer a MAP ($n = 57$ or 6.1% out of 927) were asked why. Reasons (coded from open-ended responses) were: that they had never used it before or that it was new ($n = 15$ or 26.3%), that they were not confident in making sure they had administered it correctly ($n = 13$ or 22.8%), that some believed that they needed training first or that it would be better to have an HCP administer the MAP ($n = 12$ or 21.1%) and that the MAP may be painful or too painful ($n = 9$ or 15.8%).

3.7.3 Confidence in MAP

3.7.3.1 Qualitative

Nearly all respondents indicated that they would have confidence in this type of contraceptive. Reasons for this confidence across all three countries were: perceived ease of use and easy application, including self-application, and discretion of the method. In Ghana and Kenya, safety, manageable side effects and no HCP involvement were also given as reasons.

3.7.3.2 Quantitative

The top three reasons are presented here; Supplementary Table S1 shows all reasons. Almost three quarters, 72.9%, of respondents answered "Yes" [77.8% in Ghana, 74.9% in Kenya, 66.0% in Uganda (significantly low)]. "Not sure" was selected by 20.5% of respondents overall, driven by Uganda which was significantly higher than both other countries at 25.6% (with 17.8% in Ghana and 18.2 in Kenya).

Reasons given in an open-ended question coded by the interviewers (with a pre-defined list and "Other—specify") for having confidence (those selecting option "Yes" which represents $n = 676$ or 72.9% out of 927 total sample) were: ease of use and ease of application (specified by 79.1% of respondents overall), followed by the ability to self-apply (56.1% overall). The third most common answer was duration, which was described as six months' pregnancy prevention in the CTPP (47.5% overall).

In terms of the top three reasons as to why respondents would not have confidence in this type of contraceptive (Supplementary Table S1, those selecting "Not sure" and "No" which represents $n = 251$ or 27.1% out of the 927 total sample), the most common reason was side effects (56.2% of overall respondents). Effectiveness was selected by 34.7% overall. Safety was the third most common reason, selected by 29.9% overall.

3.7.4 Consistency of use

Respondents were asked whether they would use the MAP consistently. The same wording was used in the quantitative and qualitative phases: "Would you use this contraceptive consistently (all the time), until you wish to conceive/get pregnant? This means that you would reapply a new MAP at the end of each 6-month duration."

3.7.4.1 Qualitative

For respondents, the MAP must fulfill certain expectations to be used consistently, these being: side effects that are manageable, effectiveness, and regular periods with no excessive bleeding. The majority would use the MAP consistently until they wished to get pregnant; this was on the grounds that it fulfilled its value proposition of being easy to use/apply, discreet, safe to use consistently, and that it would save money.

3.7.4.2 Quantitative

Overall, 81.2% of respondents indicated that they would use the MAP consistently [81.9% in Ghana, 86.5% in Kenya, 75.4% in Uganda (significantly low)]. Whereas 13.5% of the overall sample were not sure whether they would consistently use the MAP [12.1% in Ghana, 9.9% in Kenya, 18.4% in Uganda (significantly high)], and 5.3% of respondents overall indicated that they would not use the MAP consistently (6.0% in Ghana, 3.6% in Kenya, 6.1% in Uganda).

Respondents who indicated that they would not consistently use the MAP were asked to give reasons for which interviewers coded from a pre-defined list with "Other—specify" option. Please note that this is a small sample size ($n = 49$ in total; $n = 19$ in Ghana, $n = 11$ in Kenya, $n = 19$ in Uganda), and no analysis of statistical significance is possible. The most common reason was

if side effects were experienced ($n = 27$ overall; $n = 7$ in Ghana, $n = 7$ in Kenya, $n = 13$ in Uganda). The second most common reason was if the respondent's partner was opposed to the MAP ($n = 10$ overall; $n = 5$ in Ghana, $n = 1$ in Kenya, $n = 4$ in Uganda). A total of nine respondents overall ($n = 2$ in Ghana, $n = 3$ in Kenya, $n = 4$ in Uganda) indicated that they would take a break even if they did not experience side effects.

3.7.5 Partner influence

3.7.5.1 Quantitative

Respondents were asked: "How much impact, if any, would your partner's opinion about the microarray patch/MAP have on your desire to use it?"

Four predefined options were given. The most-chosen option, *I would not use the microarray patch/MAP unless my partner was fully supportive*, was selected by 30.9% of respondents overall (33.3% in Ghana, 26.1% in Kenya, 33.0% in Uganda). The second, *I would use the microarray patch/MAP without my partner's knowledge if he wasn't fully supportive*, was selected by 26.9% of respondents overall [32.7% in Ghana (significantly high), 22.8% in Kenya, 24.9% in Uganda]. The third, *I would use the microarray patch/MAP with my partner's knowledge even if he wasn't fully supportive*, was selected by 24.5% of respondents overall [20.0% in Ghana, 31.4% in Kenya (significantly high), 22.3% in Uganda]. The least-chosen option, *I would be hesitant to use the microarray patch/MAP if my partner wasn't fully supportive*, was selected by 17.8% of respondents overall (14.0% in Ghana, 19.8% in Kenya, 19.7% in Uganda). The results are in Supplementary Table S2.

