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Multipurpose prevention technologies for HIV, STIs & pregnancies

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Multipurpose prevention technologies for HIV, STIs & pregnancies

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Editorial: Multipurpose prevention technologies for HIV, STIs and pregnancies

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Editorial on the Research Topic
Multipurpose prevention technologies for HIV, STIs and pregnancies

Women worldwide face three overlapping risks that significantly impact their health and well-being: HIV/AIDS, sexually transmitted infections (STIs), and unintended pregnancy. In 2022, more than half of the approximately 38 million people living with HIV were women and girls (1). According to the WHO, over one million STIs are acquired every day worldwide (2) often leading to lifelong complications for females, such as infertility and chronic pelvic pain (3). Half of pregnancies each year are unintended with over 60% ending in abortion (4). These statistics underscore gender inequalities that disproportionately affect poor women with lower levels of education and limited access to modern healthcare (5). Two of the 17 Sustainable Development Goals (SDGs)—Goals 3 and 5 (Figure 1A)—are aimed at improving women's sexual and reproductive health (SRH) (6).

Multipurpose prevention technologies (MPTs) are emerging biomedical interventions to prevent two or more SRH issues simultaneously (Figure 1B) (7, 8). Male and female condoms, the only existing MPTs, have drawbacks limiting their consistent use, particularly among the most vulnerable (9–11). Novel MPTs often integrate drug delivery and medical device functions within a single product to increase adherence and overall effectiveness (7). This special issue includes 12 articles from leading researchers, healthcare providers, policymakers and program managers describing recent advances and considerations for the development, scale-up and introduction of MPTs.

Five articles feature MPTs containing the antiretroviral ***tenofovir*** (TFV), used (with emtricitabine) for HIV pre-exposure prophylaxis (PrEP) (12). Two articles focus on the ***dual prevention pill (DPP)*** for HIV and pregnancy prevention—a daily oral tablet containing tenofovir disoproxil fumarate (TDF) and emtricitabine, and an ethinyl estradiol (EE)/levonorgestrel (LNG) combined oral contraceptive. The DPP is the MPT furthest along in development, with an estimated FDA filing in 2025 (13). Segal et al. recommend DPP counselling guidelines developed by a working group to address the different labels for PrEP and oral contraceptives, including if women could safety "double up" or skip the last week of a DPP pack (the "placebo period") in alignment

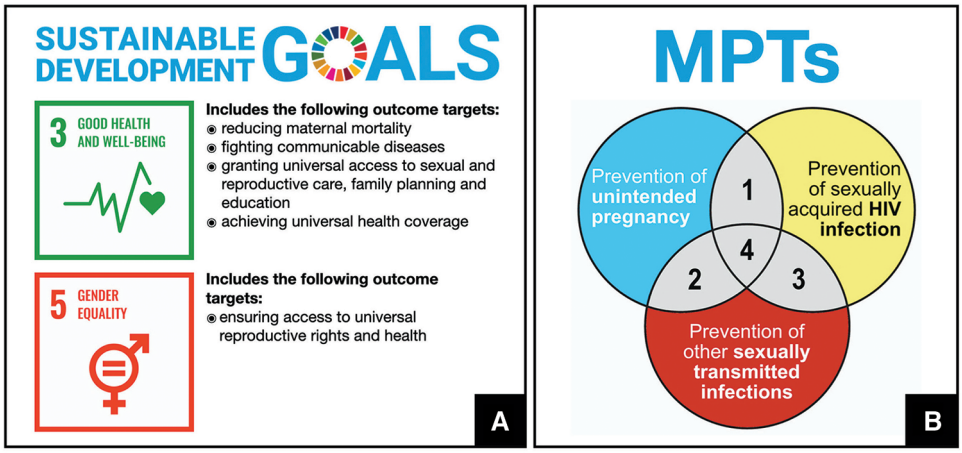

FIGURE 1
(A) Sustainable Development Goals aimed at improving the health and well-being of women. (B) Multipurpose prevention technology (MPT) products are biomedical products intended to address three inter-related sexual and reproductive health issues simultaneously: prevention of unintended pregnancy, prevention of sexually transmitted infections, prevention of sexually-acquired infection with human immunodeficiency virus (HIV).

with the oral contraceptive regimen. Milali et al. present cost-effectiveness modelling of the DPP for different populations (e.g., women in sero-discordant relationships, sex workers, general population) in Kenya, South Africa and Zimbabwe. The authors conclude that the DPP could be cost-effective and even cost-saving in populations at substantial HIV risk, but that outcomes will be sensitive to adherence, underscoring the importance of effective counselling.

Patel et al. describe pre-clinical research on 20 and 40 mg TFV doses in a ***quick-dissolving polymeric thin film*** to prevent HIV and herpes simplex virus (HSV). Results of stability, *ex vivo* HIV-1 challenge experiments, and safety assessments (tissue, microbiome, neutrophil influx, and pH) in Rhesus macaques indicate that the films were stable, safe, and efficiently delivered TFV. Two articles report on clinical trials of a vaginal ring combining TFV and LNG for HIV, HSV and pregnancy prevention. Mugo et al. demonstrate that the 90-day ***TFV/LNG ring*** is acceptable, safe, and well tolerated among Kenyan women using it for up to 90 days in a Phase IIa trial, and Tolley et al. report from a Phase I trial that the ring is acceptable among women in the Dominican Republic and the United States. Tolley et al. note that modifications to decrease the ring's size/thickness and extend its use period could further increase acceptability and emphasize the need to develop communication strategies to demystify ring use for women who are naïve to vaginal product use.

Shapley-Quinn et al. present qualitative acceptability findings from a Phase I trial of a vaginal ring that combines LNG with the antiretroviral ***dapivirine*** (DPV) for HIV and pregnancy prevention. The dapivirine ring (DVR) was the first approved vaginal microbicide and is currently being introduced in multiple African countries (14–19). The ***DPV-LNG ring,*** being developed as a line-extension of the DVR, was well-tolerated in a Phase I trial (20), with overwhelming support for a 90-day product. However, most participants felt that their personal risk of HIV infection or motivation to use the product for contraception did not outweigh their experiences of partial/complete expulsions or increased incidence of vaginal bleeding. Participants' feedback was critical for informing an updated DPV-LNG ring design being tested in a Phase I trial (21), emphasizing the importance of including qualitative research early in product development.

Gachigua et al. describe a human-centered design study assessing the potential acceptability, usability, and programmatic fit of a drug-eluting microarray patch (MAP) in Kenya. MAPs administer drugs through the skin using an array of tiny needles (22–24). Through focus group discussions with various end-user groups, mock exercises in which participants tried prototype MAPS, and key informant interviews, the authors conclude that MAPs are acceptable for both HIV prevention and as an MPT.

Five papers in this special issue discuss overall considerations or provide recommendations for ongoing MPT development. Bhushan et al. share their novel conceptual model for use in developing and testing MPT acceptability. The model, developed in the context of a scoping review of previously conducted end-user research, builds on previous conceptual models and incorporates influencing factors (individual, partner, provider, community) with MPT acceptability factors (including overall acceptability and relative acceptability to other products) as drivers of MPT preference, adoption and use.

Holt et al. describe the current MPT landscape and propose strategic actions for MPT development and introduction in low- and middle-income (LMIC) countries. Based on insights from 28 key informants (e.g., product developers, regulatory experts, policymakers, community stakeholders) from multiple regions, the authors provide recommendations in six areas: technical challenges and opportunities; regulatory pathways; advancing from pre-clinical to clinical development; cost and market potential; market access; and product introduction and roll-out. A commentary by Dam et al. contains insights from the donor

agency perspective highlighting three factors requiring global, regional, and local stakeholder coordination to successfully introduce and scale-up MPTs: (i) procurement and supply chain barriers; (ii) potential burden on health systems; and (iii) impact on current programs.

Two articles call for expanding MPT development beyond the current products that focus primarily on HIV and unintended pregnancy. Lu and Haddad encourage more research on products to prevent non-HIV STIs, outlining a strategy that includes harnessing the large potential market for non-HIV STI prevention in developed countries that could engage investors who have not yet partnered with MPT developers. Finally, Behrsteyn et al. urge developers to consider an array of products for women at various points in their lives including pre-conception, pregnancy, lactation, and menopause (25). Specific product combinations could include prenatal supplements with HIV and STI prevention, emergency contraception with HIV post-exposure prophylaxis, or hormone replacement therapies for menopause with HIV/STI prevention.

The breadth of choice offered by the various MPTs in development—similar to existing options for contraception—is encouraging and critical to empowering women to make important SRH decisions (26). While MPTs hold great promise, there are many challenges—scientific and technical, regulatory and approval, user acceptance and adherence, funding and resource allocation, marketing and distribution, ethical and equity considerations, education and awareness, and integration into current health systems. These challenges will require a multidisciplinary approach involving researchers, healthcare professionals, policymakers, and community stakeholders to ensure MPTs fulfil their potential in improving women's SRH outcomes.

Author contributions

BAF: Conceptualization, Writing – original draft, Writing – review & editing, Project administration. ART: Writing – review & editing, Conceptualization. HN-B: Writing – review & editing, Conceptualization. RKM: Writing – original draft, Writing – review & editing, Conceptualization.

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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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Preferred product attributes of a multipurpose vaginal ring: Findings from a phase 1 trial

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Introduction: Most women face multiple and co-occurring risks from unwanted pregnancy, human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) at some point during their lifetime. While a range of contraceptive methods exist and options for HIV prevention are increasing, to date, only male and female condoms provide multipurpose protection from both pregnancy and disease.
Methods: From September 2017 to December 2018, 60 women from the United States and the Dominican Republic, randomized 1:1 to continuous or interrupted use and 4:1 to active vs. placebo ring, participated in a Phase I trial to assess the safety and tolerability of a three-month multipurpose intravaginal ring (IVR) containing the antiviral tenofovir and the contraceptive levonorgestrel. This study examines survey responses from all participants and qualitative data from a subset of 17 women to assess acceptability of and preferences for IVR characteristics.
Results: Overall, women liked the concept of a multipurpose IVR and found it easy to insert and remove. Initial concerns about the size or thickness of the ring generally disappeared with use experience. Women weighed trade-offs between the ease of continuous use for a longer duration against concerns about hygiene and discoloration of the ring when left in place during menses. Whether randomized to continuous or interrupted use, most women found ring attributes (size, thickness, flexibility) very acceptable. They provided recommendations *via* survey and qualitative interviews for ring modifications that would further increase acceptability. Insights into women's use experiences also suggest the need for clear counseling messages and introduction strategies that can facilitate women's choice and use of prevention methods.
Discussion: Study findings suggest that a multipurpose IVR would make a valuable contribution to women's sexual and reproductive health options, and that both continuous and interrupted use strategies may be preferred.

KEYWORDS

HIV prevention, contraception, vaginal ring, product attributes, acceptability, preferences

Introduction

Across their lifespan, most women face multiple and co-occurring risks from unwanted pregnancy, HIV and other STIs (1). Between 2015 and 2019, the global burden of unintended pregnancies averaged approximately 121 million per year; more than half (61%) ended in abortion (2, 3). In 2021, approximately 1.5 million people were newly diagnosed with HIV; approximately half of new infections globally were in women, but almost two-thirds of infections in sub-Saharan Africa (63%) were among women and girls (4).

Although a range of contraceptive products exist and options for HIV prevention are increasing, women often face barriers to uptake and use of single indication prevention products, let alone use of several products to meet multiple needs. Whether for contraception or HIV prevention, barriers include women's perceptions of side effects, ease or burden of product use requirements, partner disapproval or ability to use discreetly, cost and access issues, and broader sociocultural norms (5, 6). The development of multipurpose prevention technologies (MPTs) could improve women's sexual and reproductive health (7). However, these products must be acceptable and easy to adhere to, if they are going to address women's multiple health needs (8, 9).

Intravaginal rings (IVR) are a promising platform to deliver multiple agents. To date, they have been used to deliver steroids for contraception or postmenopausal therapy, and anti-retroviral agents for HIV prevention (10). In addition, an MPT IVR containing the antiviral tenofovir and the contraceptive levonorgestrel is currently under development. Two randomized, placebo-controlled Phase I trials, conducted among low-risk women in the United States (US) and Dominican Republic (DR), evaluated the safety and tolerability of a 90-day intravaginal ring, used either continuously, for 15–90 days, or over three interrupted cycles of 28 days (11, 12). Both regimens were found to be safe and well tolerated (12). Furthermore, acceptability of the ring, whether used continuously or in an interrupted fashion, was high (13). In comparison to other prevention products, whether for pregnancy or HIV prevention, most women preferred a product that delivered two-in-one protection. While about half of participants reported changes to their menstrual cycle after initiating product use, the most common change was a reduction in bleeding quantity or duration, a change that most women liked (13).

The study, like past studies of vaginal rings also provided some insights into how vaginal ring attributes affect acceptability, including perceptions related to ring size and color (14, 15), the ease or difficulty of placement and removal (16), and concerns about whether the ring might move around in the body or be felt during sex (17, 18). In this paper, we build on the previously published acceptability data (13) to provide a more in-depth examination of user preferences for modifiable product attributes of a multipurpose IVR containing tenofovir and levonorgestrel. As new sexual and reproductive health products move through their critical path from discovery to introduction, the need to obtain timely feedback from the product's potential end users has become increasingly apparent (19).

Methods

A Phase I randomized, placebo-controlled trial was conducted between September 2017 and December 2018 to evaluate the safety and tolerability of a MPT IVR containing the antiviral tenofovir (TFV) and the contraceptive levonorgestrel (LNG) (11). A total of 60 women from two sites (Norfolk, Virginia and Santo Domingo, Dominican Republic) who were at low risk for both pregnancy and HIV were randomized 1:1 to continuous or interrupted use of a 90-day IVR, with a 4:1 ratio of receiving an active or placebo ring. A secondary objective of this trial was to assess women's experiences using the TFV/LNG IVR, including preferences for IVR attributes related to ring dimensions and continuous vs. intermittent use patterns. These acceptability data were collected through two strategies. All participants were administered survey questions at three timepoints (baseline, within the first month of use, and at three months just after ring removal). In addition, a subset of a maximum of 10 participants per site were invited to take part in qualitative interviews at months one (M1) and three (M3). These interviews were conducted in person and in Spanish in the Dominican Republic, and *via* mobile phone in English in the U.S. Interviewers in both sites were trained in qualitative data collection.

In this paper, we examine survey responses at the three-month follow-up visit (M3) on acceptability of vaginal ring characteristics (e.g., size, thickness, flexibility) with response options based on a six-point scale from very unacceptable to very acceptable. We also examine whether specific changes in ring characteristics would make the ring more, or less, acceptable. These data are disaggregated by regimen and site. The data collection instruments and approach to analysis for the acceptability objective of the trial have been described previously (13). Briefly, bivariate analyses (Fisher's exact tests and Chi-squared tests) were conducted to determine statistically significant differences. In addition, we followed a thematic analysis process to analyze and present textual data from the subset of qualitative interviews related to women's perceptions of ring characteristics.

This study was approved by the Chesapeake IRB (now Advarra; Pro00022358) at Eastern Virginia Medical School and the Institutional Review Board of Profamilia (IORG0001979) and National Bioethics Council (Conabios IORG003206). All participants provided written informed consent to participate in the clinical trial. Participants of qualitative interviews were purposively selected by an unblinded study statistician to represent the continuous and interrupted regimens. They provided a separate written informed consent that included permission to be audio-recorded.

Findings

Reported previously (13), a total of 47 women completed baseline surveys and 18 women, 11 from the DR and 7 from the US, participated in the qualitative sub-study. In both sites, participants' mean age was 37, although women in the DR were more likely to be living with a partner (84%) than women in the US (50%). About one-third of women from the DR (32%) had ever experienced using an IVR, compared to 45% of US participants. Women in the US were more likely to use vaginal hygiene products, compared to women in the DR (**Table 1**).

Overall, women in this trial liked the idea of a multipurpose product and found the MPT vaginal ring acceptable. In the M3 survey, most participants reported IVR attributes to be very acceptable with flexibility (87.5%), mode of insertion and

TABLE 1 Menstrual hygiene management, by regimen, agent, and site.

	Regimen		Agent		Site		
	Continuous	Interrupted	Active	Placebo	DR	US	Total
Product normally used during menses (%)	$N = 25$	$N = 22$	$N = 37$	$N = 10$	$N = 25$	$N = 22$	$N = 47$
Probability for Fisher's exact test	$p = 0.355$		$p = 0.344$		$p < 0.001$		
Menstrual pads	76	63.6	70.3	70	96.0*	40.9*	70.2
Tampons	0.0	9.1	5.4	0.0	0.0*	9.1*	4.3
Both pads and tampons	24.0	22.7	24.3	20	4.0*	45.5*	23.4
Other	0.0	4.6	0.0	10	0.0*	4.6*	2.1

The star (*) denotes a probability value <0.05 using a Fisher's exact test.

removal (82.5%), smoothness (77.5%) and color (70%) ranking highest. Participants expressed somewhat lower levels of acceptability towards changes in color over time, although less than 10% found these changes to be even "a little" unacceptable, and none found them to be "somewhat" or "very" unacceptable. There were no significant differences between acceptability of ring characteristics by regimen, agent (active vs. placebo) or site (Table 2).

Qualitative interviews provide more insight into IVR attributes including women's perspectives on the ease or difficulty of insertion and removal, the acceptability of the ring's size, thickness, smoothness, and flexibility, as well as color and experiences during use, such as side effects and comfort during sex.

Insertion and removal

During the initial ring insertion visit, women were offered the opportunity to practice insertion and removal. Most participants found insertion and removal easy. For example, a 36-year-old US participant equated the insertion process to "inserting a regular tampon." She went on to explain, *"They're easy to use, just fold and insert so you don't need to be a rocket scientist to figure it out."* (Continuous use, #207) In a similar way, a 34-year-old participant from the DR explained, *"Because you only have to grab the ring and take it out. You enter your finger, and you find it. And when you touch it, you try to pull it, slowly. Yes, it was easy."* (Continuous user, #123) Six women, some from each site, had used an IVR previously, either NuvaRing as a contraceptive, or in a different clinical trial. Some of these women equated their experience with the study product to those previous experiences.

A few women ($n = 3$) expressed initial concern about inserting the IVR properly. In such cases, the staff were able to provide guidance. One U.S. participant doubted her ability to correctly insert the ring, explaining that she was "*not completely comfortable with that, only because when I did put it in myself, it wasn't far back enough. So, I would prefer to be with them (clinic staff) when I put it back in.*" (Continuous use, #212) However, with practice, even women who expressed initial reservations about insertion or removal described the process as *easy* or *smooth sailing.*

> *Wow that experience was, wow! I inserted it very well, because I had already inserted rings before […] But to take it out, wow … . We took over 20 min for me to be able to take it out. … She (clinician) then had me lie down, and she said "Look, I am going to try to help a little to show you how you are going to do it. But imagine that it's not me, but you, that is going to do it." And then she did it, and she asked me to insert it again, and … everything was perfect. So now I know how to remove it. Now I have inserted it twice and removed it twice. (39-year-old mother of 3 in the DR, #124)*

Size and thickness

Relatedly, more than half of sub-study participants ($n = 11$)—all but two of them from the DR, were initially concerned about the size or thickness of the ring. At first sight, women worried about whether it would fit inside their bodies, whether the ring might move around during daily activities, or whether their partner might feel the ring during sex. Those concerns usually disappeared after insertion or initial use. When asked what her first thoughts were, a DR participant exclaimed,

> *A little big! I had never inserted anything in there, so … I mean, not even my fingers, I don't. … Yes. To insert something up there, no, no, never. In my vagina, no. I saw that ring and I said wow, and I touched it. It was a little thick. But what I saw is not the same as what I feel. I was surprised by what I saw, but after I inserted it, everything is perfect. It doesn't bother me or anything. (43-year-old mother of 4 in the DR, #121)*

Smoothness and flexibility

Most women found the smoothness and flexibility of the ring to be *fine*. As one DR participant described, *it's plastic or rubber … is not uncomfortable.* Another said, *the color, the flexibility that you can bend it easily… it is all good.* Only two women, both from the DR, initially described the ring as "*rough*".

> *When I Saw it? I thought, "Oh my God, that is thick and rough!" [Laughter.] I thought it was going to be smaller! I thought it'd be something. Oh my God. I found it to be rough. Oh my God. But what can you do? Onward. But it was, it was easy. (32-year-old mother of two in DR, #119)*

TABLE 2 Acceptability of ring characteristics by regimen and site at M3.