Overall, 51.4% of respondents would use the MAP if their partner was not fully supportive (24.5% with his knowledge and 26.9% without), and 48.7% would either not use it or would be hesitant to use it if their partner was not fully supportive. Slightly more respondents state they are more likely to use without his knowledge than with if not supportive; this could relate to the importance of discretion as part of the perceived value of the MAP.

3.7.6 Access and training on use

Respondents in both phases of the study were asked about where they would like to access the MAP, where they would like to use it, and how they would want to receive training or information on application.

3.7.6.1 Qualitative

Respondents were asked where they would like to obtain the MAP (between healthcare facilities—hospitals or clinics—and pharmacies/drugstores) and where they would use it, including if this would differ between the first application and subsequent uses. In Ghana, around three quarters of respondents preferred to obtain the MAP from pharmacies/drugstores and one quarter from healthcare facilities; in Kenya, the split was roughly even, and in Uganda, the majority preferred healthcare facilities. Reasons for preferring one type of access point were very similar across the three countries. Healthcare facilities were perceived as having knowledgeable staff, being trustworthy, being sources of information, and from a small minority of respondents, that they could trust that the medication supplied there is authentic. Pharmacies/drugstores were perceived as being convenient, familiar, simple, without queues, and discreet; a small minority of respondents in Ghana mentioned being questioned in hospitals but not in pharmacies.

In terms of where to use the MAP, it was almost unanimous in Kenya and Uganda that respondents preferred to use the MAP at the place obtained for the first use, and at home for subsequent applications. The reasons for this were that they could learn how to use it from HCPs and ask questions the first time, and then have the benefit of privacy at home from then on. In Ghana, however, around half of respondents indicated that they would want to use the MAP at home every time, including the first application. The reasons given for this were privacy, and a perception that the MAP would be straightforward to apply provided that it came with instructions.

3.7.6.2 Quantitative

Overall, 48.3% of respondents indicated that they would wish to obtain the MAP from a healthcare facility (19.0% in Ghana (significantly low), 71.9% in Kenya (significantly high), 55.0% in Uganda). A pharmacy/drugstore was preferred by 40.8% of respondents (73.7% in Ghana (significantly high), 19.5% in Kenya (significantly low), 28.2% in Uganda). Other options, which were from a Community Health Worker and from a mobile clinic/health provider, were preferred by 5.9% and 2.2% respectively overall. More respondents in Ghana reported that they had recently obtained their contraceptives from a pharmacy compared to Kenya and Uganda, and fewer respondents in Ghana reported having obtained their contraceptives from a healthcare facility than in Kenya and Uganda.

Respondents were also asked: "Assuming you have to apply the microarray patch/MAP yourself, how would you prefer to receive training or information on how to do it?" *Training from a doctor/nurse/Community Health Worker* was preferred by 56.6% of respondents overall (20.0% in Ghana (significantly low); 62.3% in Kenya, 73.6% in Uganda (significantly high)). *Instructions on packaging* was preferred by 31.1% of respondents overall [61.3% in Ghana (significantly high), 28.8% in Kenya, 14.8% in Uganda]. *Training from a pharmacist* was the least preferred option overall, selected by 12.2% of respondents (18.7% in Ghana, 8.9% in Kenya, 11.6% in Uganda).

3.8 Tertiary objective

3.8.1 Interest, intent and improvement

It is important to reiterate that this tertiary objective is indicative in nature, it should be seen as an exploration into an initial understanding of what end-users may think or project. The scope of this study did not include segmentation or determination of uptake through a modeled demand forecast.

3.8.2 Interest in finding out more

3.8.2.1 Quantitative

Respondents were asked how interested they were in finding out more about the MAP, on a scale from 1 to 5, with 1 being *Not*

at all interested, 2 being *Not very interested*, 3 being *Neither interested nor uninterested*, 4 being *Quite interested* and 5 being *Very interested*. There was high positive interest (T2B) across all countries, with 80.9% overall (85.1% Ghana, 75.6% in Kenya and 81.9% in Uganda). Looking at the top two scores (ratings 4 and 5), just under half (46.2%) of respondents selected *Very interested* and just over a third (34.7%) selected *Quite interested*. Significantly more respondents in Ghana (60.0%) selected *Very interested*, and in both Kenya and Uganda, significantly more respondents than in Ghana selected *Quite interested* (39.6% and 39.8% respectively). The results are in Supplementary Table S3. The mean score was 4.11 out of 5.0 overall [4.29 in Ghana (significantly high), 3.93 in Kenya and 4.09 in Uganda].

3.8.3 Intention to try

Respondents were asked about their likelihood to try the MAP, using a 1–5 scale, with 1 being *Definitely do not want to try*, 2 being *Probably do not want to try*, 3 being *Might or might not want to try*, 4 being *Probably want to try* and 5 being *Definitely want to try*. The question was phrased as follows: "If you learned about the microarray patch/MAP from a physician, nurse or healthcare worker and it was available to you, how interested would you be in trying it now or at some point in the future?" There was a positive score for intention to try, with 68.6% overall scoring within the T2B (74.0% in Ghana, 64.0% in Kenya and 67.6% in Uganda). Looking into the top two scores (ratings 4 and 5), overall, 29.6% of respondents selected 5: *Definitely want to try* [36.8% in Ghana (significantly high), 22.8% in Kenya, 28.8% in Uganda]. *Probably want to try* (rating 4) was selected by 39.1% of respondents overall (37.1% in Ghana, 41.3% in Kenya and 38.8% in Uganda). The results are in Supplementary Tables S4, S5. The mean score was 3.80 out of 5.0 overall (3.95 in Ghana, 3.66 in Kenya and 3.77 in Uganda).

Reasons for interest in trying given in answer to an open-ended question (by those selecting ratings 4–5) were ease of use, effectiveness, duration, and discretion. Reasons given for unlikelihood or uncertainty to try (by those selecting ratings 1–3) were concerns relating to its application, its newness, potential of side effects, satisfaction with what is already being used and a desire for more information.

3.8.4 Comparative value

3.8.4.1 Qualitative

Respondents reported that a MAP could provide benefits compared to existing long-acting contraception in that it could removes the dependency and need to visit a healthcare facility, which would save time and money (on travelling). Lower HCP involvement was perceived to mean greater privacy. A MAP was perceived as less painful and easier to use than other long-acting contraceptive methods as it would not result in permanent scarring like a contraceptive implant or a deep needle penetration like an intra-muscular injection.

3.8.4.2 Quantitative

Respondents were asked: "To what extent do you feel the microarray patch/MAP is a better form of contraception/family planning, compared to other options you are aware of?" The scale used was 1–5, with 1 being *It offers something worse than other options I know about*, 2 being *It offers nothing better than other options I know about*, 3 being *It offers something slightly better than other options I know about*, 4 being *It offers something noticeably better than other options I know about* and 5 being *It offers something significantly better than other options I know about*. Overall 73.0% of respondents gave a generally positive rating (5, 4 and 3) and 47.0% gave a T2B positive rating (5 and 4) [53.0% in Ghana, 25.7% in Kenya (significantly low) and 61.8% in Uganda (significantly high)]. Overall, 25.4% of respondents selected option 5 [32.1% in Ghana, 12.2% in Kenya (significantly low) and 31.4% in Uganda]. Option 4 was selected by 21.7% of respondents overall [21.0% in Ghana, 13.5% in Kenya (Significantly low) and 30.4% in Uganda (significantly high), option 3 was selected by 26.0% (28.9% in Ghana, 26.7 in Kenya and 22.3 in Uganda)]. The results are in Table 9.

The mean score was 3.37 overall [3.61 in Ghana, 2.76 in Kenya (significantly low) and 3.73 in Uganda] out of 5.0.

Those respondents who selected ratings scale scores 3, 4 and 5 were then asked to explain why in an open-ended question. The top reasons for selecting positive comparative scores for a MAP were perceived as easier to apply/use, self-administration, and removal of need for HCP (convenience), a "long" duration of pregnancy prevention (6 months) and that it is seen as discreet/private. The results are available in Supplementary Tables S6, S7.

4 Discussion

This paper describes user insights for a contraceptive MAP focusing on preferred product attributes and the value proposition to inform further product development and eventual introduction and promotion of the method. The most widely preferred attribute set for the contraceptive MAP identified by our study is a hand-applied, circular patch measuring approximately two centimeters in diameter that can be self-administered, is applied to the upper arm, and has signals across all stages of application and removal upon administration of drug. The ideal MAP would be applied within a few seconds, provide contraceptive protection for 6 months, and have a return to natural fertility within 6–12 months after the labeled duration of protection. Conducting this study early in the development of the contraceptive MAP was important so developers can align the product designs to end-user preferences and maximize the potential for uptake once available in the market.

There are several published studies that describe user preferences and attitudes for a contraceptive, HIV prevention or MPT MAP. The studies range in methodology and geographic location, but the findings are similar across all with respect to the size, shape, administration location, skin reaction and duration of protection (Supplementary Tables S8, S9) (39–43). Consistently, smaller, round patches applied to the upper arm and in some cases, the thigh, were preferred across all studies that examined those attributes for a contraceptive, HIV prevention, or MPT MAP (39–42). Similar to other studies, our study found that no visible skin irritation or long-lasting markings were most preferred (42, 43).

Participants from two different studies expressed their preference for six months duration of pregnancy protection when presented with the option indicating a desire for a longer-acting option (41–43). Furthermore, our study confirms that one patch is preferred over multiple patches to achieve the duration of protection as multiple patches are seen to be less discreet with greater potential for pain or increased side effects (39, 42).

Two other studies found that the MAP can be perceived as "too good to be true" when it is described as painless with little or no skin rash and a short administration or wear time (39, 41). For this reason, developers are exploring ways to assure end-users that the product has been applied correctly including signals like clicking sounds and color change (39, 41, 42). Our study demonstrated a preference for a color change or clicking sound at all three stages of application. Yet, concerns were raised about the clicking sound being too loud to be discreet or for the color change to disappear too quickly leading to user error. It will be important for developers to continue to test the feedback mechanisms for their MAP product with actual use to ensure it meets end-user expectations around discretion and confidence with administration.