	Regimen		Site		
	Continuous	Interrupted	DR	US	Total
	(*n* = 21)	(*n* = 19)	(*n* = 24)	(*n* = 16)	(*n* = 40)
Size (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	4.8	0.0	0.0	6.3	2.5
A little unacceptable	4.8	0.0	4.2	0.0	2.5
A little acceptable	14.3	5.3	16.7	0.0	10.0
Somewhat acceptable	19.1	36.8	20.8	37.5	27.5
Very acceptable	57.1	57.9	58.3	56.3	57.5
Thickness (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	9.5	0.0	0.0	12.5	5.0
A little unacceptable	4.8	0.0	4.2	0.0	2.5
A little acceptable	9.5	15.8	20.8	0.0	12.5
Somewhat acceptable	14.3	21.1	20.8	12.5	17.5
Very acceptable	61.9	63.2	54.2	75.0	62.5
Flexibility (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	0.0	0.0	0.0	0.0	0.0
A little unacceptable	4.8	0.0	0.0	6.3	2.5
A little acceptable	4.8	5.3	8.3	0.0	5.0
Somewhat acceptable	4.8	5.3	4.2	6.3	5.0
Very acceptable	85.7	89.5	87.5	87.5	87.5
Color (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	0.0	0.0	0.0	0.0	0.0
A little unacceptable	0.0	5.3	0.0	6.3	2.5
A little acceptable	9.5	10.5	16.7	0.0	10.0
Somewhat acceptable	14.3	21.1	12.5	25.0	17.5
Very acceptable	76.2	63.2	70.8	68.8	70.0
Smoothness (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	0.0	0.0	0.0	0.0	0.0
A little unacceptable	0.0	5.3	0.0	6.3	2.5
A little acceptable	4.8	10.5	8.3	6.3	2.5
Somewhat acceptable	9.5	15.8	12.5	12.5	12.5
Very acceptable	85.7	68.4	79.2	75.0	77.5
Way it is inserted/removed (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	4.8	0.0	0.0	6.3	2.5
A little unacceptable	0.0	5.3	0.0	6.3	2.5
A little acceptable	0.0	0.0	0.0	0.0	0.0
Somewhat acceptable	19.1	5.3	12.5	12.5	12.5
Very acceptable	76.2	89.5	87.5	75.0	82.5
Change in color over time (%)					
Very unacceptable	0.0	0.0	0.0	0.0	0.0
Somewhat unacceptable	4.8	0.0	4.2	0.0	2.5
A little unacceptable	0.0	10.5	0.0	12.5	5.0
A little acceptable	19.1	10.5	16.7	12.5	15.0
Somewhat acceptable	23.8	21.1	29.2	12.5	22.5
Very acceptable	52.4	57.9	50.0	62.5	55.0

The use experience

Few women ($n = 4$) reporting experiencing any side effects from ring use and none worried about symptoms they experienced. Three women described some changes to their menstrual cycles, accompanied by headache or nausea, that were noticeable. The fourth described stronger mood swings after using the ring. However, none reported these changes as

problems, and most wondered whether they changes were due the ring itself, or to the biopsies or their normal menstrual cycle.

> *There's something I mentioned to my coordinator. I think it might've been a headache or—I can't remember what the symptom was but I think she had said it was more likely related to my biopsy. (INT 2) For the most part, positive. Towards the end I did notice just one side effect. I noticed that I would get pretty bitchy just before my period. That was something that I haven't really experienced in the years of having my period. (27-year-old mother of one in US on active cyclic ring, #215)*

Regardless of any initial concerns about the size, thickness or flexibility of the ring, most qualitative sub-study participants ($n = 11$) reported not being able to feel the ring during their day-to-day activities, including during sex. Indeed, when asked about their sexual experience during ring use, most women described disliking the requirement to use condoms during the trial. While a few women ($n = 4$) reported that their partners were able to feel the IVR during sex, only two women reported this to be a problem. A 31-year-old participant from the US site explained,

> *The only other negative thing I remember from it was that during sex, my husband told me that he could feel it and that it was almost scratching him. After I talked to the doctor and study coordinator about it, they thought that it was probably that hard piece that doesn't bend and that maybe that was rubbing up against him or something … . Then, depending on which time we were having sex, sometimes it didn't bother me and other times I would feel it. I would feel like I wasn't necessarily feeling the ring, but it was just feeling like a pain in my lower abdomen. It would feel like something was kind of hitting up against your side. That was uncomfortable. I remember those two things during sex that were sporadic. Sometimes it was fine for him and sometimes it wasn't. Sometimes it was fine for me and sometimes it wasn't. (31-year-old U.S. woman, no children on continuous ring, #212)*

In contrast, another participant whose partner could feel the ring remarked,

> *We have great sex, it's awesome. What you're probably asking is if he felt the ring and he did. Sometimes when we have sex, he can like feel the ring, but it doesn't bother him. He can kind of just like feel that it's there. (28-year-old US woman, one child on continuous ring, #217)*

Color

When asked about any changes in the ring color over time, women remarked on two different aspects. Women generally liked the "*transparency*" of the ring and several noted that the ring "*appears to have a white medication*" inside. A Dominican woman in the interrupted use arm further described how "*When it was removed the second time in the second month it was changing. The liquid was going away. The third time it was completely gone." (26-year-old DR woman, mother of 3, #117)* For some, the ability to see the medication inside was a benefit, "*it allows you to see if anything is going wrong. If it changes colors, then you know (that the medicine is leaving the ring).*" (*39-year-old mother of 3 in the DR* #124).

In addition, several participants also described a change in the exterior appearance of the ring over time. Women generally stated that such changes were due to menstruation and were therefore acceptable. Only two women, both from the DR, found changes to ring color after menses less than appealing.

> *A little ring, a white little ring. Then, when the menstruation comes the color changes. As the bleeding came, it changed color, it was like brown now. Completely brown … AND WHAT DO YOU THINK ABOUT THE COLOR CHANGE? It was because of the medication or the menstruation. Do you understand me? It gets dirty, that's what I think. (26-year-old DR woman with 3 children, interrupted use, #117)*

Duration

Women generally preferred a ring that could be used continuously for three months or, as on DR participant said, "*Yes, for my whole life! Put it in and that's it. That it just stays right there. I didn't have any issue with the time.*" Several women compared using a longer-acting IVR to using an IUD. However, when considering continuous use for three or more months, women raised several caveats related to menstrual hygiene management. First was the idea that they should be able to remove the ring periodically to clean it. A US participant explained,

> *So now cleanliness is something I've thought about. You know, if this is something that goes out on the market and it is a three-month ring, if women take it out quickly to rinse it off, is that okay? That's something I'm sure other women are going to wonder about. (45-year-old US woman with 7 children, interrupted use, 214)*

A second concern for several participants in the US, but none in the DR, related to the compatibility of continuous IVR use with use of menstrual hygiene products, including tampons and the menstrual cup.

> *I guess one sort of concern I have is, for the purpose of the study, I was told I cannot use my menstrual cup, but I can use tampons. I feel that had a bit to do with why I chose to do the study because I don't necessarily know if I would have if I had to only use pads. I'm curious if it's a thing for the purposes of the study or if using a cup with this product would be a complication. That would affect my interest in it if it were a product on the shelf. (27-year-old US woman, one child, interrupted use, 215)*

Recommendations for IVR modifications

At M3, participants rated whether potential changes to the MPT IVR would make the ring less or more acceptable (Table 3). At least half of participants indicated that making the ring smaller would increase acceptability. Overall, about 40% of participants recommended making the ring thinner and/or more flexible, while smaller proportions of participants recommended changes to color or smoothness. Interestingly, women in the interrupted use regimen were significantly more likely to recommend providing an applicator for insertion or removal (42.9%) compared to women in the continuous use arm (10.5%).

Data from the qualitative sub-study followed a similar pattern. About half of IDI participants found the ring acceptable just as it was. "*No, the size is good. The color, the flexibility that you can bend it easily… it is all good. For me, everything. I wouldn't change anything.*" (37-year-old DR woman in the interrupted use arm, #118) A few others suggested changes not for themselves, but because others might prefer such modifications. For example, when recommended that the ring be *thinner*, she added, "*But, even though I didn't find it to be difficult, maybe someone would find it uncomfortable. And that would make it easier.*" (36-year-old DR woman, continuous use, #125).

Discussion

Participants in early-stage prevention clinical trials may differ from the end-users who eventually use the products being evaluated. Nevertheless, the value of engaging potential end-users earlier in the product development pipeline has been increasingly acknowledged (9, 20, 21). In this trial, participants were likely to be at lower risk for pregnancy, HIV and other STIs. They were also willing to be randomized to an experimental product or a placebo, come for frequent clinic visits, undergo biopsies, abstain from sex and/or use condoms. Over a third of participants had some experience using an IVR, either in previous research or as a contraceptive method. Yet, they provided important insights into attributes of the 90-day TFV/LNG IVR and potential strategies to support their introduction and use in the future.

A first insight is that concerns about size, thickness, and flexibility of the IVR tended to be transient and were linked to women's perceptions about their ability to insert or remove the ring. These concerns were mostly dispelled once a woman experienced actual use. Qualitative sub-study participants from the DR were more likely to express initial concerns about ring size than US participants. It is possible that, for some women, a lack of previous experience seeing and using an IVR, or other vaginal hygiene products gave rise to initial concerns. Overall, trial participants from both sites found the ring easy to insert and remove—particularly with some practice. These findings are line with those of a systematic review of vaginal ring acceptability for contraceptive or HIV indications from low- and middle-income countries. Across 68 studies, including both clinical trial and observational designs of different types of vaginal rings, most women rated their IVR experience as highly acceptable, and insertion and removal as easy (18, 22). Indeed, a recent literature review assessing barriers and enablers to women's uptake and use of vaginal contraception suggested that concerns about vaginal insertion as a disincentive to a product's

TABLE 3 Acceptability of potential changes to ring characteristics by regimen and site at M3.

	Regimen		Site		
	Continuous	Interrupted	DR	US	Total
	(*n* = 21)	(*n* = 19)	(*n* = 24)	(*n* = 16)	(*n* = 40)
More Acceptable (%)					
Make ring size smaller	57.1	42.1	50.0	50.0	50.0
Make ring thinner	42.9	36.8	45.8	31.3	40.0
Increase flexibility of ring	33.3	42.1	37.5	37.5	37.5
Provide applicator to insert ring	42.9*	10.5*	25.0	31.3	27.5
Make the color opaque	28.6	21.1	25.0	25.0	25.0
Make the ring less slippery	28.6	10.5	25.0	12.5	20.0
Make ring stiffer	0.0	5.3	0.0	6.3	2.5
Make ring size bigger	0.0	0.0	0.0	0.0	0.0
Make ring thicker	0.0	0.0	0.0	0.0	0.0
Less Acceptable (%)					
Make ring size bigger	52.4	57.9	50.0	62.5	55.0
Make ring thicker	57.1	42.1	54.2	43.8	50.0
Make ring stiffer	42.9	57.9	50.0	50.0	50.0
Make ring size smaller	9.5	15.8	12.5	12.5	12.5
Make ring thinner	9.5	15.8	12.5	12.5	12.5
Provide applicator to insert ring	0.0*	26.3*	12.5	12.5	12.5
Increase flexibility of ring	4.8	15.8	12.5	6.3	10.0
Make the color opaque	0.0	15.8	4.2	12.5	7.5
Make the ring less slippery	0.0	15.8	0.0	18.8	7.5

The star (*) denotes a probability value < 0.05 using a χ^2 test of association.

demand are likely overestimated (23). Indeed, numerous studies suggest that intravaginal practices are common and are engaged in for cleaning purposes, sexual pleasure, and fertility control (24–26).

Relatedly, most women reported that neither they nor their partners were able to feel the ring once in place. In two cases, however, the placement of the ring was uncomfortable. Several Phase I trials of other rings also reported some instances when women could feel the ring or might experience some cramping (16, 27). In a Phase III trial of the dapivirine HIV prevention vaginal ring, participants reported experiencing heaviness and pelvic pain especially during initial months of the trial and equated this to improper placement of the ring. Some women also reported that partners could feel the ring, leading some to preemptively remove the ring prior to sex (28). While studies in women and providers in a range of geographies reported pre-insertion concerns about a partner's discomfort during sex, actual reported impacts on daily life and sexual experience were minimal (17, 18, 29, 30). Nevertheless, for some women an intravaginal ring will not be a viable option due to challenges with ring insertion, perceptions of anatomical incompatibility, and/or perceived or experienced discomfort by a sexual partner.

A second insight relates to the relative lack of impact of IVR use on the sexual experience compared to that of condom use. As noted in the previously published acceptability paper, most trial participants preferred a 3-month injectable (75% overall) to other prevention methods. More than half of participants overall, and 75% of women from the DR site reported the reason for this preference as not interrupting sex. Ease of use and discretion were also important reasons for this preference (13). In a qualitative study with adolescent and adult heterosexual men and women and men-who-have-sex-with-men in Cape Town, South Africa, acceptability of and preferences for new prevention technologies varied by population and were based on experiences with similar products and their fit with lifestyle and sexual contexts (31). Adolescent and adult women cited their inability to negotiate consistent condom use with partners and a prevailing threat of sexual assault when describing preferences for vaginal rings or an HIV vaccine. For women, vaginal rings and vaccines could be used discreetly and long-term, unlike oral PrEP, and were under a woman's control. Adult MSM preferred an HIV vaccine, whereas adult heterosexual men preferred an oral PrEP product that was more familiar. In contrast to other groups, heterosexual men expressed distrust of vaccines and injections in general (31).

A final insight was that women weighed certain trade-offs between duration of use and potential health effects they may perceive. Most women liked the idea of continuously using an IVR for several months at a time. Indeed, in our study, some qualitative sub-study participants envisioned using a vaginal ring like a woman might use an IUD. Others suggested that a longer duration of use would be acceptable if it were possible to periodically remove the ring to clean it. Women's desire to clean the ring may have been due to observing some ring discoloration from use during menses. As reported previously, most participants either experienced no change in menses or lighter bleeding and/or fewer days of bleeding during product use (12). It is unclear whether women who have used intravaginal products like the IUD, or whose menses are light, either naturally or due to the TFV/LNG ring, will have the same desire to periodically remove and clean their ring as expressed in this study. Furthermore, while this trial found continuous use of the 90-day TFV/LNG IVR to be safe, the safety of longer durations has not been studied (12). In an open-label trial with 120 Rwandan women randomized to NuvaRing, used intermittently or continuously for 3 months, vaginal yeast infections occurred in 22% of intermittent users and 27% of continuous users. Ten percent of continuous users reported lower abdominal pain vs. none in the intermittent arm (17). In a laboratory sub-study, investigators also evaluated biofilm build-up on 415 rings used during the Rwandan study. They found bacteria—both healthy lactobacilli and bacteria such as G. vaginalis and A. vaginae associated with vaginal microbiota dysbiosis—to be present on most rings. Additionally, the density and composition of ring biomass was associated with vaginal microbiota dysbiosis, although causality could not be determined (32, 33). Regarding the TFV/LNG ring tested in this study, three clinical trials have demonstrated that the ring does not adversely affect the vaginal microbiota (12, 34, 35). In anticipation of Phase 3 trials or post-trial introduction, developing clear messages about whether, when and/or how to clean the IVR and impact of cleaning methods on contraceptive/HIV effectiveness or vaginal health is essential.

Conclusions

Our findings suggest overall high acceptability of the 90-day TFV/LNG IVR, but also point out that modifications to decrease the size and/or thickness of the ring and to possibly extend the duration of use could increase acceptability even more. Moreover, the mostly transient concerns about ring size and thickness expressed by women who are naïve to vaginal product use suggests the need for materials and/or communication strategies that can demystify the ring, how it is inserted and removed and where it sits. Finally, women's concerns about potential health effects with longer and more continuous use will require additional data and clear messages that inform women about the potential effects of ring removal and cleaning behaviors on effectiveness and vaginal health.

Data availability statement

Quantitative data will be made available without undue reservation. Access to deidentified qualitative data may be made available upon request.

Ethics statement

The studies involving human participants were reviewed and approved by Chesapeake IRB (now Advarra; Pro00022358) at

Eastern Virginia Medical School. Institutional Review Board of Profamilia (IORG0001979). National Bioethics Council (Conabios IORG003206). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ET was primarily responsible for the sub-study design, guided data analysis and drafted the paper. HH contributed to the sub-study design, analysis and interpretation of data. AT and VB were responsible for all data acquisition at the EVMS and DR sites, respectively. GD was responsible for the overall trial and contributed to sub-study design and interpretation of data. All authors provided critical review of the draft article, and approved the accuracy and integrity of the final article. 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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Microarray patch for HIV prevention and as a multipurpose prevention technology to prevent HIV and unplanned pregnancy: an assessment of potential acceptability, usability, and programmatic fit in Kenya

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Background: Microarray patches (MAPs), a novel drug delivery system, are being developed for HIV pre-exposure prophylaxis (PrEP) delivery and as a multipurpose prevention technology (MPT) to protect from both HIV and unintended pregnancy. Prevention technologies must meet the needs of target audiences, be acceptable, easy to use, and fit health system requirements.
Methodology: We explored perceptions about MAP technology and assessed usability, hypothetical acceptability, and potential programmatic fit of MAP prototypes using focus group discussions (FGD), usability exercises, and key informant interviews (KII) among key populations in Kiambu County, Kenya. Adolescent girls and young women (AGYW), female sex workers (FSW), and men who have sex with men (MSM) assessed the usability and acceptability of a MAP prototype. Male partners of AGYW/FSW assessed MAP acceptability as partners of likely users. We analyzed data using NVivo, applying an inductive approach. Health service providers and policymakers assessed programmatic fit. Usability exercise participants applied a no-drug, no-microneedle MAP prototype and assessed MAP features.
Results: We implemented 10 FGD (4 AGYW; 2 FSW; 2 MSM; 2 male partners); 47 mock use exercises (19 AGYW; 9 FSW; 8 MSM; 11 HSP); and 6 policymaker KII. Participants reported high interest in MAPs due to discreet and easy use, long-term protection, and potential for self-administration. MAP size and duration of protection were key characteristics influencing acceptability. Most AGYW preferred the MPT MAP over an HIV PrEP-only MAP. FSW saw value in both MAP indications and voiced need for MPTs that protect from other infections. Preferred duration of protection was 1–3 months. Some participants would accept a larger MAP if it provided longer protection. Participants suggested revisions to the feedback indicator to improve confidence. Policymakers described the MPT MAP as "killing

Abbreviations
AGYW, adolescent girls and young women; API, active pharmaceutical ingredient; ARV, antiretroviral; DREAMS, determined, resilient, empowered, AIDS-free, mentored and safe; FGD, focus group discussions; FSW, female sex workers; HIV, human immunodeficiency virus; IFU, instructions for use; MAP, microarray patch; MPT, multipurpose prevention technology; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

two birds with one stone," in addressing AGYW needs for both HIV protection and contraception. An MPT MAP is aligned with Kenya's policy of integrating health care programs. **Conclusions:** MAPs for HIV PrEP and as an MPT both were acceptable across participant groups. Some groups valued an MPT MAP over an HIV PrEP MAP. Prototype refinements will improve usability and confidence.

KEYWORDS

microarray patch, HIV PrEP, multipurpose prevention, contraception, Kenya, health product development, acceptability, microneedle patch

1. Introduction

In Kenya, the most recent estimated prevalence of HIV among adults was 4.9% in 2019 (1, 2), marking it as the country with the twelfth highest rate of HIV globally. In the same year, the estimated HIV prevalence for women aged 15–49 was more than twice as high as that for men aged 15–49 (6.6% vs. 3.1%). HIV infection rates among young people (15–24) accounted for 35% of new infections, with two-thirds of cases among adolescent girls and young women (AGYW) (3, 4). Also, the most recent national statistics (from 2016) showed an HIV prevalence of 18.2% among men who have sex with men (MSM) and 29.3% among female sex workers (FSW) (5). Reducing HIV infection rates among these populations is crucial for HIV epidemic control.

Likewise, unintended pregnancies in Kenya continue to be a public health burden. Although Kenya had a high contraceptive prevalence rate of about 58% for married women in 2020 (6), national survey data demonstrated that unmet need for family planning was highest among young women 20–29 years old (33%), followed by adolescent girls 15–19 years old (23%) (7). The high proportion of sexually active AGYW with unmet need for family planning in Kenya has led to a high number of unintended or mistimed pregnancies, unsafe abortions, and maternal deaths (8–10). Women, particularly AGYW, who face a persistent unmet need for contraception tend to have a higher risk of HIV infection (11–13). The high incidence of HIV among AGYW is exacerbated by low uptake of HIV prevention methods, such as pre-exposure prophylaxis (PrEP) (14, 15).