Self-administration of the MAP could enhance its appeal to end-users and the health system alike for multiple indications and overall, our results and those of other studies demonstrate a preference for self-administration with some variation (39, 41, 42). Participants' preference for administration, location to obtain, and how to learn more about the MAP aligned within each country and with current contraceptive seeking practices. In Ghana, there was a significant preference for a MAP that is self-administered and obtained from a pharmacy/drugstore with information on self-administration as part of the packaging instructions to maintain privacy. Participants from Uganda preferred administration by an HCP and participants from Kenya equally preferred self-administration and self-administration only after an initial application by an HCP. Both Kenyan and Ugandan participants preferred to obtain the MAP from a healthcare facility with training and information from an HCP as a trusted source. Although most study participants stated they currently receive contraceptives from a healthcare facility, the proportion who receive from a pharmacy was significantly higher in Ghana, which aligns with the preference for pharmacy/drugstore availability of the MAP and reluctance to attend hospitals. These results signal the need for wide availability of the method through both public and private sector outlets including pharmacies/drugstores along with appropriate training, support, and materials to HCPs and women to be able to effectively access and use the method for self-administration.

In Uganda, there was also a significant preference for use of an applicator to administer the MAP although the quantitative results indicated an overall preference for a sticky-back patch only (no applicator). In the MaxDiff exercise, participants from Uganda also expressed a greater tolerance for higher levels of pain and greater skin reaction than in Ghana or Kenya. These differences coupled with the preference for access and administration by an HCP could indicate the need for greater familiarity and assurance of the MAP product and appropriate training and knowledge that the MAP is applied correctly and working as indicated with certain groups.

Our study builds upon existing knowledge of common concerns with hormonal contraception more broadly. Studies consistently show that non-use and discontinuation of modern contraceptives is often associated with health reasons linked to side effects that impact and alter one's natural menstruation (44, 45). The potential menstrual side effects associated with the MAP as described in the CTPP included amenorrhea/no bleeding or irregular bleeding including infrequent, frequent, prolonged or heavy, but would likely resolve to regular periods or amenorrhea over time. In our study, both amenorrhea and irregular bleeding were unacceptable to most with some significant differences between countries. A significantly higher percentage of participants from Kenya perceived amenorrhea to be acceptable while a significantly higher percentage of participants from Ghana perceived it to be unacceptable. Study participants in Uganda found irregular bleeding to be significantly more unacceptable than in Ghana and Kenya. Furthermore, women in our study who reported not having confidence in the contraceptive MAP indicated this was due to concerns around the associated side effects, and for a small percentage of women, they said they would not use the method consistently if side effects were experienced. A study in India and Nigeria also looked at the effect on menstruation of a contraceptive MAP using a discrete choice methodology and the results overwhelmingly showed that a change in menstruation negatively influenced women's interest in the MAP (43).

Another side effect that women and adolescents are concerned about when choosing a contraceptive method is return to fertility and fear of being infertile if there are significant or unknown delays in return to natural fertility (46–48). However, our findings and those from Gualeni et al. did not provide a clear preference for an acceptable duration for return to natural fertility given changes in women's lives and pregnancy intentions (41). It is important to consider the level of confidence in the anticipated duration to return to fertility and counsel women appropriately.

A challenge and opportunity identified in our study and other studies is the variation of preferences across product attributes where up to a third of study participants preferred another attribute or design option. This provides developers with room for variation in the design of the final MAP, which is important given technological feasibility. It also implies that there would be end-user interest in multiple products to provide a range of options including how the MAP is applied (applicator or hand), duration of protection, application or wear time, and duration for return to natural fertility.

4.1 Additional research

The contraceptive MAP products are still early in development, and it will be important to re-test their appeal following any product design updates or changes. More qualitative research would help uncover gaps in understanding potential application of the MAP by hand vs. the MAP plus an applicator, applying one or more patches, overall patch size, or desired time to return to fertility. A more detailed exploration of women's perceptions of or interest in the method once the side effect profile is better understood will be critical given the negative reaction to

menstrual side effects such as amenorrhea and irregular bleeding. Other areas to test with end-users include instructions for use, particularly for self-administration, and packaging appeal. Messaging to end-users and appropriate counseling messages for HCPs will be important to explore, particularly around addressing concerns related to product safety and side effects.

More research is also warranted to understand the perspective of different stakeholders that influence women's decision making around contraception. HCPs are a key group as they can be guides or gatekeepers for women seeking contraception and as indicated by this research, are often a trusted source of information on new contraceptive methods. Further research in understanding how to support women who are reluctant to enter some healthcare settings is also relevant. Additional research with partners is important to understand their support in or objections to the use of a new method. Partners play a complex role and understanding what they think about the MAP. This will be critical to effectively communicate with them to garner support and reduce the need for concealing contraceptive use as nearly half of study respondents would hesitate to use the MAP if their partner were opposed.

As MAP products develop and the options are narrowed, commercial focus is critical. Data on acceptable pricing for procurers and end-users is important, as well as segmentation and demand forecasting to support decision making on funding and manufacturing needs. Demand forecasts should also take into consideration all current contraceptive options on the market to understand the shifts in the method mix with the introduction of the MAP. Furthermore, research to influence country policies around accessibility and availability of the method, particularly for self-administration, may be necessary.

5 Limitations

There are several limitations to this study. First, participants in our study did not use or try the method. Several participants raised concerns on the safety and side effect profile, which could not be tested at the time of this research. There is inherent potential for periods to either stop or become irregular when using the contraceptive MAP. This is due to giving progestin continuously for six months (49). More clinical data to define the product's safety and side effect profile is needed before reassessing end-user preferences.