New drug delivery systems are being developed to address the challenges users experience (16–18) with PrEP delivery through daily oral pills. For example, a microarray patch (MAP) is being developed to deliver an antiretroviral (ARV) for HIV PrEP, as well as alongside a hormonal contraceptive as a multipurpose technology (MPT) for women. These ARV MAPs in development have the potential to offer protection for 1 month to 3 months, depending on the active pharmaceutical ingredient (API). The MAPs have the potential for easy, discreet, and self-administered protection that could improve uptake of and adherence to HIV PrEP. Qualitative research in 2016 with South African women and health care providers indicated that an ideal HIV PrEP solution should be discreet, long acting (3–6 months), highly effective, possible to self-administer, and protect users against not only HIV but also other sexually transmitted infections and pregnancy (19). A 2019/2020 assessment in South Africa and Uganda that explored user/stakeholder preferences regarding the MAP for HIV PrEP and as an MPT (20) generated recommendations for refinements to the MAP prototype, including the feedback indicator, to improve ease of use. Using the refined MAP prototype, we conducted this early-stage product development assessment in Kenya to continue exploring user and stakeholder needs and preferences for product features that could influence acceptability, usability, and programmatic fit for a MAP delivering HIV PrEP and as an MPT.

2. Materials and methods

The ARV MAPs in development are designed to have multiple arrays, each containing hundreds of tiny (<1 mm) microneedles. Each array on the MAP has a corresponding dome above it that the user would depress to apply the patch to the skin; collectively, the domes serve as a "feedback indicator" to confirm successful application. The MAP projections would gently pierce the skin and begin to dissolve. First, the base of the projections dissolve, separating from the patch backing (**Figure 1**). After a specified wear time, the MAP backing and feedback domes would be removed and discarded. Next, the projections would fully dissolve in the skin, releasing the API into systemic circulation (21, 22). The targeted wear time for the HIV PrEP and MPT MAP is less than 20 min, at which point the MAP's adhesive layer would be discarded.

The MAP prototype used in this assessment (**Figure 2**) was representative of the aforementioned MAP currently being developed to deliver an ARV for HIV PrEP and as an MPT for delivery of both an ARV and a hormonal contraceptive. The MAP prototype had 8 feedback indicator domes indicating where microneedle arrays would be located (if it were a marketed product containing drugs). After the MAP prototype was applied to the skin, the user pressed on each dome until the domes inverted. The MAP prototypes used in this assessment were "looks like/feels like" prototypes—they did contain any microneedles and did not contain any drugs.

2.1. Study design

This descriptive exploratory study was conducted in Kenya, a country known as a leader in PrEP rollout, but where barriers continue to exist for currently available HIV prevention methods (23, 24). Within Kenya, Kiambu County was selected as the

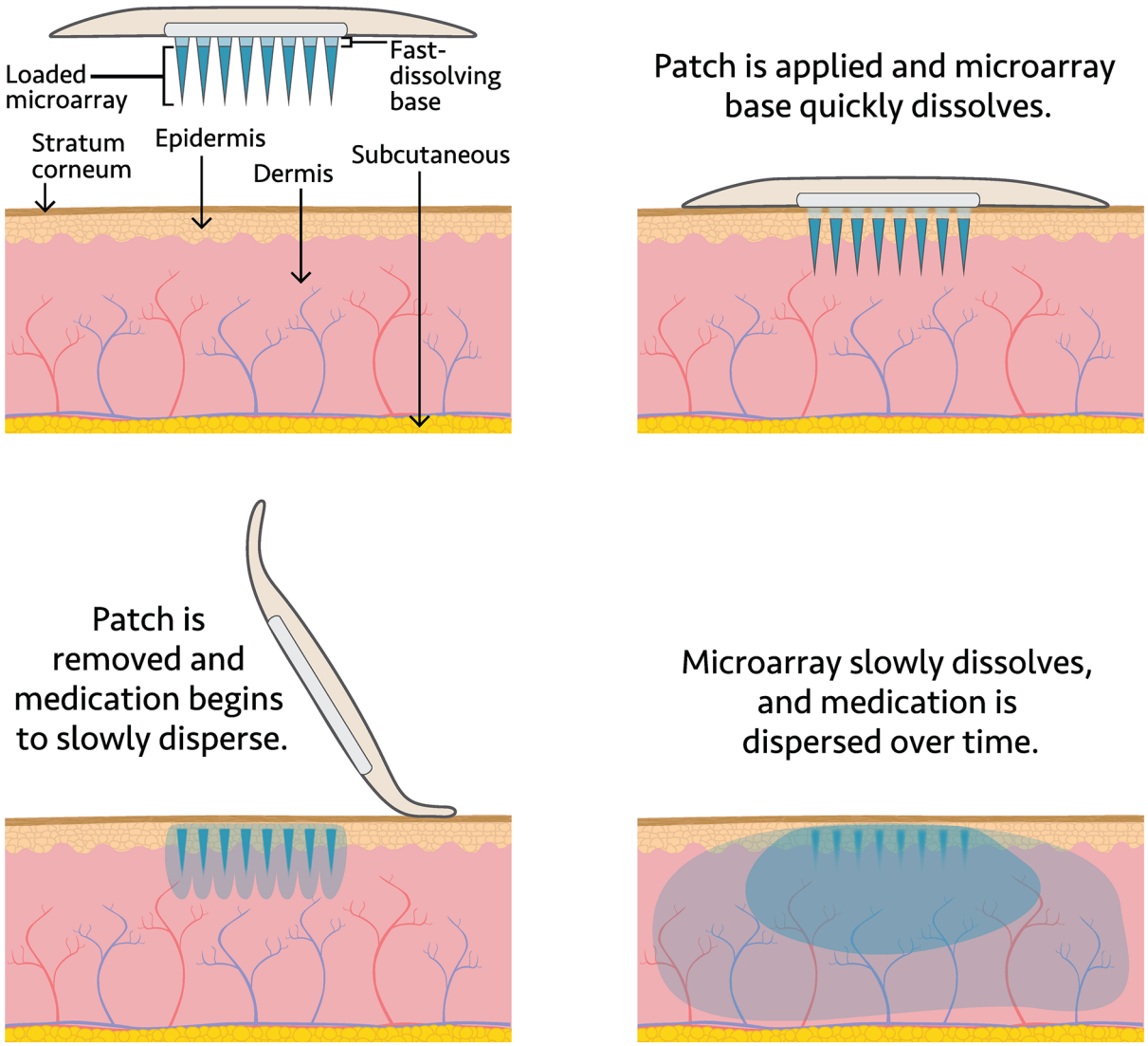

FIGURE 1
Dissolving MAP drug delivery system.

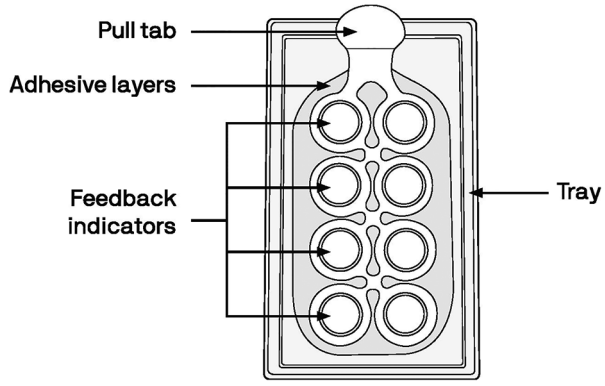

FIGURE 2
Diagram of the MAP prototype used in this assessment; dimensions were 14.5 cm × 6.25 cm (5.75 inches by 2.5 inches).

study site because it has a large proportion of AGYW, FSW, and MSM. Kiambu County hosts a high concentration of institutions of higher learning and corollary large populations of AGYW. The proximity of Kiambu County to Nairobi has resulted in a high rate of urbanization and related increase in the study populations of interest (25). In addition, the county provides access to peri-urban and rural settings. Importantly, service delivery points that serve AGYW, FSW, and MSM with HIV testing services were accessible and interested in study collaboration, as they are all owned and managed by LVCT Health.

The objectives of the study were to assess (a) usability of a MAP prototype (no drug or microneedles) for ease of use and design features, (b) hypothetical acceptability of MAP technology for HIV PrEP and/or as an MPT, and (c) potential programmatic fit of MAP technology within the Kenya health care system. Study participants included adolescent girls (AG,

15–17 years) and young women (YW, 18–24 years); FSW; MSM; male sexual partners of AGYW and FSW; health service providers; and national and county policymakers and managers. MSM assessed the MAP prototype for HIV prevention only.

Sampling for qualitative data collection considered the homogeneity of the populations and followed general guidance around the sample sizes required to reach saturation (26). The research team worked with staff at the five participating health facilities to select AGYW, FSW, male sexual partners of AGYW and FSW, and MSM participants for focus group discussions (FGD) *via* purposive typical case sampling whereby every third client from each of the target populations was asked to participate. Male sexual partners of YW were recruited *via* referral from their partners. We also purposively sampled national stakeholders and county-level health managers with experience in PrEP and contraceptive service provision and commodity management to assess the potential programmatic fit of MAPs for HIV PrEP and as an MPT.

We based our sample size ($n = 14$ per user group) for the mock use exercise on general guidance about appropriate sample sizes for usability testing (27). Because self-care products in Kenya, such as HIV self-testing (28), are usually delivered initially in health facilities where providers are able to assist, we also engaged providers to evaluate usability of the prototype *via* a simulated use exercise in which they were asked to provide additional support to mock clients.

2.2. Data collection and analysis

Primary data collection included a mock use exercise with a MAP prototype followed by in-depth interviews and a self-administered questionnaire with AG, YW, FSW, MSM, and health service providers. In addition, FGD were held with AGYW, FSW, male partners of AGYW and FSW, and MSM. Participants in these two data collection efforts were distinct from one another. Finally, key informant interviews were conducted with county and national stakeholders. In both data collection efforts, user perceptions and preferences about product features that could affect acceptability were explored, including MAP size, duration of protection, site of application, wear time, feedback indicator, and packaging. The mock use exercise consisted of orienting the participants to the MAP prototype through an informed consent process. Participants who consented were given instructions for use (IFU) (**Supplementary material S1**) and a MAP prototype and were asked to follow the instructions to apply the MAP on their body. During this activity, the participants were encouraged to "think out loud" and describe what they were doing. Simultaneously, a research assistant observed the mock use to document use errors, difficulties, close calls, and surprises across all steps of MAP application (handling, opening package, using instructions, practicing applying the patch, activating the feedback indicator, removing the patch). An in-depth interview was conducted to capture user perspectives after mock use, including a survey in which participants rated perceived importance and relative satisfaction with MAP features. Data collection methods are summarized in **Table 1**.

The data collection instruments were translated into Kiswahili and pretested to identify ambiguity and clarify language. The FGD guide and semi-structured interview questionnaire were pretested with AGYW, FSW, MSM, and male partners at drop-in centers and DREAMS program sites in Nairobi County. The key informant interview questionnaire was pretested with providers and stakeholders in facilities in Nairobi County that did not participate in this study.

Data were collected in "safe spaces" identified by the facilities (where they usually meet confidentially with clients to discuss health issues). When a safe space was not available, clients were asked to suggest a meeting place within their community and interviewers assessed the location prior to the meetings to check whether it was conducive for data collection according to interview and research ethics requirements.

Qualitative data were transcribed verbatim in Microsoft Word (Microsoft Corporation, USA), translated as necessary, and analyzed applying an inductive approach using NVivo^{TM} R (QSR International Pty Ltd; Doncaster, Australia). A coding framework was developed, initially based on the study objectives and then expanded in a data analysis workshop. Coding and qualitative data analysis were done collaboratively by the research team,

TABLE 1 Data collection methods, by study objective.

Study objective	User group	Data collection methods used
Usability of MAP prototypes	AG, YW, FSW, MSM, and health service providers	• Mock use exercise in which participants used the MAP prototype according to the instructions for use; researchers followed a standardized observation checklist to record correct use, use errors, close calls, difficulties, surprises; video recorded or photographed; duration of 15–30 min • In-depth interviews after mock use: audio recorded; duration of 45 min • Self-administered questionnaire in which participants ranked the MAP features and level of satisfaction with each feature in order of importance; duration of 15 min
Hypothetical acceptability of MAP technology for HIV PrEP and/or as an MPT	AGYW, FSW, male partners of AGYW and FSW, and MSM	Focus group discussions: audio recorded; duration of up to 90 min
Programmatic fit of MAP technology within the Kenya health care system	Health service providers and national/county-level stakeholders	Key informant interviews: audio recorded; duration of up to 45 min

AGYW, adolescent girls and young women; FSW, female sex workers; MAP, microarray patch; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

noting comparisons (where appropriate) for the different target populations.

Quantitative data (ranking of MAP features and satisfaction from the self-administered questionnaire and mock use exercise observation checklist) were analyzed using Microsoft Excel version 2016 or a rainbow spreadsheet (29) with filters for user populations and usability steps. Data were cleaned and reviewed after entry into the spreadsheets; incomplete, inaccurate, or irrelevant data were identified and rectified after consultation with at least two members of the research team.

2.3. Ethics approval

The AMREF Ethics and Scientific Review Committee granted ethics approval for this study (approval number: P770/2020). Letters confirming approval to conduct the study were shared with county partners and clinic and drop-in center sites after meetings to sensitize the county representatives on the proposed study. The Kiambu County Health Research Unit also granted approval to conduct the research (reference number: KIAMBU/HRDU/22/03/08/RA_OTISO). Written informed consent was obtained for all study procedures, including audio, photo, and video recording, as warranted by each data collection method.

3. Results

Between February and April 2022, we collected data from 47 participants in a mock use exercise and conducted ten FGD and six stakeholder interviews (Table 2). The stakeholder interviews were conducted with three county managers and three national managers.

3.1. Usability of the MAP prototype

The research team observed 47 participants during simulated use of the MAP prototype (Table 3). Observations were recorded as either correct use or one of the four standardized categories employed in usability testing (30). The majority of the 47 participants reviewed the instructions before engaging in the mock exercise. The four participants who did not review the instructions experienced user errors. Successful completion of all steps in the mock use exercise was low for all user groups, ranging from 13% for MSM to 46% for providers. About a quarter of AG (29%), YW (25%), and FSW (22%) successfully accomplished the mock use exercise.

The most problematic task observed for all population groups except providers was cleaning of the application site (both user error and difficulty). For AGYW, the second highest number of

TABLE 2 Study participants, by user group and data collection method.

Data collection method	AGYW	FSW	MSM	Providers	Male partners of AGYW/FSW	Total number of participants
Mock use exercise	19	9	8	11	0	47
Focus group discussions	4	2	2	0	2	10 groups (total of 74 participants)
Stakeholder interviews						6

AGYW, adolescent girls and young women; FSW, female sex workers; MSM, men who have sex with men.

TABLE 3 Summary scores of mock exercise observations for all user groups ($n = 47$).

Observation	Successful use % (n)	User error % (n)	Difficulty % (n)	Close call % (n)	Surprise % (n)
Reviewed instructions	91 (43)	9 (4)	0	0	0
Fully understood instructions	30 (14)	70 (33)[a]	9 (4)[b]	0	0
Cleaned application site	47 (22)	53 (25)	0	0	0
Easily and correctly opened package	94 (44)	0	6 (3)	0	2 (1)[†]
Correctly peeled patch out of tray	98 (46)	0	0	2 (1)	0
Correctly placed MAP on skin	74 (35)	17 (8)	9 (4)	0	0
Understood feedback indicator	64 (30)	32 (15)	4 (2)	0	0
Crushed all domes	66 (31)	19 (9)	15 (7)	0	0
Comfortable wearing MAP	89 (42)	9 (4)	2 (1)[‡]	0	0
Understood wear time of 10 min	57 (27)	26 (12)	17 (8)	0	0
Successfully removed MAP	70 (33)	13 (6)	17 (8)	0	0
Understood MAP disposal instructions	79 (37)	21 (10)	0	0	0

MAP, microarray patch.
Use error: User action or lack of user action while using the MAP that leads to a different result than what is intended by the manufacturer or expected by the user.
Close call: User almost commits a use error while performing a task but recovers in time to avoid making the use error.
Use difficulty: Although users did not commit a use error, they might have difficulty performing the task (e.g., user hesitating, spending a long period of time on a task, requesting help or expressing difficulties).
Surprise: User action or lack of user action while using the medical device that was not expected by the researcher.
[a]Experienced one or multiple user errors during the mock exercise.
[b]Experienced user errors and demonstrated difficulty in accomplishing the mock exercise, with two participants showing extreme difficulty.
[†]Participant used teeth to open package.
[‡]Participant seemed nervous and later reported that she thought the MAP was an HIV test kit.

user errors and difficulties was observed for understanding wear time. For FSW and MSM, the second highest number of user errors and difficulties was observed for pressing down firmly on all feedback indicator domes, one at a time, until each dome crushed. Health service providers were observed to have the most challenges with pressing down firmly on all indicator domes one at a time until each dome crushed (use errors and difficulties) and removing the MAP layer from the skin (difficulty only). Two FSW showed extreme difficulty when using the MAP; one mistook the MAP for an HIV test kit and the other was not literate.

After the mock use exercise, participants reported their perceived importance ("not important", "undecided", or "important") and satisfaction ("dissatisfied", "neutral", or "satisfied") about a set of MAP features (Figure 3 and Supplementary material S2). The feedback indicator, patch size, and wear time were the features with the largest gaps between importance and satisfaction, indicating product design alignments that will need to be made in future product iterations.

3.2. Hypothetical acceptability of a MAP for HIV PrEP or as an MPT

All FGD participants (AGYW, FSW, MSM, male partners) and mock use participants AGYW, FSW, MSM, providers) expressed their willingness to use a MAP for either HIV protection or as an MPT when it became available. Men shared opinions from the perspective of their own hypothetical use of an HIV PrEP MAP and perspectives about women using HIV PrEP MAP or MPT MAP. The convenience of the method and longer projected wear time were noted as advantages particularly when compared to existing methods of protection (Table 4). Conversely, a few male partners noted that despite their positive perception of the MAP, they could be suspicious that somebody using it might have an HIV infection.

Preferences around the MAP design feature set varied among user groups (Table 5). More detailed results about each feature are also discussed below.

3.2.1. MAP size

In general, AGYW reported that the current size of the MAP was acceptable. For example:

"*I haven't seen anything that is wrong with the size because it can easily be covered.*" YW, mock use exercise [IDIYW002].

Service providers and FGD participants felt the size of the MAP should be smaller. They suggested the MAP should be small enough to be carried easily, possibly in a pocket or purse.

"*It can be smaller, so that when you put it in your handbag, someone should not see that it is something funny. It should look like something smart, small.*" FSW, FGD [FGDFSW001]

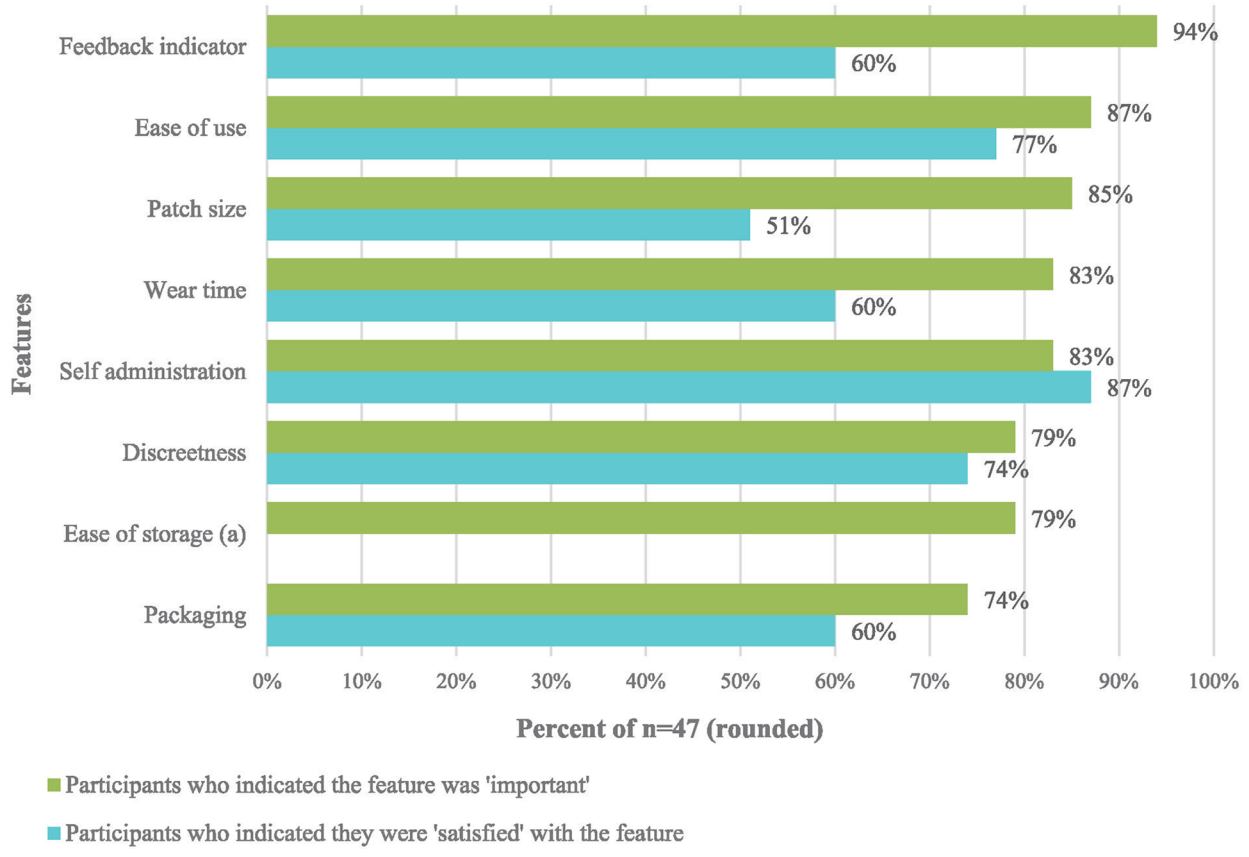

FIGURE 3
Differences between "important" and "satisfied" for MAP features after mock use by AGYW, FSW, MSM, and health service providers (n = 47).

TABLE 4 Illustrative acceptability of the MAP technology, by user group.

User group	Illustrative quote
Adolescent girls and young women	*"I would prefer patch because once you administer it the drugs get into the body. The drugs ok, you know us ladies if you go somewhere and you are late home you call mum and tell her that you may not be able to make it you will be hosted by somebody else, in that case you will miss your drugs because you have left it at home and with this it is in you."* AG, mock use [IDIAG002]
Female sex workers	*"Because, it is cool; once you place it, that is it; it is not like the PrEP oral drug that you might sometimes forget to swallow; this is good."* FSW, mock use [IDIFSW001] "*It is better to use this patch, because this patch is even easy to apply on the body anywhere. And then even when you use it, there is no one who is going to know whether there is anything that you are using."* FSW, mock use [IDIFSW001]
Male partners	*"I think this one is better because not everyone normally can bear the burden of taking pills but this one is better since you just apply it on your skin."* Male sexual partner, FGD [FGDMSP001]
Men who have sex with men	*"I like it because it is not like PrEP that you have to take every day, you can take it for a week, two weeks, monthly…yeah."* MSM, mock use [IDIMSM001]
Providers	*"The patch is much better than the oral PrEP. I have interacted with adolescent girls and young women. From my experience condoms are not consistently used. Still the patch will be better."* Provider, mock use [IDIHSP001]

TABLE 5 Summary of MAP feature preferences, by user group.

User group	Size	Wear time, in minutes	Duration of protection, in months	Two most preferred sites of application
Adolescent girls and young women	Acceptable	1–10	1	Thigh, arm
Female sex workers	Smaller	5–10	3–12	Upper arm, lower arm, thigh
Male partners	Smaller	10	<1 (7 days)	Arm, thigh
Men who have sex with men	Smaller	5–10	At least a week	Upper arm, lower arm, chest
Providers	Smaller	2–15	1–3	Inside upper arm

"*It's too long…some clients would not like to be seen by their partners…it would raise some alarm or queries."* Provider, mock use exercise [IDIHSP001].

"*I wish it was smaller. It is big in that when you carry it you can't put it in a smaller purse."* Male partner of AGYW, FGD [FGDMSP001].

In particular, FGD participants recommended the MAP be about 7 cm × 7 cm (about 2.75 inches square), similar in size to a nicotine patch, deworming medicine patch, or Elastoplast (bandage).

3.2.2. Wear time

Most participants preferred a short period of wear time (≤10 min) because it would be reasonable, convenient for busy lifestyles, and allow discreet application. Adolescent girls preferred the shortest wear time. A few participants mentioned that they preferred longer wear times (30–60 min or even 24 h), primarily to ensure that the drug had been fully delivered.

"*One minute. It should be something that works fast."* AG, FGD [IDIAG001].

"*10 min is good for me. It is a reasonable time, anyone can get those ten minutes. Let's say you go to work in the morning and wake up at 7am, you can still be able to get the ten minutes to apply the patch. Ten minutes is okay.*" YW, mock use [IDIYW003].

"*I think those 10 min are okay, because even if you are at home, and you have bathed and put it on, by the time you finish getting ready, those 10 min will have passed. I think that time is okay those 10 min will not prevent you from doing your normal business."* FSW, FGD [FGDFSW001].

"*If am applying it to a client it should take ten minutes. It should not take long since there might be other clients waiting."* Provider, mock use [IDIHSP002].

"*Because you can set apart five to ten minutes knowing that you are applying some medication and then after ten minutes you go and do your chores."* MSM, mock use [IDIMSM001].

3.2.3. Duration of protection

The majority of AGYW preferred at least a 1-month duration of protection because it offered greater convenience and flexibility within their sexual and reproductive life. All providers proposed that the duration of protection should last between 1 and 3 months. One provider explained that shorter periods would not cure the problem of non-compliance with PrEP, and concomitantly, longer periods would reduce the burden of regular client visits to health facilities.

"*I would say so to reduce clients from coming back to the facility. My cry is actually for the clients since as a provider I will always be here. As you can see calling clients is sometimes hectic. They say they are not available on certain days."* Provider, mock use [IDIHSP002].

FSW stated their preference for longer periods of protection than AGYW. It appeared that longer periods were favored because the FSW had had experience with injectable contraceptives (3-month protection) and/or contraceptive implants that had much longer periods of protection.

"*In fact, not even for 1 month; if I find for a whole year, I can be very happy."* FSW, FGD [FGDFSW001].

Providers and policymakers expressed preference for a longer-term duration of protection (3–6 months) to improve protection and simplify resupply.

However, MSM and FSW also said having even 1 week of protection would be better than oral daily pills for HIV protection.

3.2.4. MAP application site

After mock use, most participants preferred the MAP application site to be on the thigh (large surface, discreet) or the forearm or upper arm (ease of access, convenient). In FGD, the three most preferred sites were the upper arm, lower arm, or thigh. AG also mentioned the stomach as a third preference and YW mentioned under the breast and the rib cage as being

appropriate application sites. Most providers preferred the inside upper arm, similar to placement for contraceptive implants (ease of access, does not invade client's privacy). Some mock use participants (AGYW) were confused about where to apply the MAP and wanted more guidance.

3.3. Programmatic fit of the MAP within the Kenya health care system

There was a general consensus among stakeholders that the MAP technology, whether HIV only or as an MPT, was a revolutionary innovation whose introduction would be very timely within the Kenya health care system. Overall, stakeholders preferred the MPT MAP over the HIV-only MAP. Stakeholders noted that the MPT MAP aligned well with the integrated health services policy currently in place in Kenya (31).

"*I think the combined would work better because it will make the integration of service easier. That this is a PrEP and a family planning and then it is dealing with two birds with one stone. I like the integration part, because we are looking at integrating services and integrating HIV to other services. So, you are killing two birds with one stone. At least that it does so we don't have to deal with issues of unwanted pregnancies and abortions and complications of unwanted pregnancies and everything so that's a plus for the women. As we know, we are dealing with two pandemics here, the pandemic of unintended pregnancies and the pandemic of HIV especially women between 15 and 24 years. So having a product that helps you to address those two things together, it is very beneficial. From our data we can see we are getting many new HIV infections in that age. Then we are currently focusing on service integration, integrating PrEP into SRH and SRH into PrEP. We are currently trying to put systems in place to actualize integration.*" Female, national-level key informant interview [IDIKII002].

Additionally, stakeholders noted that an MPT MAP would save client time, reduce stigma associated with HIV prevention by combining with less stigmatized family planning services, reduce the pill burden associated with taking oral PrEP and of taking multiple drugs at different times and the service provider/facility burden of dispensing them, and be attractive to AGYW who are keen to prevent pregnancy at the expense of HIV protection. The stakeholders felt that an MPT MAP would be received with high enthusiasm/interest among AGYW, FSW, and providers. On the other hand, it was noted that the HIV PrEP MAP would be preferred by male users and female clients who had intolerance for hormonal contraceptives.

In general, stakeholders perceived the MAP technology favorably and identified product benefits as being its potential for discreetness, ease of application, long-term protection, and self-administration. For example, the simplified administration offered by the MAP would provide flexibility in terms of who can deliver the MAP and where it can be distributed/delivered, thus helping improve the overall efficiency of health services. Stakeholders mentioned that the MAP technology could likely improve PrEP uptake by redressing the major problems associated with oral PrEP.

"*Uptake of PrEP in the country is still low. Let us be honest, oral PrEP uptake is still low and one key challenge is the small things the end users raised were not addressed. The issue of the rattling sound of the tablet, the tablet is so big, the color looks like an ARV, you know, those small things. So, I'm very excited about this new product.*" Female, national-level key informant interview [IDIKII002].

Stakeholders agreed that the minimum duration of protection should be 3 months, to coincide with the recommended HIV retesting period and the schedule for injectable contraception. They also felt that MAPs should come in different durations of protection (3 months, 6 months, and 1 year) to address the needs of different users and that the package color should indicate duration.

Stakeholders identified multiple access points for a MAP product, including both facility-based and home-based self-care options.

"*For me, I see this product having a broad spectrum of delivery points. I see it beyond the current delivery point like for the oral PrEP. I see it as a self-empowering product which should be delivered at the comfort of somebody's home or even privacy. Just like a HIV self-test kit, buy in the chemist, go with it at home, when I am free, test.*" Female, national-level key informant interview [IDIKII002].

Several potential risks and/or unanswered questions were raised by stakeholders. These included the need for clarifying information about which drug(s) would be used in the MAP and the impact/safety; how to reverse the long-term MAP HIV prevention and contraceptive drugs in the body if they started having adverse effects on users; how the MAP feedback indicator would ensure that potential users have the optimal dosage of the prescribed drug(s); the sensation of using microneedles, including pain and side effects on skin; how to build user confidence that medication is actually delivered if no sensation; and the potential impact of repeated MAP applications (possible scarring). Stakeholders also raised the possibility of improper MAP use, both from the perspective of the technology and the intended user group (AG).

"*So, there is a risk of misuse because maybe of a client not understanding that if the duration of the product is 30 days. You see there is nothing being left there (nothing left inside the skin like the depo); how do you convince me that just that one application has left enough drugs to protect me for 30 days, you might find some people repeating the administration and that is a risk.*" Female, national-level key informant interview [IDIKII001].

"*I foresee this spilling over even in schools because it is very easy to administer. Those in school may opt for such a product and, as I had said, the policy currently for the in-school is age-appropriate information and abstinence, but because it is easy to administer this product, it will be easily administered even in school. We will not have a way of monitoring…how will we monitor that? So, I do not know how we will restrict this product to ensure that it is only maybe those children who can consent…in our country it is 18 years; it is only accessible to those above 18 years.*" Female, national-level key informant interview [IDIKII003].

A final concern, raised by policymakers, was the possible environmental impact of improper waste disposal.

"*Yes, plastic is harmful for the environment and that is why am suggesting there should be instructions on how to dispose it. We can also explain to the client how to dispose; is it burning it, or?*" Provider, mock use [IDIHSP002].

4. Discussion

In our study, all user groups expressed willingness to use MAPs as a stand-alone HIV prevention technology. Users showed a strong preference for MAP technology over other currently available HIV prevention methods (oral PrEP, condoms). Women, providers, and stakeholders expressed strong interest in an MPT MAP—sometimes in preference to a stand-alone HIV PrEP MAP. Some potential users also expressed preference for the contraceptive MAP concept over existing contraceptives because it would be easy to use, discreet, and self-administered. The strong interest in the MAP technology was related primarily to its potential for discreet use and self-administration, ease of application, and long-term protection. MAP size and duration of protection were seen as key characteristics influencing acceptability. Some participants—especially MSM/FSW, who preferred long-term protection—would accept a larger MAP if it provided longer protection. Most AGYW preferred the MPT MAP over an HIV PrEP-only MAP and preferred 1-month protection. This finding in support of an MPT option is consistent with the results of the Tablets, Ring, Injections as Options (TRIO) study in which young women aged 18–30 in Kenya and South Africa perceived high value for an MPT (32, 33), and preferred a longer duration as well as discreet protection (34, 35). Similarly, results from a discrete choice experiment among women and adolescents in South Africa reported likely limited uptake and health impact among adolescent women unless the new PrEP products also provide pregnancy protection (33, 36). An assessment of the potential for MPTs in Nigeria, South Africa, and Uganda also found that 93% of women surveyed preferred an MPT product to either an HIV-only or contraceptive-only product (37). Because Kenyan AGYW seeking contraception frequently have high HIV risk (38), an MPT option could be particularly beneficial for this user group. Policymakers in this study also noted that the MPT MAP could address needs of AGYW who are keen on avoiding pregnancy but also are at risk of HIV.

FSW often have overlapping burdens: high risk of HIV, unmet need for contraception, and increased likelihood of contracting a sexually transmitted infection (39). FSW saw value in both MAP indications and voiced a need for MPTs that protect from other infections besides HIV. FSW wanted duration of protection consistent with injectable contraception. Other user groups, such as women living with HIV, have also identified a longer-acting injectable as preferred over daily oral tablets when a multipurpose technology concept offered an antiretroviral for HIV treatment co-administered with a hormonal contraceptive (40). However, this may reflect respondent bias in that injectable contraception is well accepted in Kenya, thereby making it a familiar benchmark technology.

Male partner support can be an important influence on AGYW and FSW who are interested in using HIV PrEP (41–44). In this study, male partners were supportive of MAP use, although they mentioned that partner use of an MPT MAP might give rise to suspicions around partner fidelity and serostatus. Male partners of young Kenyan and South African women in the TRIO study, while being supportive of MPT use generally, also expressed similar concerns about product use disclosure (45).

MSM viewed the HIV PrEP MAP as being a viable option, which is noteworthy given that MSM in Kenya show low adherence to a daily PrEP regimen (46, 47). A recent programmatic surveillance of PrEP program rollout in Kenya also showed substantial missed opportunities for PrEP initiation for MSM, as well as high levels of PrEP discontinuation at 1 month (48). In other studies (49, 50), MSM have noted their preferences for longer-acting PrEP options. Use of novel delivery platforms such as the MAP could be important for MSM, because PrEP discontinuation is not uncommon.

Providers and stakeholders preferred an MPT MAP and expressed that an MPT MAP could ease workload in health facilities and is aligned with Kenya's policy of integrating health care programs. The MPT MAP was identified by stakeholders as a revolutionary technology that has the potential to "kill two birds with one stone." Enthusiasm for MPTs has been documented by health care providers in Kenya and South Africa where one South African nurse explained that provision of an MPT to YW could "kill two birds with one stone" (51). This finding strongly parallels our study findings, with one stakeholder using the exact same language to illustrate their point. Regardless of type of MAP (i.e., HIV PrEP, MPT as well as a contraceptive MAP), stakeholders felt that the technology could ease the burden of existing methods for users, providers, and the health care system.

In this study, Kenyan participants evaluated a second-generation prototype design that had been refined based on participant experiences with earlier prototypes in South Africa and Uganda (20). The MAP prototype used in the Kenya assessment was designed to be scaled for different numbers of arrays, depending on API potency. The second-generation prototype had an improved feedback indicator that was optimized for ease of use through (a) reduced number of handling tabs; (b) larger arrays, enabling fewer domes to press; (c) material chosen for optimized inversion force; (d) refined dome design to ensure no rebound; and (e) cutouts to increase flexibility (to accommodate different body locations).

The mock use exercise identified several areas in need of further product iteration. Most participants (70%) across all user groups had some difficulty understanding the IFU, in part due to low literacy and poor comprehension of images. Participants recommended simplifying the language and making the graphics more distinct to improve clarity. Importantly, users need a MAP orientation and demonstration before use. This is similar to the MAP assessment in Uganda, where participants who were oriented to the MAP solely by the IFU experienced more

difficulty using the MAP during mock use. In contrast, mock use participants in South Africa were recruited from FGD where they saw a demonstration of the MAP and had an opportunity to familiarize themselves with the device, resulting in a more successful user experience. Even with the refinements made to the current MAP prototype and IFU to improve clarity and ease of use, the Kenya results indicate that the potential user will benefit from an orientation and product demonstration before their first use.

Although most participants (74%) were able to place the MAP on the skin correctly, potential users across all groups wanted more guidance on exact placement of the MAP on the skin. YW displayed the most difficulty in this regard. Mitigation for this would be to integrate more direct counsel on freedom of choice for the application site when orienting the potential user to the device. Alternatively, a specific site could be identified as the best possible location and potential users could be instructed to apply in that location.

Across all groups, some participants (34%) struggled with activating the MAP feedback indicator by, for example, not crushing all domes or not pressing firmly enough to completely crush the domes. Providers were able to complete this step successfully, yet they felt that it took too much effort to crush the domes. This design issue could be remedied by providing more explanation on how the MAP works during orientation and/or in the IFU. Investigating the use of more pliable dome material and how it might result in reliable insertion of the MAP projections would be another potential option to address this concern.

Most users (73%) had difficulty understanding wear time of the device because they found interpreting the clock on the IFU challenging. Providers were able to interpret the clock correctly; however, they noted that it may be difficult for their clients. Using digital time in the IFU may help overcome this issue.

Some participants (30%) had difficulty removing the MAP layer, which could be resolved by providing a pull tab. Most participants (79%) understood instructions for device disposal, and some felt that disposal could be a health hazard. Information on safe disposal will be added to the IFU.

This study indicates that additional refinements are needed to optimize the MAP prototype, including the feedback indicator. These refinements could improve confidence in appropriate delivery, especially for low-literate and AGYW user groups, particularly if they have not had specific counseling about the MAP before use. Similar to results from the South Africa and Uganda assessments (20), these results from Kenya show a strong interest in a MAP as a drug delivery platform and desire for an MPT MAP that is long acting.

The use of mixed methods in this study strengthens the robust nature of the findings. The study is limited by the relatively small geographic distribution of participants (only from Kiambu County); however, participants from varied settings (urban, peri-urban, and rural) were included. Preferences about a contraceptive MAP were inferred from responses about an MPT MAP. Specific questions about a contraceptive MAP were deleted from data collection tools because results from the instrument pretesting indicated that no additional insights would be collected with contraceptive-specific questions. Data were analyzed with a focus on user group rather than these varied settings, so some additional nuance and learning may still be uncovered. Because the usability testing was not with a microarray patch containing microneedles, some skin reactions (from wearing the patch), side effects (e.g., pain) at the wear site could not be assessed thus biasing potential user acceptability more favorably. Additionally, many of the MSM and some of the FSW appeared to have been intoxicated when they participated in the mock use exercise, potentially affecting their ability to perform adequately. On the other hand, their level of sobriety may be representative of their real-life situations and data collected would reflect that reality. Nonetheless, engaging users and stakeholders in early-stage product development gives an opportunity to refine MAP design to better meet user needs. Users/stakeholders want to be part of the process of developing new products and moving them forward, and this type of mixed methods assessment offers an ideal opportunity for this involvement.

5. Conclusions

Participants reported high potential acceptability of MAP as a drug delivery system for both for HIV PrEP and as an MPT. Health service providers and policymakers felt MAP could be integrated into the HIV and family planning health care systems. Some potential target audiences seemed to value a MPT MAP over an HIV PrEP-only MAP—specifically, AGYW, health service providers, and policymakers. Reducing the overall MAP size and number of arrays would likely improve acceptability, the feasibility of which is dependent on successfully formulating a higher-potency ARV to be delivered by MAP. Further prototype modifications, such as refining the feedback indicator to provide greater confidence of successful application and instructing users when to remove the MAP, are recommended to improve confidence and acceptability.

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.

Ethics statement

The studies involving human participants were reviewed and approved by AMREF Ethics and Scientific Review Committee (approval number: P770/2020) and Kiambu County Health Research Unit (reference number: KIAMBU/HRDU/22/03/08/RA_OTISO). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SGG, RK, AN, MK-B, LO: contributed to the design and implementation of the study and analysis of the results. CJ: provided financial and technical oversight of the study. PSC: prepared the initial draft. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1125159/full#supplementary-material.