We do not recommend drawing broad conclusions across and between different country populations. The qualitative portion of the study is indicative in nature, and further, qualitative samples often fluctuate as not all questions are asked or answered. The scope of our research did not include development of data for a segmentation analysis, a forecast or modeling, product pricing or price sensitivity evaluation. The research and the flow of the stimuli was organized in such a way that we cannot concretely answer questions about the preference for two patches, patch size, reasoning for applicator use, or choice on desired time to return to fertility. Reversing the questions on one vs. two patches may influence responses and preference of two patches over one. Showing only larger size patches that are likely more technically feasible may have rendered different responses. Introducing the use of an applicator with the patch sooner may also have resulted in different levels of acceptability for an applicator.

In terms of the body map stimuli the middle/center/front of the thigh was omitted. Respondents were given the options for upper inner or outer thigh; however, the middle/center/front of the thigh is a credible location for MAP application.

Finally, our study only reflects women's perceptions of the MAP product category and does not explore trade-offs with other current or new contraceptive methods. Contraceptive choice is paramount for quality family planning programming and any new method introduced will attract users who have not previously used a method, have discontinued or have switched from an existing method. Understanding end-users' rationale for making trade-offs among many contraceptive products is important for decision-making for family planning programs and funding.

6 Conclusion

The results across the three countries demonstrate that the contraceptive MAP has a high and broad level of appeal amongst all groups of women who participated in the study and has a strong value proposition around important contraceptive needs such as ease of use, convenience, and discretion. This study confirms women's preferences from other studies for product-specific attributes of a contraceptive, HIV prevention or MPT MAP such as shape, size, location of administration and duration of protection while also understanding preferences for additional attributes and other aspects that define its value proposition in the contraceptive method mix. The majority of study participants responded positively to the option for self-administration as it encompassed all three aspects of the method's value proposition. Future research should include actual use of the product to understand end-users' perspectives on the side effects, feedback mechanism, and pain or skin reaction to provide more feedback on the acceptability of those product aspects.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Council for Scientific and Industrial Research (CSIR-IRB) in Ghana (approval ID: CSIR/IRB/AL/VOL1-002); Amref Health Africa Ethics and Scientific Review Committee (Amref ESRC) in Kenya (approval ID: AMREF—ESRC P1080/2021); Mildmay Uganda Research Ethics Committee (MUREC) in Uganda

(approval ID: MUREC-2021-62). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ME: Writing – original draft, Writing – review & editing. RE: Writing – original draft, Writing – review & editing. M-ES: Writing – original draft. JL: Writing – original draft, Writing – review & editing. TW: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that they all work for private companies: Routes2Results and TW Consulting. TW was employed by LLC.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2024.1351692/full#supplementary-material

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The role of economic evaluations in advancing HIV multipurpose prevention technologies in early-stage development

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Product development is a high-risk undertaking, especially so when investments are prioritized for low- and middle-income countries (LMICs) where markets may be smaller, fragile, and resource-constrained. New HIV prevention technologies, such as the dapivirine vaginal ring (DVR) and long-acting injectable cabotegravir (CAB-LA), are being introduced to these markets with one indication, meeting different needs of groups such as adolescent girls and young women (AGYW) and female sex workers (FSWs) in settings with high HIV burden. However, limited supply and demand have made their uptake a challenge. Economic evaluations conducted before Phase III trials can help optimize the potential public health value proposition of products in early-stage research and development (R&D), targeting investments in the development pathway that result in products likely to be available and taken up. Public investors in the HIV prevention pipeline, in particular those focused on innovative presentations such as multipurpose prevention technologies (MPTs), can leverage early economic evaluations to understand the intrinsic uncertainty in market characterization. In this perspective piece, we reflect on the role of economic evaluations in early product development and on methodological considerations that are central to these analyses. We also discuss methods, in quantitative and qualitative research that can be deployed in early economic evaluations to address uncertainty, with examples applied to the development of future technologies for HIV prevention and MPTs.

KEYWORDS

economic evaluation, low- and middle-income countries, multipurpose prevention technologies, HIV, prevention, product development, research and development

Introduction

Economic evaluations analyze new products or technologies in comparison with already available ones to assess incremental cost and health impact (1). They collate the available evidence up through the current stage of development and can use modelling, addressing uncertainty linked to incomplete trial data, variable clinical pathways, future costs, broadly defined markets, among others (2). These economic evaluations are usually conducted in late-stage product development (i.e., once safety and initial data on efficacy have been collected), to inform introduction and reimbursement decisions. However, the

information gained when economic evaluations are conducted early in the research and development (R&D) process allows funders, future investors, and product developers to prioritize resources and support resource allocation decisions across portfolios. Early insights are of relevance when investing in products prioritized for access in low-and-middle income countries (LMICs). LMIC markets experience unique challenges such as overburdened health care systems, new and complex regulatory systems, and limited resources or multiple payers with different decision making criteria, contributing to a less predictable market (3).