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Cost-effectiveness of the dual prevention pill for contraception and HIV pre-exposure prophylaxis

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Introduction: Women in sub-Saharan Africa (SSA) experience the world's highest rates of both HIV infection and unintended pregnancy. The Dual Prevention Pill (DPP) is a novel multipurpose prevention technology (MPT) that co-formulates HIV pre-exposure prophylaxis (PrEP) and combined hormonal oral contraception into a single daily pill. As a dual indication product, the DPP may be preferred by women facing these overlapping health risks. However, most SSA countries face severe healthcare resource constraints. Research is needed to assess whether, in what populations, and in what use cases the DPP would be cost-effective.

Methods: We augmented an agent-based SSA HIV model with maternal health parameters including unintended pregnancy, abortion, and maternal mortality. Based on a previous market analysis, we assumed a primary DPP user population of current oral contraceptive users ages 25–49, and alternative user populations in different risk groups (age 15–24, sex workers, HIV-serodiscordant couples) and baseline product use profiles (unmet need for contraception, oral PrEP use, condom use). In three geographies (western Kenya, Zimbabwe, South Africa), we estimated HIV infections averted, pregnancies averted, disability-adjusted life-years (DALYs) averted, and the incremental cost-effectiveness ratio (ICER) over a 30-year time horizon, assuming equivalent adherence to the DPP as to oral contraceptives, higher adherence, or lower adherence.

Results: The DPP is likely to be a cost-effective alternative to oral PrEP among users in need of contraception. Among women not already using PrEP, the DPP is likely to be cost-saving in sex workers and serodiscordant couples. The DPP is unlikely to be cost-effective in oral contraceptive users in the general population. Switching from oral contraception to the DPP could be net harmful in some settings and populations if it were to substantially reduces adherence to oral contraception. Results were robust to a range of time horizons or discount rates.

Conclusion: The DPP has the potential to be cost-effective and cost-saving in populations at substantial HIV risk. Outcomes are sensitive to adherence, implying that effective counseling and decision-making tools for users considering the DPP will be essential. More research is needed to understand real-life adherence patterns and ensure health benefits achieved from contraception alone are not lost.

KEYWORDS

dual prevention pill, prEP, oral contraception pill, HIV, cost-Effectiveness, daly, hiv prevention, multipurpose prevention technologies

Introduction

In 2019, HIV/AIDS was the leading cause of death while pregnancy and delivery complications were the second-leading cause of death among women of reproductive age in sub-Saharan Africa (SSA) (1). Women in SSA experience the world's highest rates of HIV infection (2–4) and of unintended pregnancy (3, 4). In 2021, women and girls accounted for 63% of all new HIV infections in SSA, with over 540,000 new HIV infections in total (5). Meanwhile, the unintended pregnancy rate in SSA is 91 per 1,000 women aged 15 to 49, the highest of any region (6).

While oral pre-exposure prophylaxis was first approved by the US Food and Drug administration (FDA) in 2012, availability and uptake of oral pre-exposure prophylaxis (PrEP) for HIV prevention among women in SSA has been low due to limited funding for the HIV response and slow, relatively fragmented rollout experiences in many countries. Further, the impact of oral PrEP has been hindered by low adherence and continuation rates due to a range of challenges at the structural, community, and individual level, including PrEP stigma and pill burden (7–9). Meanwhile, in SSA efforts to satisfy unmet need for contraception have also struggled to expand, with <1% growth in modern contraceptive prevalence (MCPR) since 2017, compared to more rapid growth in the decade prior (10).

These statistics suggest a need for additional prevention options to meet the diverse needs and preferences of women facing dual health risks of HIV and unintended pregnancy. Multipurpose prevention technologies (MPTs) are products that provide protection from two or more reproductive health issues, including unintended pregnancy, HIV, and other sexually transmitted infections. Currently, the only available MPTs for HIV and pregnancy prevention are male and female condoms, which are non-discreet, often reliant on partner negotiation, and sub-optimally effective with typical use (11). The Dual Prevention Pill (DPP), which co-formulates the active ingredients of combined hormonal oral contraceptives and oral PrEP into a single daily pill, is likely to be the next MPT to reach markets (12). Because the DPP combines two products that are already widely approved, including by the US FDA, regulatory submissions will leverage evidence from bioequivalence studies, a relatively short development pathway, with possible licensure as early as 2024 (12, 13). Evidence from family planning suggests that use of modern contraception increases when more methods become available, as a wider set of options improves the ability to meet user needs over time (14). As a new method option, the DPP therefore offers the opportunity to expand choice and potentially increase PrEP and/or contraceptive coverage. Multiple preference studies have also found that women, partners, and matriarchs would prefer MPTs over single indication HIV prevention products (15–17).

Despite these potential benefits, future availability of the DPP in SSA is uncertain because most SSA countries face severe healthcare resource constraints and need to make difficult tradeoffs in terms of health care service prioritization. For example, during early introduction of oral PrEP, many countries did not prioritize provision of oral PrEP to women in the general population (i.e., outside of specific high-risk groups such as sex workers) because it was not shown to be cost-effective in this population (18). However, more recent evidence suggests that oral PrEP may be cost-effective for women in the general population in high-incidence areas of SSA, especially if PrEP is concentrated in seasons of risk, such as 3-month periods when women have condomless sex (19). As the DPP development proceeds, SSA health authorities will need evidence on cost-effectiveness to inform DPP introduction and scale-up decision-making, including identification of priority populations and geographies, target-setting, and optimization of HIV prevention and contraception method mixes.

To understand the potential cost-effectiveness of the DPP, we used agent-based modeling of HIV transmission and unintended pregnancy in three SSA countries: Kenya, Zimbabwe, and South Africa. We considered DPP use among current OCP users, who are likely to have the highest demand for the DPP, as well as women with unmet need for contraception or who use condoms for contraception, in whom the DPP could provide a more effective form of contraception. We also considered different risk groups, including female sex workers and women with HIV-positive partners, in whom PrEP was previously shown to be more cost-effective than in other population groups (18). Finally, we considered that DPP adherence may differ from OCP adherence, including potentially lower adherence to DPP compared to OCP due to its larger pill size and potential for additional side effects. This analysis was initially performed to inform DPP development, but could help inform future planning for the availability of the DPP in SSA and may have implications for the development of future MPTs.

Methods

Model description

Analyses were conducted using the Epidemiological MODeling (EMOD) software, an agent-based network model of sexual and vertical HIV transmission (20, 21). Sexual HIV transmission is modeled using a network of marital, informal, transitory, and commercial sexual relationships, each with distinct age/sex patterns of formation and dissolution, and vertical transmission is modeled upon live birth by an HIV-positive mother (22, 23). Patterns of HIV prevalence and incidence by age, sex, and over time have been compared to population-based survey data in multiple SSA settings, including successful prospective validation of an HIV incidence prediction in a blinded, multi-country community-randomized controlled trial (21).

Model fit to settings

We configured the EMOD model to fit demographic and HIV trends in western Kenya, South Africa and Zimbabwe using setting-specific census, fertility, and mortality estimates as well as HIV prevalence, incidence and ART coverage (24–26). Kenya has

a very wide range of HIV prevalence, from <0.1% in eastern regions to >25% in its western regions (27). Accordingly, this analysis focused only on the high-prevalence Nyanza region in western Kenya, composed of the six counties of Homa Bay, Kisii, Kisumu, Nyamira, Migori, and Siaya. These three settings of western Kenya, South Africa, and Zimbabwe were selected based on high need, potential demand (28), enabling policies, regulatory environments and high HIV prevalence (**Supplementary Material Table S1** in Supporting Information).

Model calibration to HIV epidemic trends in each setting was performed by varying sexual behavior parameters using parallel simultaneous perturbation optimization, a form of stochastic gradient descent designed for parallel computing (29, 30). Among all model parameter combinations tested, we selected 250 parameter sets that best fit epidemic trends using a roulette sampling technique (31).

DPP intervention assumptions

DPP scale-up scenarios (**Table 1**) were designed with input from the DPP Consortium (32), a collaboration of researchers, funders, advocates, and prospective implementers, including experts from both HIV prevention and family planning (33). In our main analysis, we simulated DPP provision to current OCP users ages 25 to 49, in whom uptake and adherence rates to OCPs and oral PrEP are generally higher than in adolescent girls and young women (AGYW) (34). We assumed DPP adherence would be equivalent to OCP adherence, leading to no change in pregnancy risk and a 90% reduction in HIV risk (Scenario 1). We additionally simulated DPP provision to alternative populations: AGYW ages 15 to 24 years (Scenario 2), female sex workers (FSW, Scenario 3), and HIV-negative women in stable serodiscordant couples (Scenario 4). Because there is no available data on real-life DPP use and it is not yet known how the DPP will impact adherence, we also analyzed a range of alternative DPP adherence pattern leading to HIV and pregnancy prevention effectiveness between 30% and 95% (Scenarios 5 through 8). We refer to these risk reduction rates as "effective protection" because they are intended to reflect the variable effectiveness rates that would result from different use patterns and adherence rates. While it is hypothesized that the DPP may increase adherence, assessing outcomes with more pessimistic assumptions around effective protection is important to understanding the potential impact across a wide range of use scenarios.

Counterfactual assumptions

Counterfactual assumptions were used to determine the scenario against which each DPP scenario was compared in order to assess incremental health impacts and costs. In most of our analyses (Scenarios 1 through 8 and 11 through 16) we assumed that, in the absence of DPP, users would instead use OCP with typical use, with a 90% lower annual risk of pregnancy compared to having unmet need for contraception (35, 36). Other counterfactual assumptions included having unmet need for contraception (Scenario 9), using male condoms (assuming 75.5% effectiveness against pregnancy and 80% effectiveness against HIV, Scenario 10) (35, 36), using PrEP (assuming 73% reduction in HIV risk, Scenario 11), and delivering both PrEP and OCP simultaneously (with 73% HIV risk reduction and 90% pregnancy risk reduction, Scenario 12).

Reproductive health assumptions

For analyses in which the counterfactual included unmet need for contraception (Scenarios 9 and 11), a less effective form of

TABLE 1 Scenarios in which DPP cost-effectiveness was analyzed (scenario 1 serves as a primary analysis). Each scenario was run for Kenya, Zimbabwe, and South Africa.

Scenario	Population	DPP Effective Protection for both HIV Pregnancy*	Comparison scenario
1	Ages 25–49	90%	OCP users (assumed receive 90% effective protection against pregnancy with no effect on HIV acquisition)
2	Ages 15–24		
3	Sex workers		
4	Serodiscordant		
5	Ages 25–49	30%	
6		61%	
7		73%	
8		95%	
9	Ages 25–49	90%	Unmet need to contraception (no effect on HIV or pregnancy)
10	Ages 25–49	90%	Condom users (90% effective protection against pregnancy, 80% effective protection against HIV)
11	Ages 25–49	90%	PrEP with 73% effective protection against HIV (no effect on pregnancy)
12	Ages 25–49	90%	PrEP with 73% effective protection against HIV, plus OCP with 90% effective against pregnancy
13	Ages 25–49	90%	Same as Scenario 1 modeled over a 20-year time horizon
14	Ages 25–49	90%	Same as Scenario 1 modeled over a 40-year time horizon
15	Ages 25–49	90%	Same as Scenario 1 analyzed with a 0% annual discount rate
16	Ages 25–49	90%	Same as Scenario 1 analyzed with a 6% annual discount rate

*Reduction in HIV acquisition risk as a result of different patterns of DPP adherence. The difference between this number and 90% is additional used to model the differential risk of unintended pregnancy as described in Methods.

contraception (Scenario 10), or differential adherence to contraception with the DPP vs. OCP (Scenarios 5 through 8), we incorporated health effects of increased or decreased rates of unintended pregnancy. For women with unmet need for contraception, unintended pregnancy was assumed to occur at an annual rate of 34%, accounting for lower observed fertility among sexually active women who do not desire pregnancy compared to women who desire pregnancy, even when no method is used (37). Pregnancy risk reduction was applied to this baseline rate, e.g., OCP with typical use resulted in a 3.4% annual risk of pregnancy (35, 36).

We calculated disability-adjusted life-years (DALYs) caused by HIV or unintended pregnancy by factoring in years of life lost (YLLs) and years lived with disability (YLDs). Disability weights and life expectancies used can be found in **Supplementary Material Tables S2 and S3** in the Supporting Information. DALYs averted were calculated as the difference between the DALYs with DPP rollout and the counterfactual. Pregnancy-related mortality rate associated to unintended pregnancy were calculated using the values in Table 3 with the equation:

$$P_{preg}(F_{livebirth}M_{livebirth} + F_{abortion}M_{abortion} + F_{miscarriage}M_{miscarriage} + F_{stillbirth}M_{stillbirth})$$

where P_{preg} is the annual probability of becoming pregnant, $F_{livebirth}$ is the proportion of unintended pregnancies ending in live birth, $M_{livebirth}$ is the maternal mortality rate associated with live birth with an unintended pregnancy, $F_{abortion}$ is the proportion of unintended pregnancies ending in abortion, $M_{abortion}$ is the abortion mortality rate, $F_{miscarriage}$ is the proportion of unintended pregnancies ending in miscarriage, $M_{miscarriage}$ is the maternal mortality rate from miscarriage, $F_{stillbirth}$ is the proportion of pregnancies ending in stillbirth, and $M_{stilbirth}$ is the maternal mortality rate from stillbirth.

TABLE 2 Assumptions for costs (2021 USD) of different HIV and contraceptive products based on contraceptive data from riley T et al. and Jamieson et al. (4, 38) and cost of goods sold (COGS) estimates from the Clinton Health Access Initiative. We assumed co-delivery of PrEP and OCP would reduce total delivery costs by 6% compared to separate delivery (39).

DPP provision (per person-year)	Cost
First year of use, 2025–2027	$166
Subsequent years of use, 2025–2027	$145
First year of use, 2028+	$146
Subsequent years of use, 2028+	$125
Oral PrEP provision (per person-year)	
First year of use, 2025–2027	$135
Subsequent years of use, 2025–2027	$114
First year of use, 2028+	$122
Subsequent years of use, 2028+	$101
OCP	
Per person-year	$12.5
Condoms	
Per person-year	$2.46
ART	
Per person-year	$257

Cost assumptions

We estimated the net cost to the healthcare system of each DPP implementation scenario relative to its corresponding counterfactual. Costs included the commodity and delivery costs of contraceptive and PrEP products (Table 2) as well as health care costs associated with HIV infection (Table 2) and unintended pregnancy (Table 3). All costs are reported in 2021 USD and accrued over a 30-year time horizon with 3% annual discounting. In sensitivity analysis, costs were accrued over a 20- or 40-year time horizon with a 0% or 6% annual discount rate (Scenarios 13–16).

Cost-effectiveness calculations

For each scenario, we generated model outputs of disability-adjusted life-years (DALYs) (43, 44), HIV infections averted, pregnancies averted, and costs. Net cost included DPP provision cost minus the cost of the alternative treatment (OCP or PrEP, if using), and minus maternal health and HIV treatment costs avoided through averted pregnancies and HIV infections. We generated incremental cost-effectiveness ratio (ICER) (45, 46) as

TABLE 3 Assumptions for costs (2021 USD) and outcomes of unintended pregnancy based on pregnancy and maternal health outcome data from riley T et al (4) and delivery and abortion costs adapted from johns et al (40) and lince-deroche et al (41, 42) with adjustments based on country-specific personnel costs from riley T et al (4).

Health outcome	% of pregnancies	Associated costs	Maternal deaths/100,000 births or abortions
Live birth	49.6%	Kenya: $74 South Africa: $138 Zimbabwe: $86	Kenya: 391 South Africa: 140 Zimbabwe: 391
Miscarriage	11.9%		
Stillbirth	1.7%		
Induced abortion (safe)	9.2%	Kenya: $76 South Africa: $114 Zimbabwe: $89	Kenya: 152 South Africa: 26 Zimbabwe: 152
Induced abortion (less safe)	10.0%	Kenya: $89 South Africa: $125 Zimbabwe: $108	
Induced abortion (least safe)	17.6%	$0	

follows:

$$\text{ICER} = \frac{\begin{array}{c}\text{DPP cost} - \text{avoided OCP cost} - \text{avoided PrEP cost} \\ - \text{avoided pregnancy costs} - \text{avoided HIV treatment costs}\end{array}}{\begin{array}{c}\text{DALYs averted due to HIV prevention} \\ + \text{DALYs averted due to pregnancy prevention}\end{array}}$$

In the main analysis, we analyzed the outcomes over a 30-year time horizon with 3% annual discount rate. In sensitivity analysis, we tested time horizons of 20 and 40 years, and discount rates of 0% or 6% annual discounting. To generate confidence intervals, we conducted bootstrap resampling from 250 repeated simulation runs for each scenario and its respective counterfactual.

Results

Impact of the DPP on HIV infections and pregnancies

The number of HIV infections that could be averted per DPP user, in a scenario where this user would otherwise would not use PrEP, was lowest in Nyanza, Kenya and highest in South Africa (Figure 1), a reflection of the differences in HIV incidence across these settings (Supplementary Material Table S1). The number of infections averted was relatively modest among current OCP users with ages 25 to 49 (Figure 1) The highest number of infections averted, across all groups analyzed, was among female sex workers in South Africa, with an estimated 358.7–386.9 infections averted per 1,000 users per year. In Kenya and Zimbabwe, the largest number of infections averted was among women in stable serodiscordant couples, with 52.9–60.8 infections averted per 1,000 users per year in Kenya and 25.8–44.2 infections averted per 1,000 users per year in Zimbabwe.

In scenarios in which the DPP increased contraceptive use, unintended pregnancies averted were also substantial (Table 4). Among women with unmet need for contraception, the DPP could avert on average 225 pregnancies per 1,000 users per year in all settings. Among condom users, DPP could avert on average 36 pregnancies per 1,000 users per year. Among OCP users with ages 25 to 49, if the DPP were to increase contraceptive adherence resulting in an increase of effective protection from 90% to 95%, it could avert 13 pregnancies per 1,000 users per year. On the other hand, if the DPP were to decrease contraceptive adherence leading to a decrease in effective protection from 90% to 73%, 61%, or 30%, it could lead to 43, 75, or 150 additional unintended pregnancies per 1,000 users per year.

Net health impact of the DPP

The net health impact, measured by DALYs averted, of the DPP's HIV and family planning effects was beneficial in most scenarios. The DPP was the most beneficial in sex workers and serodiscordant couples, whose risk of HIV was the highest, and among women with unmet need for contraception, for whom the DPP averted the most unintended pregnancies. In South Africa, the net benefit of the DPP was also high among adolescent girls and young women even if they would otherwise use OCP, on par with the benefit to older women with unmet need for contraception (Figure 2).

The DPP was estimated to be net harmful in a subset of settings and scenarios that explored potential reductions in contraceptive adherence and effective protection, relative to the use of OCP alone. Among OCP users ages 25–49 in Kenya, the DPP would be net harmful if efficacy effective protection against unintended pregnancy were to decline from 90% with OCP alone to 60% with DPP. In Zimbabwe, the DPP would still be net beneficial (but not cost-effective) with 60% effective protection, but would be net harmful with 30% effective protection. In South Africa, the DPP would be beneficial even with 30% effective protection because the health risks from HIV outweigh the risks of unintended pregnancy in this higher-incidence setting.

Cost-effectiveness of the DPP

The cost-effectiveness of the DPP depended on HIV incidence in settings and populations where it would be implemented, with lower ICERs (greater cost-effectiveness) in the higher incidence setting of South Africa (green bars in Figure 3). Across all settings, the ICER of DPP was estimated to be in the thousands to tens of thousands of USD current OCP users ages 25–49 (Scenario 1) due to lower incidence compared to other population groups (Figure 3). Thresholds for cost-effectiveness are generally in the US$500–800 range for HIV services (47, 48), and lower for domestically-funded health services in low-income countries (49). Thus, it is not likely that the DPP will be cost-effective in older OCP users, even if adherence levels and effective protection are maintained when switching from the OCP to the DPP.

However, the DPP is more likely to be cost-effective for current in sex workers and women in stable serodiscordant couples, regardless of whether they currently use OCP, PrEP, both OCP or PrEP, or neither product. In these populations, the DPP averted substantial health systems costs by avoiding HIV treatment and obstetric costs. As a result, the DPP was not only beneficial and cost-effective, but was cost-saving among both sex workers and serodiscordant couples in South Africa, and among serodiscordant couples in Kenya. In Zimbabwe, the DPP was not cost-saving over a 30-year time horizon but was potentially cost-effective among serodiscordant couples (ICER = US$642, 95% CI: $432-$988).