Currently, HIV infection remains a global challenge, with approximately 1.3 million [1.0 million–1.7 million] new infections in 2022 (4), 51% of which were reported in sub-Saharan Africa (SSA) (4). Although substantial decreases in HIV transmission and AIDS-related deaths were observed between 2005 and 2015, mainly due to the scale up of antiretroviral therapy (ART) for treatment and for prevention, the rate in reduction of new infections has plateaued in recent years (4). Of an estimated 250,000 [150,000–360,000] adolescent girls and young women (AGYW) acquiring HIV in 2021 globally, 82% of them were living in SSA (5), with new HIV infections among AGYW declining slower than among their male counterparts (rate of decline 42% vs. 56%, respectively) (5). Reducing HIV transmission among key populations, such as female sex workers (FSWs), AGYW and pregnant and breastfeeding people (PBFP), remains an important challenge, particularly in SSA (5).

An expanding number of biomedical HIV prevention technologies with demonstrated efficacy in clinical trials and, where relevant, feasibility and acceptability data are either currently available or soon to be available (6). These include daily oral antiretroviral (ARV) pills for pre-exposure prophylaxis (PrEP), the monthly dapivirine vaginal ring (DVR) and long-acting cabotegravir for HIV prevention (CAB-LA), an intramuscular injectable form of PrEP (7). Efficacy studies in SSA have shown monthly DVR and bi-monthly CAB-LA to effectively reduce the risk of HIV infection. Monthly DVR demonstrated a reduction in the risk of HIV infection among African women of 31% and 27% in two Phase 3 multi-site placebo-controlled studies (8, 9) and HPTN 084 reported the risk of HIV infection in the injectable cabotegravir group was reduced by 91% compared to the control group using oral PrEP (10). There are data to suggest implementation of the monthly DVR is feasible, while acceptability data are mixed. Some studies show the ring to be more acceptable than oral PrEP to AGYW while other studies suggest that acceptability varies across countries and usage during sex and menses (11). Data from the DELIVER and B-PROTECTED studies suggest DVR is safe to use during pregnancy and breastfeeding (12). However, the introduction and uptake of these products has been limited due to supply and demand challenges. DVR was prequalified and was recommended by the World Health Organization in 2020 and 2021, respectively, and regulatory approval from several countries in SSA has followed since then (13). Yet, it was not added to the South African Essential Medicines List (14), which guides the national health agenda, due to lack of studies comparing it to the current standard of care of oral PrEP and it being considered expensive at the initially proposed price of R300 per month compared to R52 for oral PrEP (14). Additionally, while CAB-LA has shown to be safe and efficacious and early implementation studies suggest high adherence rates (15), its introduction has been limited due to challenges relating to supply barriers in LMICs, implementation hurdles, and price (16). In 2022, ViiV, the product developer, signed a voluntary license with Medicines Patent Pool to enable manufacture of CAB-LA by generic companies, aiming to improve availability medium term (17).

While these efforts are underway to improve the introduction and scale up of currently or soon-to-be available HIV biomedical interventions, further work is needed to ensure future HIV prevention options meet women's varied needs including expanding choice by diversifying HIV prevention offering. Ongoing early development focuses on innovative combinations such as multipurpose technologies (MPTs), which aim to address the multiple needs of AGYW and others who are at risk for HIV, other STIs, and unwanted pregnancies (18). There are currently a number of MPTs in the pipeline such as oral pills, long acting injectables and implants with dual indication for HIV prevention and the prevention of unwanted pregnancies (19). Despite this agenda, investment for new HIV prevention products has flattened over the last eight years (20, 21). Continued engagement including identification of commercial partners as these novel MPTs move through clinical development is needed. MPTs represent a unique business case, providing a potential dual market in both high-income countries (HIC) and LMICs.

Economic evaluations have become common in preparation for market introduction as part of health technology assessments (HTAs) with the intention of establishing cost-effectiveness for payer coverage (2). Opportunities to shape a product's target profile, business case and its readiness for introduction can be created by undertaking economic evaluations earlier in the development pathway.

Undertaking economic evaluations earlier in development poses a few challenges. The treatment of uncertainty is one of them. Therefore, an economic evaluation conducted early in development often relies on both quantitative and qualitative methods to address this uncertainty in the absence of observed estimates. Because economic evaluations at this stage are frequently conducted in-house, there are limited examples available to the public and limited methodological guidance. This can result in omissions of costs, inappropriate comparators and characterization of uncertainty or assumptions, among others (22). However, there are use case examples for how these evaluations are leveraged for internal decision making (2, 23) and to mitigate the risks (23) and high costs of late-stage development (23). In this context, they can provide valuable insights into clinical trial design (23, 24), into target populations or other drivers that improve value for money (25, 26) and can guide decisions on what data need to be collected at the next phase of development (27) so that uncertainty is reduced when introduction decisions are made by policy makers and payers. Importantly, these early analyses can inform product developers' decisions on how to improve a product's eventual value for money, helping refine the target product profile as well as informing which product to

prioritise across a given portfolio, focusing resources on those most promising products for further development and those most appropriate for a future programme (Figure 1).

Here we reflect on two methodological considerations that are central to early economic evaluations (approaches to uncertainty and the role of qualitative research). Either qualitative or quantitative data can be used to inform economic evaluations. In particular, early in the product development, researchers will focus on literature reviews and expert elicitation to parameterize model-based economic evaluations. We have described two methodological aspects of model-based economic evaluations that are key at this stage, namely, the use of qualitative data to inform model parameters and structure and the value of uncertainty analyses as main outputs to inform decisions. Using examples, we provide snapshots on how they might be applied to the context of the HIV MPT development landscape. The purpose of this paper is to illustrate the mixed method approach needed in early R&D and its applicability to HIV MPTs. Although early economic evaluation examples are limited, these examples can be applied to the development of future technologies for HIV prevention and MPTs.

Approaches to dealing with uncertainty

During early R&D, the data available to characterize products are limited and will evolve as the technology progresses in development. Data limitations include no efficacy, safety data, a limited target product profile, and limited awareness of the implementation pathway and usability of the product. To address these limitations, more attention has been paid in the last decade to the use of combined models of disease progression and pharmacodynamics linked to economic models (2, 22–24, 28–32). These linked models may then be used to inform trial design, guide strategic development decisions (33), and define and refine the target product profile and assumptions providing measurable value propositions, which emphasizes the need, the benefits, and its comparison to other products (34). Linked model outputs include estimates of efficacy, dosing regimen, pharmacokinetics, among others. These outputs can guide clinical development and help reframe value propositions once new data are collected during the different stages of clinical trials, providing an iterative framework for decision making (35, 36), future trial design (25), and the preparation of strategies for reimbursement and pricing (2, 29, 32, 37–39). Though researchers often emphasize the uncertainty that comes with modelling early in the development process as a limitation of early economic modelling (2, 22–24, 28–32), the framing and communication of this uncertainty becomes the objective of these analyses and future evidence generation will revolve around addressing this uncertainty. The framing of uncertainty and how to address it influences the methods used and the choice of output parameters. Deterministic and probabilistic sensitivity analyses as well as threshold analyses can be conducted across a broad range of parameters (e.g., expected efficacy with price, probable implementation strategies). These combinations help determine the viability of a future technology. Though similar analyses may be used later in product development, early insights that clarify trade-offs between product attributes inform developers on the specific product characteristics that could and must be optimised in future development.

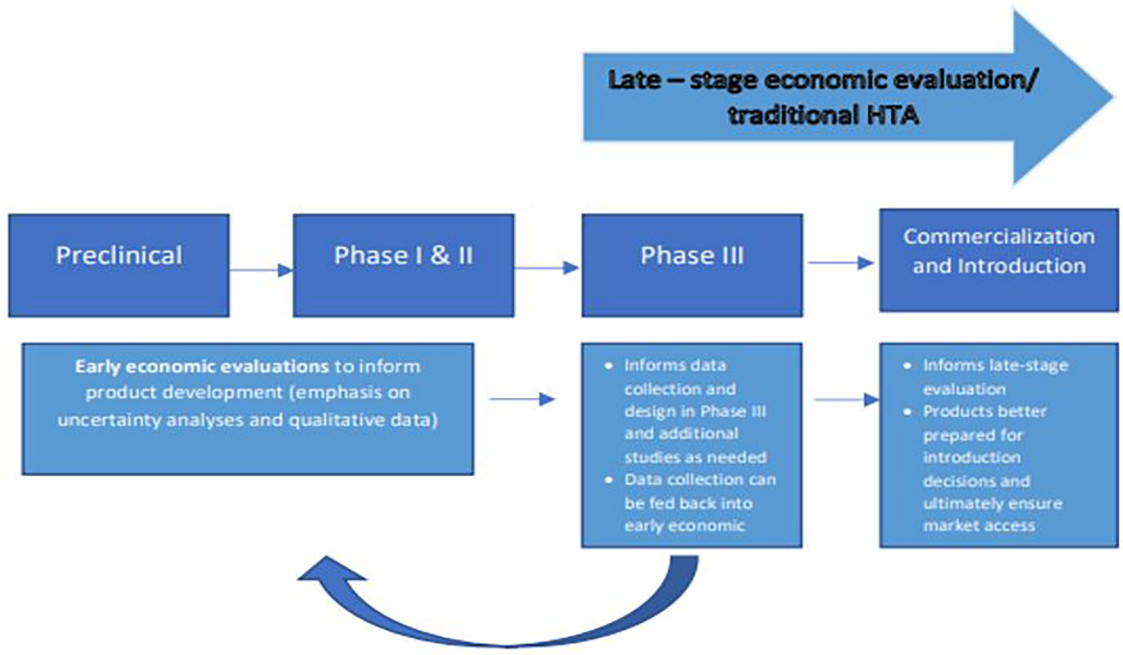

FIGURE 1
Illustration of product development process and example of the value early economic evaluation can provide if integrated into the development pathway, leading to products better prepared for introduction.

For example, in the context of novel products for HIV prevention, Dugdale et al. selected three countries with a range of HIV epidemic characteristics to model cost effectiveness of novel HIV broadly neutralizing antibodies (bnAbs) for infant prophylaxis (25). Alongside a base case, bnAbs were modelled using sensitivity analysis across a range of varying parameters (e.g., efficacy, cost, different implementation strategies, different target populations) to determine parameter space of likely market feasibility (25). This information is critical, providing key parameters for product development targets for characteristics such as, efficacy, price, effect duration, and validating the potential cost effectiveness of implementation strategies to guide future HIV bnAb trials. As HIV prevention products and MPTs progress in development, evaluating the drivers of cost effectiveness can be used to tailor trials, guide future data collection, and better prepare a product for introduction (through complete evidence packages), increasing the likelihood of affordable, acceptable, scalable, and widely available technologies.