The DPP is likely to a cost-effective alternative for PrEP users who are concurrently using OCP or have unmet need for contraception, especially if their adherence and, therefore, effective protection improves on the DPP relative to PrEP alone (Figure 3, Scenarios 11 and 12). This is due to the relatively small cost differential between PrEP and DPP (Table 2), making

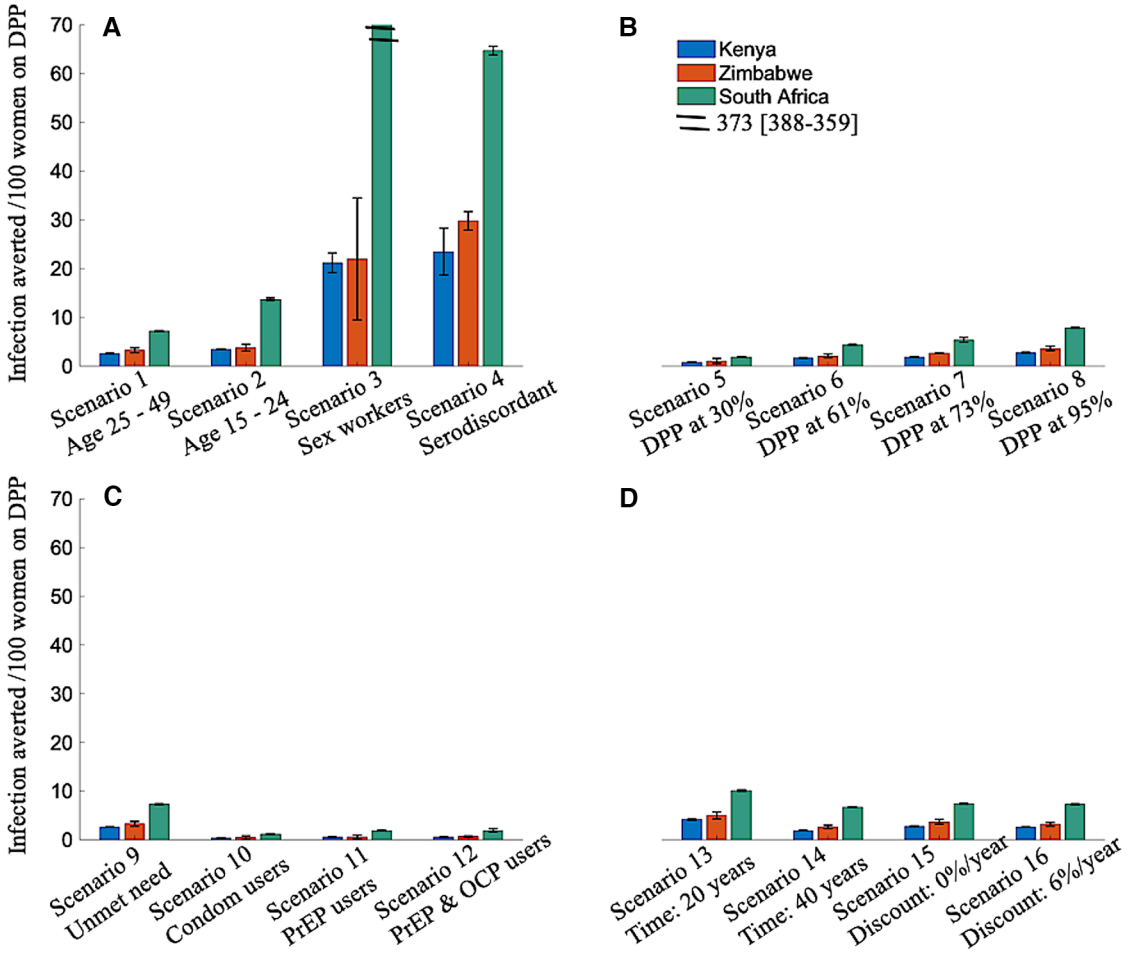

FIGURE 1
HIV infection averted per 1000 people on DPP across different populations (A), effective protection based on different adherence levels (B), alternative methods for HIV and pregnancy prevention (C), and time horizons and discount rates (D)

TABLE 4 Number of pregnancies averted per 1,000 users per year in all settings.

Scenario	Contraceptive assumptions	Pregnancies averted per 1,000 users per year
1–4, 12–16	DPP does not change contraceptive adherence	0
5	DPP reduces contraceptive effective protection from 90% to 30%	−150
6	DPP reduces contraceptive effective protection from 90% to 61%	−75
7	DPP reduces contraceptive effective protection from 90% to 73%	−43
8	DPP increases contraceptive effective protection from 90% to 95%	13
9, 11	Women with unmet need uptake DPP	225
10	Condom users will uptake DPP	36

it possible to obtain the benefits of the DPP at relatively low incremental cost.

Among women with unmet need for contraception, the DPP was beneficial, but was unlikely to be cost-effective (ICER > $4,000 per DALY averted). The DPP among condom users was even less cost-effective, given the partial protection against HIV and pregnancy from condom use alone. This is due to the relatively high cost of the DPP, despite its substantial health benefits as a contraceptive for those who would not otherwise use a highly effective contraceptive method.

Our findings were robust to changes in the time horizon of analysis (20 to 40 years) and annual economic discount rate (0% to 3%) (Figures 1, 2, 3, Panel D).

Discussion

This study used agent-based mathematical modeling to estimate the cost-effectiveness of the DPP across different populations and use cases in Nyanza, Kenya, Zimbabwe, and South Africa, taking into account the health impacts and costs from HIV and pregnancy prevention. We found that the DPP could have wide-ranging health economic implications, from health benefits with potential for cost-savings (in female sex workers and serodiscordant couples), to benefits that are unlikely

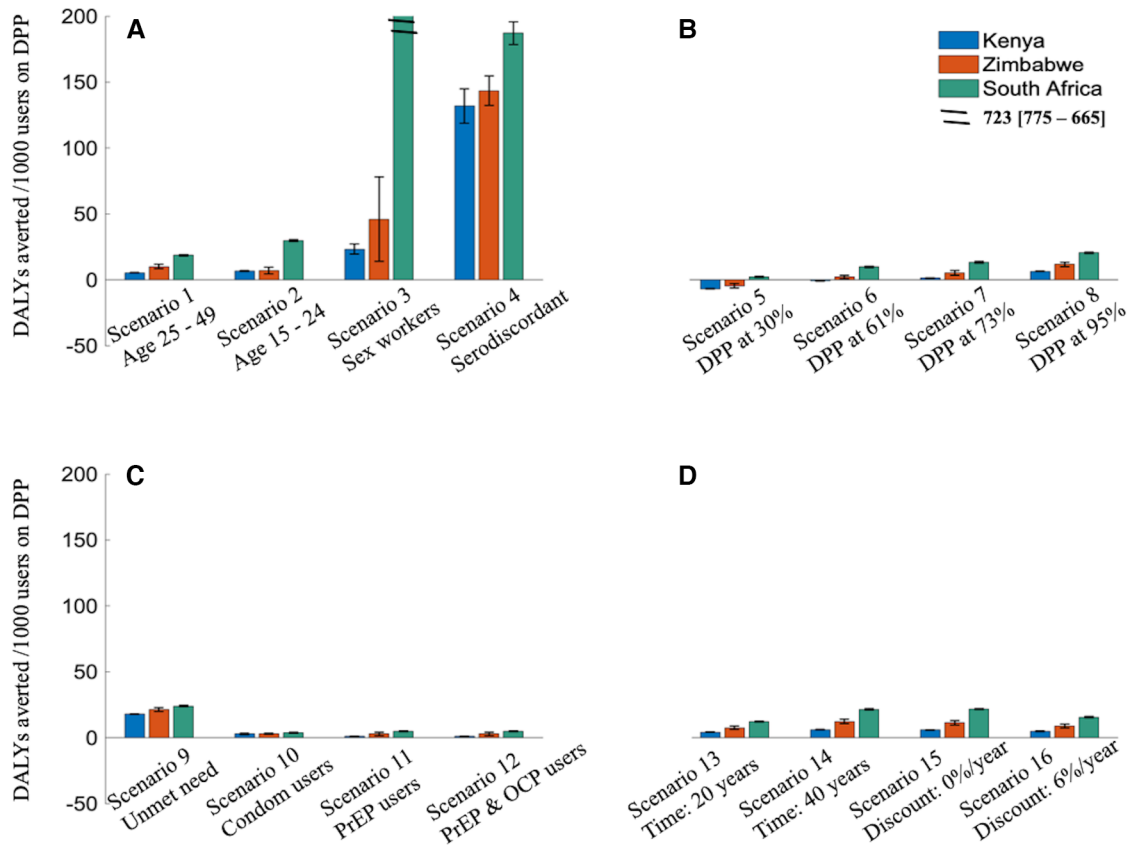

FIGURE 2
DALYs averted per 1,000 people on DPP across different populations (A), effective protection based on different adherence levels (B), alternative methods for HIV and pregnancy prevention (C), and time horizons and discount rates (D)

to be cost-effective (in OCP users ages 25–49), to a potential for net harm (in OCP users who substantially reduce adherence after switching to the DPP). These results reflect similar trends to those seen in recent oral PrEP modeling, where cost-effectiveness varies widely by population and geography (18).

While cost-effectiveness provides a critical input to understanding future intervention costs and impact, it is only one of the many considerations in this decision-making process. Experience with oral PrEP has demonstrated that narrowly focusing on risk may have unintended negative consequences, including perpetuating stigma (50). These learnings underscore the need to ensure decision-making based on cost-effectiveness is balanced with broader programmatic and social considerations. However, understanding the groups and sub-populations among whom the DPP is most likely to be cost-effective will remain a crucial input to informing investment decision-making and ensuring budgets are effectively allocated to meet program goals.

Our analysis suggests that the DPP could be a cost-effective, and in some cases cost-saving, method of expanding PrEP use among women at high risk of HIV but is unlikely to be a cost-effective method to expand contraceptive use among women with lower HIV risk, even in the context of relatively high rates of unintended pregnancy. The lack of cost-effectiveness among women with unmet need for contraception is driven in part by declining HIV incidence in the general population, and in part by the high cost of the PrEP component of DPP. Because the cost of family planning alone is much lower than the projected cost of the DPP, addressing SSA's high unmet need for contraception will likely require redoubled efforts to improve family planning access, with more selective DPP use among women with greater HIV risk.

Cost-effectiveness was highly dependent on the setting in which DPP would be implemented, with higher HIV incidence leading to greater cost-effectiveness. Of the three settings modeled, cost-saving was more likely among high-incidence populations in South Africa. Given declining incidence and progress toward treatment targets in many parts of SSA, the DPP may not be a cost-effective alternative to existing options for many of SSA's women of reproductive age. Our results suggest that a "one size fits all" strategy is unlikely to lead to efficient and effective use of the DPP, and guidelines around its use are likely to require setting-specific health analyses and program planning.

Despite potential benefits offered by DPP, our analysis suggests that switching from OCP use to DPP use could be net harmful in some populations and settings if adherence decreases substantially. This is because, depending on the level of HIV risk in a given population segment, the health risks from unintended pregnancy can in some cases outweigh the health benefits from HIV prevention. On the other hand, the DPP may increase adherence

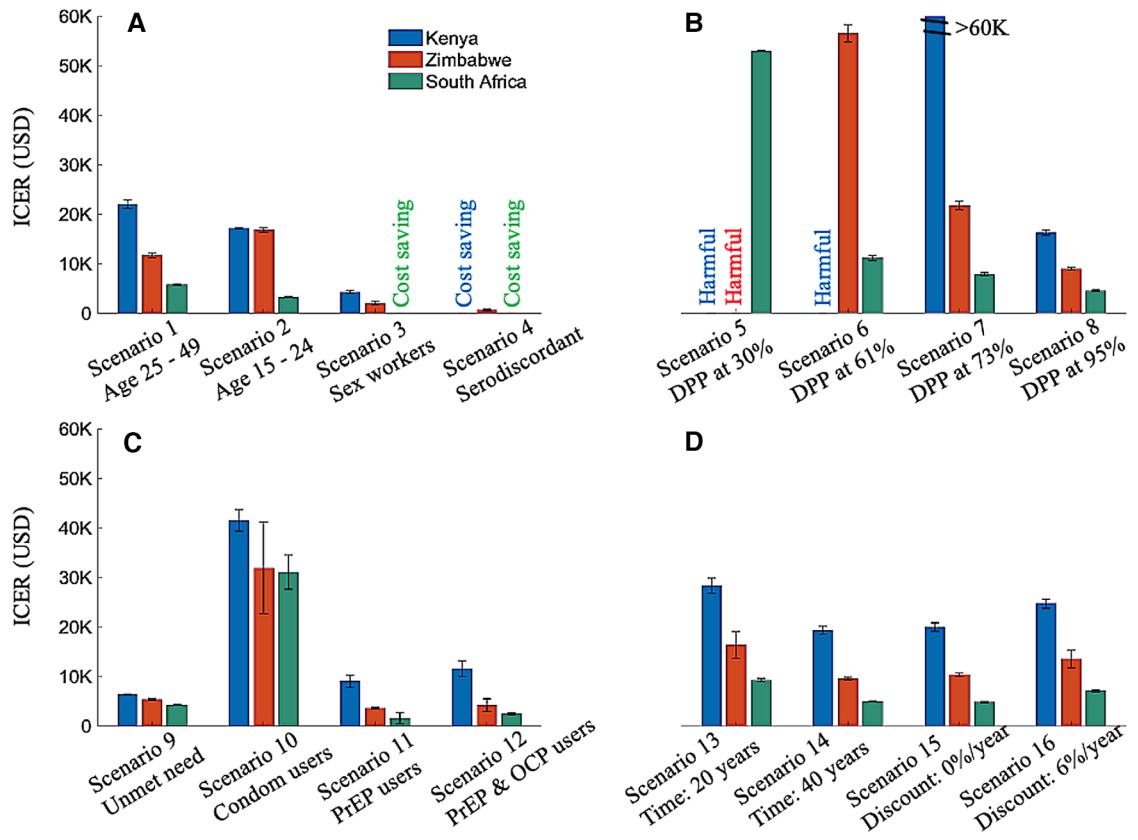

FIGURE 3
Cost-effectiveness of DPP across different populations (A), effective protection based on different adherence levels (B), alternative methods for HIV and pregnancy prevention (C), and time horizons and discount rates (D)

among existing oral PrEP or OCP users due to the increased motivation to prevent both unintended pregnancy and HIV with a combined product. Our modeling demonstrates that this would lead to increased likelihood of cost-effectiveness. Careful monitoring, clear messaging, and effective counseling strategies will be critical to support informed choice among potential users. Future analyses could leverage forthcoming adherence data from clinical crossover studies to understand the implications of DPP adherence on risks and benefits for current OCP users.

Limitations

Our analysis has several important limitations. First, we did not consider risk self-assessment (e.g., oral PrEP use concentrated into times of high-risk or multiple sexual partnerships). Evidence from oral PrEP suggests that users can time PrEP usage in risk-informed manners (38, 51–54). If this applies to DPP use, the DPP is likely more cost-effective than current analysis suggests. However, because the DPP is a dual indication product, it may not be suitable for users who would cycle on and off according to perceived risk from current partners, as usage patterns for contraception may not fully align with periods of risk for HIV acquisition. Ongoing risk-informed use could be explored in future research if determined to be relevant to DPP use patterns.

Second, we did not include incremental risks of neonatal mortality or child morbidity for children born as a result of unintended pregnancy. In our literature search, we found mixed results on the impact of unintended pregnancies on health outcomes of the child (55–57). In some cases, women were less likely to indicate a pregnancy was unwanted if it ended in neonatal death (57). Further study of health outcomes from unintended pregnancies are needed to quantify additional burdens due to putative increases in neonatal and child mortality and to socioeconomic burdens on individuals and society (58–61).

Third, we only considered DPP initiation among women using OCP, male condoms, or with unmet need for contraception. We did not consider alternative forms of contraception, ranging from less effective methods such as withdrawal, to more effective methods such as injections, implants, and intrauterine devices. Important questions remain about whether women currently using longer-acting forms of contraception would be recommended to use DPP, given than oral contraceptive methods tend to be less effective than longer-acting methods with typical use (62).

Fourth, our analysis only estimated DPP impact and cost-effectiveness in specific population segments and use cases, but did not estimate the total demand for DPP across the populations modeled, patterns of usage over the reproductive lifecourse, or the aggregate effect of DPP introduction on HIV and unintended pregnancy rates. Introduction of new contraceptive methods has

generally tended to increase overall contraceptive use by meeting the needs and preferences of more users (14). Preliminary evidence from PrEP research suggests that expanded PrEP method mix may also increase overall use (63). However, the ability to receive and adherence to the DPP is likely to vary over the reproductive lifecourse due to factors including reproductive health knowledge, marital status, and pregnancy intentions. The effect of a dual-indication product such as DPP on overall coverage for each use case, and in aggregate over the lifecourse, is not currently known and warrants further research.

Fifth, we focused exclusively on the DPP and not other MPT products. At the time of writing, the DPP is the only MPT in late-stage development and appears likely to be the first MPT to reach markets since the male condom. However, it is worth noting that additional MPTs are in earlier stages of the discovery and development process, including injections, implants, and vaginal rings, films, and gels. As the landscape of viable MPT products becomes clearer, our analysis will require revision to account for potential product alternatives, an indeed a possible array of MPT method options offering women more choices than the DPP alone.

Finally, like all models, our model is a simplification of a complex process. We attempted to capture important aspects of HIV and unintended pregnancy, but our results are only an approximation of heterogeneous populations and health risks. Results should be used with caution and in context, and updated as new evidence accrues.

Conclusion

With the potential to be the first MPT for HIV and pregnancy to be introduced since male and female condoms, the DPP has the potential to provide significant health benefits for some groups of women. The DPP is most likely to be cost-effective among populations at high HIV risk or as an alternative to oral PrEP use with or without concurrent OCP use, and it may be cost-saving in some populations and settings with particularly high HIV incidence. Effective counseling and decision-making tools for prospective users will be important, as outcomes are sensitive to adherence.

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

MPM, DR, JC, DE, SJ and AB contributed to conception and design of the study. MPM, DK and AB performed the formal analysis with HK contributing on the development of the code. MPM, DK, IP, DR, AO and AB performed data curation. MPM wrote the first draft of the manuscript with DK contributing on the Methods section. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1144217/full#supplementary-material.

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Equipping providers to offer novel MPTs: Developing counseling messages for the Dual Prevention Pill in clinical studies and beyond

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Introduction: The pipeline for multi-purpose prevention technologies includes products that simultaneously prevent HIV, pregnancy and/or other sexually transmitted infections. Among these, the Dual Prevention Pill (DPP) is a daily pill co-formulating oral pre-exposure prophylaxis (PrEP), and combined oral contraception (COC). Clinical cross-over acceptability studies for the DPP require training providers to counsel on a combined product. From February 2021–April 2022, a working group of eight HIV and FP experts with clinical and implementation expertise developed counseling recommendations for the DPP based on existing PrEP/COC guidance.

Assessment of policy/guidelines options and implications: The working group conducted a mapping of counseling messages from COC and oral PrEP guidance and provider training materials. Six topics were prioritized: uptake, missed pills, side effects, discontinuation and switching, drug interactions and monitoring. Additional evidence and experts were consulted to answer outstanding questions and counseling recommendations for the DPP were developed. *Missed pills* was the topic with the most complexity, raising questions about whether women could "double up" on missed pills or skip the last week of the pack to recover protection faster. *Uptake* required aligning the time to reach protective levels for both DPP components and explaining the need to take DPP pills during week 4 of the pack. The potential intensity of DPP *side effects*, given the combination of oral PrEP with COC, was an important consideration. *Discontinuation and switching* looked at managing risk of HIV and unintended pregnancy when stopping or switching from the DPP. Guidance on *drug interactions* contended with differing contraindications for COC and PrEP. *Monitoring* required balancing clinical requirements with potential user burden.

Actionable recommendations: The working group developed counseling recommendations for the DPP to be tested in clinical acceptability studies. *Uptake*: Take one pill every day for the DPP until the pack is empty. Days 1–21 contain COC and oral PrEP. Days 22–28 do not contain COC to allow for monthly bleeding, but do contain oral PrEP and pills should be taken to maintain HIV protection. Take the DPP for 7 consecutive days to reach protective levels against pregnancy and HIV. *Missed pills*: If you miss 1 pill multiple times in a month or 2+ consecutive pills, take the DPP as soon as you remember. Do not take more than 2 pills in a day. If 2+ consecutive pills are missed, only take the

last missed pill and discard the other missed pills. *Side effects*: You may experience side effects when you start using the DPP, including changes to monthly bleeding. Side effects are typically mild and go away without treatment. *Discontinuation/switching*: If you decide to discontinue use of the DPP, but want to be protected from HIV and/or unintended pregnancy, in most cases, you can begin using PrEP or another contraceptive method right away. *Drug interactions*: There are no drug-drug interactions from combining oral PrEP and COC in the DPP. Certain medications are not recommended due to their contraindication with oral PrEP or COC. *Monitoring*: You will need to get an HIV test prior to initiating or restarting the DPP, and every 3 months during DPP use. Your provider may recommend other screening or testing.

Discussion: Developing recommendations for the DPP as a novel MPT posed unique challenges, with implications for efficacy, cost, and user and provider comprehension and burden. Incorporating counseling recommendations into clinical cross-over acceptability studies allows for real-time feedback from providers and users. Supporting women with information to use the DPP correctly and confidently is critically important for eventual scale and commercialization.

KEYWORDS

pre-exposure prophylaxis, oral contraception, HIV prevention, family planning, sexual and reproductive health, multi-purpose prevention technologies, service delivery, provider counseling

1. Introduction

Despite dedicated efforts to reduce unmet need for family planning (FP) and HIV incidence globally, cisgender women encounter barriers to accessing contraception and HIV prevention in many settings, hindering progress toward global targets. Across sub-Saharan Africa, women of reproductive age account for 65% of new HIV infections among adults ages 15–49 and have varying levels of unmet need for FP, ranging from 8% in Botswana to 27% in Angola among all women of reproductive age (1, 2). Adolescent girls and young women (AGYW) ages 15–24 bear a greater HIV disease burden, comprising a staggering 77% of new infections among young people and nearly half among women ages 15–49 in the region (1). Globally, AGYW also have the highest levels of unmet need for FP (3). Oral pre-exposure prophylaxis (PrEP) can be a highly effective daily antiretroviral (ARV)-based pill for HIV prevention, but uptake, continuation and effective use by cisgender women has lagged since its approval by the U.S. Food & Drug Administration (FDA) in 2012 (4). Daily pill-taking remains a challenge for many women, who may require discretion to be able to use PrEP, as intimate partner violence can contribute to low rates of continued use, among other factors (5, 6). Though uptake of oral PrEP in sub-Saharan Africa has rapidly grown since 2020, and two additional PrEP options—the dapivirine vaginal ring (PrEP ring) and injectable cabotegravir (CAB for PrEP)—have been approved in several African countries (7), programs have been slow to integrate FP and HIV prevention services despite the layered sexual and reproductive health (SRH) needs of women and girls (8).

Within this context, multi-purpose prevention technologies (MPTs) that simultaneously prevent pregnancy, HIV and/or other sexually transmitted infections (STIs) could address persistent shortcomings in women's access to comprehensive SRH services. Multiple discrete choice experiments have found that women and heterosexual couples prefer MPTs to single-indication HIV prevention products and prefer novel MPT formulations to male condoms (9, 10). One modeling study in South Africa estimated that MPTs preventing both pregnancy and HIV could quadruple demand for HIV prevention products among adolescent girls compared to products that consist solely of HIV prevention medication (11). Growing investment in MPT research and development (R&D) (12) signals the potential for MPTs to transform the prevention field: the MPT pipeline contains 28 products with diverse delivery forms and formulations as of December 2022, including oral tablets, intravaginal rings, injectables and implants (13).

Among these, the Dual Prevention Pill (DPP) is a daily pill co-formulating tenofovir disoproxil and emtricitabine (TDF/FTC), the only approved formulation of oral PrEP for cisgender women, and levonorgestrel and ethinyl estradiol (LNG/EE), a combined oral contraceptive (COC). While the majority of MPTs in development are in the pre-clinical phase, the DPP only requires a bioequivalence study to demonstrate that its drug components are bioequivalent in combination compared to oral PrEP and COC taken separately (14). With this streamlined regulatory process, the DPP under development is likely to complete FDA regulatory requirements for approval and could reach the market in 2024. Pending regulatory approval, the DPP will be the next MPT to market and the only MPT alternative to male and female condoms for the foreseeable future.

Clinical cross-over acceptability studies for the DPP in South Africa (15) ($n = 96$) and Zimbabwe (16) ($n = 30$) are currently evaluating adherence, acceptability and preference for a single, over-encapsulated DPP compared to two separate PrEP and COC tablets in cisgender women ages 16–40 who are interested in using an HIV prevention product in combination with a contraceptive method. These studies require providers to counsel

participants on a novel MPT, particularly on instructions for use, which will differ from counseling on separate oral PrEP and COC products (17). FP providers are well-versed in counseling on voluntarism and informed choice, where they explain the risks and benefits of available methods and support clients to choose and use the method they prefer (18). They have expressed that training on PrEP and HIV prevention services would build their confidence to deliver them alongside FP (8). Yet due to long-siloed FP and HIV services (8), approaches to counseling for and delivery of HIV and FP are different, and integrated services are not consistently or uniformly provided, which could slow down rollout of novel MPTs like the DPP in places where women would be more likely to access it.

Reconciling counseling guidance for oral PrEP and COC is needed to develop guidelines and training materials for providers to counsel on the DPP in clinical cross-over acceptability studies and for future DPP service delivery. Lessons from delivering the DPP in these studies can inform provider counseling approaches to offering comprehensive PrEP and FP options in real-world settings, including the DPP and future MPTs. In February 2021, a working group of eight experts across the FP/SRH and HIV disciplines, with clinical expertise and implementation experience, was assembled. Working group members came from product developers, implementing partners, research organizations and development agencies, the majority of which are also involved in planning for the introduction of the DPP. From February 2021–April 2022, this working group developed counseling recommendations for the DPP based on existing oral PrEP and COC guidance to inform provider counseling in DPP acceptability studies.

2. Assessment of policy/guidelines options and implications

2.1. Methodology

To develop counseling recommendations for the DPP, the working group conducted a mapping of counseling messages from existing COC and oral PrEP guidance and relevant provider training materials, recognizing that the DPP is not yet available for use. Several assumptions were agreed upon to guide inclusion criteria. Counseling recommendations would focus specifically on the DPP as a novel product, and on counseling areas most in need of reconciliation between oral PrEP and COC. Recommendations would presume that the client has already received informed choice counseling on the full range of HIV prevention and contraceptive methods available and has selected the DPP. Ideally, comprehensive counseling covering broader SRH issues such as gender-based violence will have also been performed, but was outside the scope of this analysis. In addition, DPP counseling recommendations assume the client meets medical eligibility requirements for both the COC and oral PrEP components of the DPP, including FP screening and a negative HIV test. Lastly, recommendations were developed based on the understanding that the DPP will follow a 28-day regimen, with three weeks of co-formulated PrEP/COC pills followed by one week of PrEP pills only, which has important implications for some counseling topics. Of note, the terms "cisgender women" and "women" are used throughout this manuscript to be consistent with the study population in DPP clinical cross-over acceptability studies, and to distinguish this population from prevention literature and guidance pertaining to cisgender men. The authors recognize that communities are gender-diverse, and that some people for whom DPP may be an option would not identify or be categorized as cisgender women.

Eleven PrEP and COC counseling guidance materials and tools were included in the initial mapping (19–29) (**Table 1**). The World Health Organization (WHO) was the primary source of information for guidance on oral PrEP and COC. Once materials for inclusion were selected, relevant information was categorized by counseling topic. For each topic, we distilled where oral PrEP and COC guidance converged and diverged. We then identified outstanding questions and core elements to address in counseling for the DPP. Six topics were prioritized based on clinical

TABLE 1 Primary counseling guidance materials and tools consulted for oral PrEP and COC.

Product	Author	Title	Chapter/ Module
Oral PrEP	WHO	Implementation Tool for Pre-Exposure Prophylaxis of HIV Infection	Module 1: Clinical
			Module 10: Testing Providers
			Module 11: PrEP Users
			Module 12: Adolescents and Young Adults
	WHO	Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach (2021)	N/A
	WHO	Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance. Technical Brief	N/A
	OPTIONS Consortium	Provider Training Package: Effective Delivery of Oral PrEP for Adolescent Girls and Young Women	N/A
	Southern African HIV Clinicians Society	PrEP Training Curriculum in Southern Africa	N/A
	FHI 360	Guidance on Providing Informed-Choice Counseling on Sexual Health for Women Interested in PrEP	N/A
COC	WHO	Family Planning: A Global Handbook for Providers	Providing Combined Oral Contraceptives
	Population Council	Balanced Counseling Strategy Plus (BCS+)	Counseling Cards
			Method Brochures
	Population Services International	Counseling for Choice (C4C): The Choice Book for Providers	N/A

relevance for DPP acceptability studies: (1) uptake, (2) missed pills, (3) side effects, (4) discontinuation and switching, (5) drug interactions and (6) monitoring.

Additional literature and subject matter experts were consulted outside of the sources included in the initial mapping to answer specific outstanding questions. These include WHO's updated HIV guidelines, which were released after the initial mapping was completed (30). Subject matter experts from research institutions provided supplementary contextual information about available literature and their perspectives on gaps in data, namely on oral PrEP toxicity and missed pills guidance (see Acknowledgments for more information). Counseling recommendations for the DPP were developed from all available information and refined based on working group discussions and consensus.

Preliminary counseling recommendations were reviewed by researchers at the Population Council, sponsors for the DPP clinical cross-over acceptability studies, and Wits Reproductive Health and HIV Institute, implementing partner for the DPP acceptability study in South Africa. Acceptability study protocols were adapted to reflect counseling messages for the DPP developed by the working group.

2.2. Analysis

2.2.1. Missed pills

Missed pills was the counseling topic requiring the most attention when reconciling oral PrEP and COC guidance, as it had greater points of divergence in guidance documents and real-world implementation than the other five topics included in the mapping (**Figure 1**). COC and oral PrEP guidance on missed pills overlap in a few areas, stipulating that: pills can be taken at any time of day; in the case of one missed pill, the client should take the missed dose as soon as they remember; and in the case of multiple missed pills, the client should consider using a back-up method or avoiding sex to prevent HIV and pregnancy.

However, COC and oral PrEP guidance and practice diverge for counseling on multiple missed pills (defined as 1 missed pill multiple times in a month or 2+ consecutive missed pills), primarily pertaining to the quantity and timing of missed pills in a month. For COCs, taking two pills at a time in the event of a missed dose, or "doubling up," is common practice and can be done multiple times throughout the month. By contrast, WHO guidance permits "occasional" doubling up on oral PrEP and advises against taking more than two PrEP tablets in one day. The guidance is unclear on how clients should proceed in cases of 2+ missed oral PrEP pills (21), and there is limited published evidence on toxicity of multiple PrEP doses in cisgender women. Differences in quantities of missed pills have implications for recommending use of a back-up method: COC users are counseled to consider emergency contraception (EC) if they have condomless sex within five days of 3+ missed pills, while oral PrEP users are advised to consider post-exposure prophylaxis (PEP) if they have condomless sex within three days of missed pills, with no quantity of missed pills specified. The working group considered the feasibility of aligning recommendations for taking EC and PEP in cases of multiple missed DPP pills to simplify counseling messages for users.

Assessing whether and how often clients could reasonably double up on the DPP, particularly given the paucity of data on oral PrEP toxicity in cisgender women, required additional desk research and expert consultation. Most studies with findings on double-dosing of oral PrEP have only been conducted with cisgender men who have sex with men (31, 32), leading WHO to recommend event-driven PrEP for this population in its guidelines (30). Recent research suggests that a single double-dose of oral PrEP pills in women is safe and would only increase protection back to a steady-state level in the event of a missed pill (33, 34).

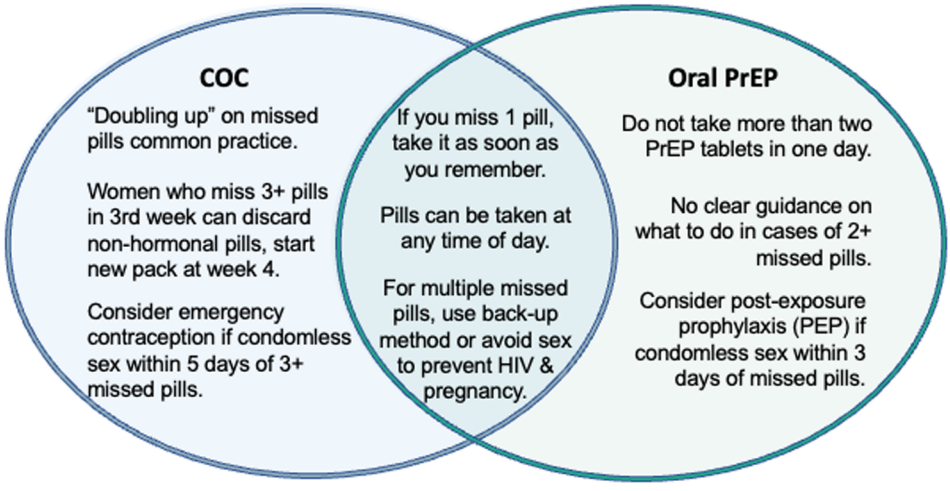

FIGURE 1
Illustrative example of summarized COC and oral PrEP missed pills guidance.

Timing of missed pills is particularly critical for COC users in light of two considerations: (1) 7 consecutive days of COC use are required to reach protective levels against pregnancy (26) and (2) in a 28-day COC pack, the last week (week 4, or days 22–28) contains non-hormonal pills, or placebos. As such, missing multiple COC pills in weeks 1 and 3, which are the weeks that follow and precede week 4, respectively, could increase risk of unintended pregnancy by extending the period of time without hormonal pills beyond what is recommended (**Figure 2**). COC guidance permits a client who misses 3+ pills in week 3 of the month to discard the remaining pills and instead begin a new pack, enabling them to recoup pregnancy protection faster. Otherwise, use of a back-up method is recommended until the client has taken COCs for 7 consecutive days.

Conversely, all oral PrEP pills in a monthly regimen contain the same active pharmaceutical ingredients (APIs); therefore, timing of missed PrEP pills within the month does not alter risk of HIV acquisition. As a combined product, the DPP will also follow a 28-day regimen that includes 3 weeks (days 1–21) of co-formulated PrEP/COC pills followed by 1 week (days 22–28) of oral PrEP pills only. This allows for monthly bleeding in week 4, as COCs do, while maintaining protection against HIV. Formulating counseling recommendations for the DPP required weighing whether users could discard a DPP pack at week 4, in the event of multiple missed DPP pills in week 3, which aligns with COC practice and would lessen the time needed to use a back-up method for pregnancy prevention, but would confer additional supply and cost implications from disposing oral PrEP pills (which are more expensive than COCs and as such, increase the cost of DPP pills as well).

2.2.2. Uptake

COC and oral PrEP guidance on uptake both recommend daily use during periods of increased risk of unintended pregnancy or HIV, even if the client does not have sex every day; use of a back-up method until full protective levels against pregnancy or HIV have been reached; taking one pill every day for the method to be effective and linking pill-taking to a daily activity to promote habitual use.

Guidance related to uptake differed on the time to reach protective levels of COC and oral PrEP. While COC guidance states that it takes up to 7 days to confer full protection against pregnancy, oral PrEP guidance documents varied: the 2017 WHO PrEP implementation tool and 2021 consolidated guidelines on HIV prevention state that it takes 7 consecutive days of PrEP use to build up protective levels against HIV (19, 30), yet the U.S. Centers for Disease Control and Prevention's (CDC) 2021 clinical practice guideline stipulates that 20 days of daily dosing is needed for maximum protection in cervicovaginal tissues (35). Because the research protocol for the DPP acceptability studies initially referenced CDC's data, the working group grappled with which source to utilize in its counseling recommendations, as it would impact how long clients would be counseled to use a back-up method at DPP initiation. Longer use of a back-up method could affect client acceptability of the DPP, particularly for COC users who are accustomed to using a back-up method for a shorter period.

Recommendations for uptake also reconciled instructions for use given that COC packs contain 21 days of COC pills followed by 7 days of non-hormonal pills, while oral PrEP tablets have no set order and are taken daily throughout the month. Because the non-hormonal pills in a COC pack are placebos, users may opt to discard them and start a new pack early. A key reason COC users do this is to avoid menstruation, which is a component of client self-care and satisfaction with the method (36). Clear counseling that week 4 of the DPP pack contains oral PrEP pills, which are not placebos and are needed to maintain protection against HIV, will be new to many COC users and critical to ensure correct use of the DPP.

2.2.3. Side effects

COC and oral PrEP guidance both emphasize that side effects are typically not harmful, reduce over time, can often be self-managed and are not experienced by every user. They reinforce the importance of counseling clients on the most common side effects, how to manage or minimize them (e.g., by taking a pill the same time each day) and dispelling myths and misconceptions.

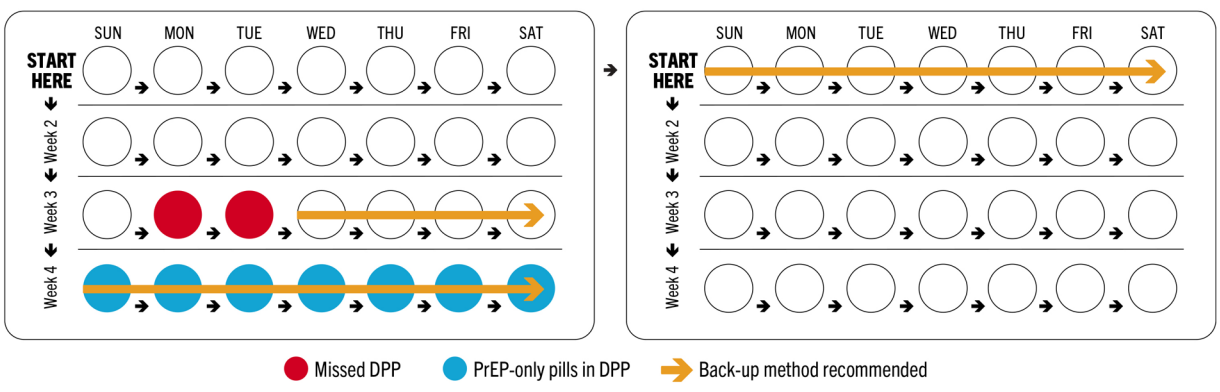

FIGURE 2
Illustration of timeline to recover pregnancy protection after multiple missed DPP pills.

However, there is little overlap between types of side effects for COC and oral PrEP, requiring counseling messages for the DPP to outline potential side effects from each component rather than harmonizing them. Of particular importance in COC guidance is describing potential changes in bleeding patterns, which are commonly experienced with COC use but not with oral PrEP. Furthermore, time to resolution of side effects differs: PrEP side effects tend to dissipate after the first few weeks of use, while side effects for COCs may subside over the first few months. The potential for increased intensity of side effects with the DPP, given the co-formulation of oral PrEP and COC, is unknown, as is whether intensity of side effects could be further exacerbated by doubling up on missed doses.

2.2.4. Discontinuation and switching

COC and oral PrEP guidance both underscore that the desire to use COC or PrEP can change over the life course, including due to perception of risk and side effects, and providers should employ informed choice counseling to discuss other available prevention options for women who want to discontinue or switch, emphasizing that they can do so at any time. Both oral PrEP and COCs have high discontinuation rates (37, 38). Counseling on the DPP requires clearly explaining how to manage the risks of HIV and unintended pregnancy when discontinuing or switching from the DPP to other prevention methods.

There are several scenarios related to discontinuation and switching on which a client may require counseling. Healthcare providers who offer the DPP will be trained to provide client-centered counseling to users who wish to discontinue the DPP. The counseling will ensure that clients understand their choices and are able to make decisions that fit their needs and lifestyle and will support them to achieve effective method switching (for FP, PrEP or both) if and when desired. Women who wish to become pregnant but still want to have protection against HIV may discontinue use of the DPP and can choose to continue use of oral PrEP or switch to another available HIV prevention option (e.g., condoms, PrEP ring or CAB for PrEP, where available). Women who no longer regard themselves at risk of HIV but do not wish to become pregnant can choose an alternative FP method. Women who want both FP and HIV prevention, but do not wish to use the DPP, can choose another combination of prevention methods that better suits their needs and preferences. Lastly, women who want neither FP nor HIV prevention can choose to use no method.