Central role of qualitative data

The context and setting where the future technologies will be delivered is one of the key determinants of market viability and return on investment. Expert elicitation is key to synthesize opinions of stakeholders and fully understand the use case and context of a potential technology. Unlike in later-stage economic evaluations where data is more readily available, early economic evaluations place a heavier emphasis on expert opinions (2, 29, 32, 37–39) that can be used to complement the literature review, the existing trial data, and to illustrate uncertainty (29) in the absence of empirical data. For example, focus groups and key informant interviews (KIIs) can be used to validate assumptions and models (40). These expert opinions address uncertainty in the clinical pathway (32) through identification of clinical endpoints or patient target groups for testing as well as delivery strategies that may be possible in the future and their challenges (32). However, methods to conduct expert elicitation and to analyse the qualitative results are not standardized (41). Despite the lack of consensus on methods, expert opinion can help anchor key assumptions in early analyses (41). In the absence of performance data for an early-stage product, expert elicitation can also identify correlates that will serve as predictors of future performance. In the HIV prevention context, experts may use reference products such as oral, vaginal or injectable PrEP (6). An example is Unitaid's work when conducting conducted KIIs with global experts in HIV prevention, contraception and STIs, identifying key considerations for MPT development. Considerations included challenges to development and approval, but also variables and definitions guiding the development of an investment case, and the definition of decision points to advancing from pre-clinical to later stages of development (19). Key considerations identified by these KIIs can inform the MPT landscape for developers, providing insight into opportunities and challenges early in the development process. As public investors prioritize products for investment at an early stage of development, stakeholder inputs can help compensate for gaps in evidence, recommend implementation scenarios, and identify priority populations.

Discussion

As useful as early economic evaluations are, they do present certain limitations. Using data from early trials may not reflect future clinical results or the ultimate patient population, making market viability difficult to assess. Additionally, it may not be possible to cover all possible scenarios and deciding the most important parameters to be considered will be essential yet mainly driven by the selection of stakeholders consulted. Data on future market competitors, public policy evolution, and manufacturing costs at scale will need to be estimated and arranged into scenarios where the likelihood of occurrence is unknown. However, in a time of growing development costs and with a higher proportion of funding for HIV prevention coming from public investment, MPTs can offer a unique business case, one with an expanded market and opportunities in both LMICs and HICs, making their development and commercialization feasible. Feeding into this business case, early economic evaluations provide an early look at implementation costs of a product, within target populations, and among indications that may improve PD efficiency and offer early insight into potential returns and economic feasibility. Additionally, investing resources into early and iterative economic modeling can produce stronger, better prepared products, and avoid the risk of expending resources carrying products through development that may be ill-suited for markets of interest.

Addressing uncertainty as one of the outputs of these early analyses can help improve upon decisions, model parameters, trial and product design, pricing, and lay groundwork for eventual market access. While stakeholder elicitation represents a resource to address evidence gaps, as data becomes available, these economic models can be further refined and improved in an iterative process. Finally, as products for HIV prevention and multipurpose prevention progress in development to phase 2 and 3, transparent business cases will facilitate engagement with commercial partners. Leveraging uncertainty analyses and qualitative data collection methods early on can refine the value proposition and strengthen those business cases, setting up products early for success.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Author contributions

KC: Conceptualization, Methodology, Resources, Visualization, Writing – original draft. ST-R: Conceptualization, Methodology,

Writing – review & editing, Resources. MM: Writing – review & editing. BYH: Writing – review & editing. EK-W: Conceptualization, Writing – review & editing. DT: Conceptualization, Writing – review & editing; GBG: Conceptualization, Methodology, Resources, Supervision, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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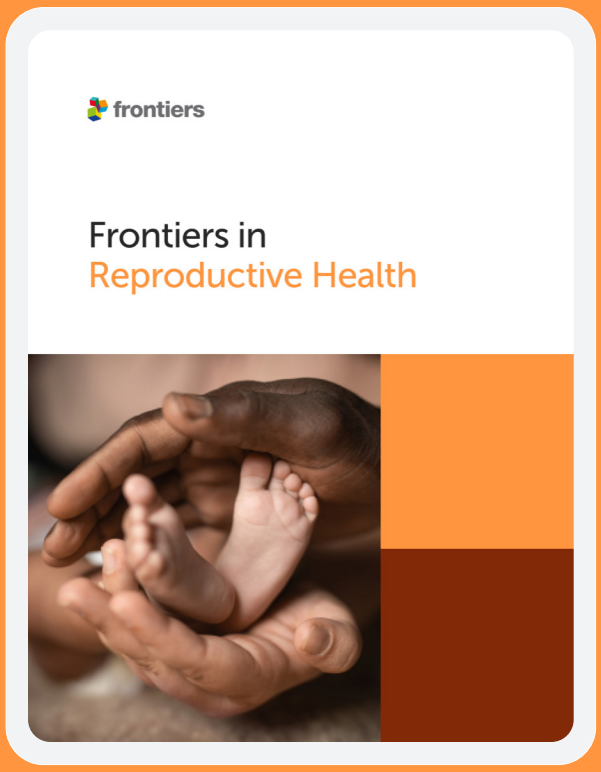

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