In most cases, a client can switch from the DPP to other FP and/or HIV prevention methods, including separate COC and/or oral PrEP products, right away. To ensure protection against HIV for clients who are stopping or switching, oral PrEP guidance suggests that providers recommend any of the following: take oral PrEP for 7 days after the last potential exposure before discontinuation; consider PEP if there is potential exposure before starting a new method and take an HIV test before restarting oral PrEP or starting a new HIV prevention method. Per COC guidance, providers should caution clients that their return to fertility is immediate in case of discontinuation. If a client wants to switch to another method and pregnancy can be reasonably ruled out using a checklist or a pregnancy test (26), the transition to a traditional COC or alternate contraceptive method can be expedited.

2.2.5. Drug interactions

COC and oral PrEP guidance on drug interactions were the most straightforward to reconcile for the DPP among the prioritized counseling topics. The key message, drawn particularly from oral PrEP guidance and supported by published literature, is that PrEP and hormonal contraceptives can be safely and effectively taken simultaneously (39). Oral PrEP and COC have contraindications with different types of medicines, limiting the extent to which they could be integrated in counseling messages for the DPP. Contraindications for use of either oral PrEP or COC will be addressed as part of the medical eligibility determination when selecting a prevention method.

2.2.6. Monitoring

There is essentially no overlap of monitoring requirements for COC and oral PrEP in counseling guidance. Most women can safely use COC and it can be initiated with no blood or other laboratory tests. A blood pressure test is recommended, but not required, prior to initiation of COC and annually thereafter. Clients are encouraged to revisit health providers annually and counseled to seek follow-up care if they are not satisfied with the method, cannot tolerate the side effects or experience symptoms associated with cardiovascular issues, but regular clinical monitoring is not required. Oral PrEP guidance is more complex; a negative HIV test is required prior to initiation and regularly thereafter (e.g., every three months), and depending on services offered and a client's profile, providers may also recommend creatinine screening, hepatitis B and/or C testing and STI screening or testing. (In 2022, the WHO released a technical brief on differentiating and simplifying PrEP delivery, which reduced complexity in required monitoring (40).) Developing monitoring recommendations for the DPP requires balancing these clinical requirements for oral PrEP with potential burden on clients, particularly for PrEP-naïve users who will be new to more extensive HIV monitoring, as well as health facility capacity to offer testing and screening services, which may be more limited in resource-constrained settings.

3. Actionable recommendations

Based on the analysis of COC and PrEP guidance outlined above, including discussion of outstanding questions and evidence gaps for the DPP, the working group developed the following counseling recommendations for the DPP. The recommendations provide a starting point for counseling on a novel MPT well in advance of product introduction, which can be adapted for and tested in clinical cross-over acceptability studies, and iterated upon based on findings. These messages are written for providers to share with clients after they have selected the DPP. They are intended to guide provider conversations with

clients, recognizing that clients will have individual needs and questions that may require discussion beyond the messages included here. Additional messages will be needed for the initial FP and HIV prevention counseling session, so that users are aware of the DPP alongside a range of other prevention methods, but the development of these messages is outside the scope of this analysis.

3.1. Uptake (for new users or users who are restarting the DPP)

- Take one pill every day for the DPP to be effective until the pack is empty, even if you do not have sex every day.
- Each pack is a 28-day regimen. Days 1–21 contain COC and oral PrEP, and protect against pregnancy and HIV. Days 22–28 do not contain COC to allow for monthly bleeding; however, they do contain oral PrEP and pills should be taken to maintain HIV protection.
- Take the DPP for 7 consecutive days to reach protective levels against pregnancy and HIV. A back-up protection method should be used during this time.
  - COCs are protective against pregnancy right away if you start them within 5 days after the start of your monthly bleeding, and they take 7 days to confer full protection if taken at any other time during your menstrual cycle.
- It is common to have changes to your monthly bleeding when you use COCs. Common changes with the DPP may include irregular bleeding in the first few months, followed by lighter bleeding, shorter bleeding, spotting (dots of blood) and/or more regular bleeding (29).
- The DPP does not protect against other STIs. Use condoms for triple protection.
- Note to provider:
  - If a client wants to skip monthly bleeding and begin a new pack at the start of week 4, she can be counseled to do so and there are no foreseen risks. However, this is contingent on sufficient supply of refills.
  - If the client vomits after taking a DPP pill, she should follow the missed pills guidance.

3.2. Missed pills

- If you miss 1 pill one time in a month: take DPP as soon as you remember, even if it means taking 2 pills in one day. Do not take more than 2 pills in a day. Keep going with the pack. Any missed pills can increase your risk of pregnancy and HIV acquisition.
- If you miss 1 pill multiple times in a month or 2+ consecutive pills: take DPP as soon as you remember, even if it means taking 2 pills in one day. Do not take more than 2 pills in a day.
  - If 2+ consecutive pills are missed, you should only take the last missed pill as soon as possible, even if it means taking 2 pills in one day, and discard the other missed pills. Continue with the pack.
  - Option 1: Continue the pack through week 3 and then begin a new pack at the start of week 4. Note to provider: this is intended to recoup pregnancy protection faster and is contingent on a sufficient supply of refills.
  - Option 2: Continue through the end of the pack and use a back-up method (e.g., condoms) for pregnancy prevention for up to 3 weeks. Note to provider: 7 consecutive days of DPP pills containing COC are required to recoup pregnancy protection.
- Any missed pills can increase your risk of pregnancy and HIV acquisition. Missed pills in weeks 1 and 3 of the pack may further increase your risk of pregnancy.
  - Consider EC for pregnancy prevention if you have condomless sex within 5 days of 3+ missed pills.
  - Consider PEP for HIV prevention if you have condomless sex within 3 days of missed pills.
- Note to provider: If the client vomits within 2 hours after taking a DPP pill, she should take another pill from her pack as soon as possible, then continue with the pack. If vomiting or diarrhea continues for more than 2 days, she should follow 2+ missed pills guidance above.

3.3. Side effects

- You may experience side effects when you start using the DPP. Side effects are not signs of illness. They are typically mild and go away without treatment. Some women do not experience any side effects.
  - Common side effects with COCs include: headache, breast tenderness, weight change and possibly others. They usually lessen or stop within the first few months of use.
  - Common side effects with oral PrEP include: nausea, headache, abdominal cramping and vomiting. They usually lessen or stop within the first few weeks of use.
- It is common to have changes to your monthly bleeding when you use COCs. Common changes with the DPP may include irregular bleeding in the first few months, followed by lighter bleeding, shorter bleeding, spotting (dots of blood) and/or more regular bleeding.
- If you experience side effects, keep taking the DPP. Skipping pills increases risk of pregnancy and HIV acquisition, and can worsen some side effects. Try to take the DPP at the same time every day to minimize side effects. Try to link pill-taking to a daily activity to help you remember (e.g., with a meal, during your morning routine). Taking a pill at the same time each day can help reduce irregular bleeding and taking a pill with food can help avoid nausea.
- Speak to your healthcare provider if you have concerns about side effects or would like guidance on how to manage them. If you experience repeated headaches, you should speak to your provider.

3.4. Discontinuation/switching

- You may decide to discontinue use of the DPP or switch to another method of HIV prevention and/or contraception at

any time. If you decide to discontinue use of the DPP, a provider can help you determine whether another prevention method is a better fit for your lifestyle and preferences.
- If you think that you have been exposed to HIV, you should continue taking the DPP for 7 days before discontinuing to ensure that you maintain protection during this period.
- If you discontinue use of the DPP, but want to be protected from HIV:
  - In most cases, you can begin using oral PrEP on its own or another biomedical HIV prevention method right away.
  - If there has been a lapse in DPP or PrEP use, a provider may recommend that you take an HIV test prior to starting a new HIV prevention method, even if your last routine HIV test was less than 3 months ago.
  - If you think you have been exposed to HIV after stopping use of the DPP, but before starting a new prevention HIV method, your provider may recommend PEP.
- If you discontinue use of the DPP, but do not want to become pregnant:
  - In most cases, you can begin using another contraceptive method right away. If you want to switch to another hormonal contraceptive method, a provider may ask you a few questions to be reasonably certain that you are not pregnant or have other contraindications to a method beforehand. Note to provider: See pregnancy checklist on page 463 of WHO's FP Handbook (26).

3.5. Drug interactions

- There are no drug-drug interactions from combining oral PrEP and COC in the DPP. Use of hormonal contraceptives while taking PrEP is safe and effective.
- Certain medications are not recommended for women interested in the DPP due to their contraindication with COC, including but not limited to certain anticonvulsants, lamotrigine, rifampicin and rifabutin. Note to provider: Refer to the WHO FP Handbook and the WHO Medical Eligibility for Contraceptive Use for the full list of COC contraindications (26, 41).
- Certain medications are not recommended for women interested in the DPP due to their contraindication with oral PrEP, including but not limited to adefovir and certain medications that reduce renal function. Note to provider: Refer to the CDC's PrEP guidelines (2021) for the full list of PrEP contraindications (35).

3.6. Monitoring

- You will need to get an HIV test prior to initiating or restarting the DPP, and every 3 months during DPP use (Table 2). Your provider may also ask you to take an HIV test one month after initiation. It is possible that these HIV tests could be HIV self-tests.
  - If you think you have had a recent HIV exposure (e.g., within the past 72 hours), your provider may offer you PEP and transition you to the DPP after completing PEP and HIV testing.
  - Your provider may also recommend EC if you have had condomless sex within the past 5 days.
- A very small percentage of people will not be eligible for the DPP because oral PrEP is not recommended for users with reduced kidney function. Your provider may ask you to do creatinine screening within the first few months of DPP initiation (e.g., if you are 30+ years old or have comorbidities) and may recommend additional screening every 6–12 months.
- Your provider may recommend testing for hepatitis B and C at DPP initiation, and hepatitis C annually thereafter. Your provider may also recommend vaccination and/or additional testing in the future. You can initiate the DPP before your hepatitis B and C results are available.
- Your provider may recommend STI screening or testing every 3–6 months.
- Your provider may recommend you take a blood pressure test prior to initiating the DPP and annually thereafter.

4. Discussion

Comprehensive counseling by providers is one of the core tenets of quality SRH/HIV services. In FP literature, high-quality

TABLE 2 DPP monitoring recommendations.

DPP Monitoring Recommendations						
	Initiation	3 Months	6 Months	9 Months	12 Months	Notes
HIV Testing	✓	✓	✓	✓	✓	Recommended every 3 months.
Creatinine Screening	✓		✓		✓	Optional for those <30 years old without kidney-related co-morbidities. Recommended once within the first few months of DPP initiation for those 30+ years old without co-morbidities. Recommended every 6–12 months for individuals with co-morbidities.
Blood Pressure Testing	✓				✓	Recommended at initiation and then on an annual basis.
Hepatitis B Testing	✓					Recommended at initiation. Vaccination or additional testing may be recommended in the future.
Hepatitis C Testing	✓				✓	Recommended at initiation and then on an annual basis. Vaccination or additional testing may be recommended in the future.
STI Screening or Testing	✓		✓		✓	Recommended every 3–6 months.

contraceptive counseling—which is client-centered and prioritizes voluntarism and informed choice—is associated with contraceptive use and method continuation (42–44). Similarly, for oral PrEP, provider-initiated counseling that includes information on perceived risk as well as strategies for managing side effects and adherence supports continued use (45, 46). Through counseling, providers serve as a crucial access point to women's awareness of the available prevention methods, their key characteristics, how to use their selected method correctly and how to manage associated side effects.

Yet there are significant and documented barriers to providers' successful delivery of contraceptive counseling (47, 48). In some cases, providers' knowledge of methods is inadequate or incorrect (42). Counseling can be influenced by providers' own experience with contraception and their biases about what methods are most suitable for women (e.g., for young women, unmarried women or women living with HIV) (49, 50). For example, a commonly cited bias is that AGYW are not good candidates for COC or oral PrEP due to their inability to take a daily pill and that for women living with HIV, the use of COC increases pill burden (i.e., needing to take two pills versus one) (49, 51). Notably, formative research with providers conducted to inform DPP acceptability studies found that providers described the DPP as having the potential to lessen the burden of taking two separate pills for COC and oral PrEP as well as to reduce the frequency and increase the efficiency of clinic visits (17).

In settings where FP and HIV services have been integrated, and where counseling on novel MPTs like the DPP will be required, additional barriers exist. Providers are often short on time and when new methods are introduced, their time is further stretched to attend trainings, incorporate new counseling messages and documentation requirements and to manage women's questions and concerns (49, 52). Among FP providers, a lack of training for HIV testing as well as to screen for and/or provide oral PrEP can contribute to a lack of confidence in discussing PrEP with women and feelings that it is "out of scope" (8, 53).

Reconciling counseling messages for missed pills was challenging due to divergent guidance for COC and oral PrEP. However, even within FP literature, client instructions on missed pills are not well understood. Research shows that more than 60% of oral contraceptive users know what to do when one pill is missed but far fewer know what to do when two or more pills are missed (54). To remedy confusion, providers are recommended to give simple, straightforward instructions—both verbally and written, including the use of graphics—as well as a contact for questions in the event of a missed pill (55). Taking this advice into consideration, the working group endeavored to develop counseling recommendations that are simple, concise and can be easily understood and acted upon by providers and users alike. For future MPT delivery forms, in particular longer-acting and/or provider-administered products, some counseling topics, like missed doses, may be irrelevant or easier to reconcile.

End-user research with potential DPP users, providers and male partners found that side effects are one of the largest concerns of both prospective DPP clients and providers (56), which could have implications for user acceptability and provider willingness to offer the DPP. For both COC and oral PrEP, the provision of information on side effects and how to manage them improves outcomes and continued use (46, 57, 58). Counseling users to understand potential changes to bleeding patterns is key to user satisfaction and continuation with other FP methods (59, 60), and by extension, is expected to be critical to effective use of the DPP. According to the Method Information Index, which is a measure of quality contraceptive counseling, women should be informed about the possibility of side effects with their selected method, how to manage them if they occur and alternate FP methods, including other oral contraceptives (61). Counseling messages on the latter will need to be developed to situate the DPP within the broader contraceptive method mix.

5. Conclusion

Developing recommendations for the DPP as a novel MPT posed unique challenges, with implications for efficacy, cost and user and provider comprehension and burden. Incorporating DPP counseling recommendations into clinical cross-over acceptability studies is an opportunity to receive feedback in real-time from both providers and users on their clarity and utility. Such feedback allows for iterative revision to increase the ease of delivery for providers as well as user comprehension and efficacy (62). Fine-tuning the counseling messages so that women can use the method correctly and confidently is critically important for eventual scale and commercialization of the DPP.

Author contributions

All authors comprised the working group that conceptualized and conducted the analysis of oral PrEP and COC guidance and developed counseling recommendations for the DPP: AC, LBH, SH, KH, CJ, EL, JM and MM as working group members and subject matter experts and KS and DMH as coordinators who convened the working group and iterated on the analysis and recommendations based on group discussions. KS and DMH wrote the draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

SH is employed by Viatris, a developer of a DPP. LBH is employed by the Population Council, a non-profit developer of reproductive health products, including a different DPP. The work described in this paper does not specifically pertain to research and development of a DPP product.

The remaining 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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Optimizing the pipeline of multipurpose prevention technologies: opportunities across women's reproductive lifespans

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HIV/AIDS and maternal mortality are the two leading causes of death among women of reproductive age in sub-Saharan Africa. A growing body of research investigates opportunities for multipurpose prevention technologies (MPTs) that prevent unintended pregnancy, HIV, and/or other sexually transmitted infections (STIs) with a single product. More than two dozen MPTs are currently in development, most of them combining contraception with HIV pre-exposure prophylaxis, with or without protection from other STIs. If successful, such MPTs could offer women benefits at multiple levels: greater motivation for effective use; lower product administration burden; accelerated integration of HIV, STI, and reproductive health services; and opportunities to circumvent stigma by using contraception as a "fig leaf" for HIV and/or STI prevention. However, even if women find respite from product burden, lack of motivation, and/or stigma in contraceptive-containing MPTs, their use of MPTs will be interrupted, often multiple times, over the reproductive lifecourse due to desire for pregnancy, pregnancy and breastfeeding, menopause, and changes in risk. Interruptions to the benefits of MPTs could be avoided by combining HIV/STI prevention with other life-stage-appropriate reproductive health products. New product concepts could include combining prenatal supplements with HIV and STI prevention, emergency contraception with HIV post-exposure prophylaxis, or hormone replacement therapies for menopause with HIV and STI prevention. Research is needed to optimize the MPT pipeline based on the populations underserved by available options and the capacity of resource-constrained health systems to deliver novel preventative healthcare products.

KEYWORDS
HIV, PrEP (pre-exposure prophylaxis), pregnancy, prevention, contraception

Introduction

HIV/AIDS and maternal mortality are the two leading causes of death among women of reproductive age in sub-Saharan Africa and in the lowest socioeconomic quintile globally (1). These sexual and reproductive health (SRH) burdens frequently overlap because HIV infections among women primarily occur in the context of unprotected sex with men.

Multipurpose prevention technologies (MPTs) are products that serve multiple SRH preventative care needs with one product, such as preventing unintended pregnancy, HIV, and/or other sexually transmitted infections (STIs) (2). As a single product, MPTs may reduce the number of product administration events required to meet SRH needs, e.g., as

self-administered pills, vaginal inserts, or injections; or provider-administered injections, devices, or implants. For oral pills, evidence from HIV and other disease areas suggests that decreasing pill burden through "one pill, once a day" dosing is associated with substantially improved adherence (3–5). For injections, evidence from several injectable regimens (6), such as HIV PrEP (7), HIV treatment (8), and diabetes treatment (9), suggests greater user and provider satisfaction with regimens requiring fewer injections. Product satisfaction has been important determinant of adherence among users (10) and prescribing among providers (11).

Currently, the only available MPTs are condoms, which are non-discreet, difficult for women to negotiate, and less effective with typical use compared to available single-indication products (12–16). Van der Straten et al. randomized young women in South Africa and Kenya to try a placebo form of a pill, injection, or ring MPT for 1 month, then select a form to continue for another 2 months, and found that 85% of women reported preferring their MPT over condoms (17). Fortunately, the landscape of MPTs is poised for transformation. As of February 2023, there are 28 new MPTs in development, including pills, injections, implants, as well as several non-systemic product forms such as vaginal rings, films, and gels (18). A majority of these MPTs (18 of the 28) prevent pregnancy together with HIV and/or other sexually transmitted infections (STIs), while a smaller proportion combine HIV and non-HIV STI prevention.

While many could benefit from MPTs under development, it is important to recognize that not all individuals in need of a combination product will be willing or able to benefit from MPTs (**Figure 1**). Some will be excluded from benefitting from the current product pipeline, while others will experience interruptions in MPT eligibility over their reproductive lifespan, e.g., when desiring pregnancy or pregnant yet still requiring HIV and/or STI prevention. Additionally, compared to single-indication products, more individuals are likely to be excluded from using MPTs due to the collective contraindications, side effects, and screening requirements of multiple combined products.

Exclusion of important and often vulnerable populations (e.g., pregnant women) from the benefits of MPTs have implications in both the ability to implement MPT delivery effectively, and implications for health equity. Multiple innovation frameworks recommend an equity lens incorporating both patient and provider perspectives on healthcare products and implementation methods. The Health Equity Implementation Framework combines implementation and healthcare disparities research methods to integrate characteristics of the innovation (e.g., a new MPT), patient factors, provider factors, and their health system, sociopolitical, societal, and economic contexts to guide innovations that improve both implementation and health equity (19). An innovation outcomes addendum to the widely-used Consolidated Framework for Implementation Research (CFIR) similarly integrates indicators from innovation recipients (patients), innovation deliverers (providers), and key decision-makers around the goal of equitable population impact (20).

Using these frameworks as a guide, this article reviews the potential benefits, gaps, and opportunities for MPTs across the lifespan, including: (1) women not wanting to get pregnant, (2) women actively trying to get pregnant, (3) pregnant and breastfeeding women, and (4) women approaching and experiencing menopause.

Not currently desiring pregnancy

Women undergo multiple stages of need for pregnancy prevention—including young women not yet ready to begin a family, women wishing to space pregnancies, and women who have achieved their desired family size and do not desire additional pregnancies. Of these groups, adolescent girls and young women, who frequently do not yet wish to begin a family, bear a disproportionate burden of new HIV infections in sub-Saharan Africa and face unique challenges in preventing pregnancy and HIV.

Despite their elevated risk, young women tend to express greater concern about avoiding pregnancy than HIV, especially in the context of successful HIV treatment programs (21, 22). In trials of user-dependent HIV prevention products—pills, gels, and vaginal rings—younger women tend to exhibit lower product adherence (23–26). MPTs combining contraception and HIV prevention may unlock stronger motivation to use HIV prevention effectively (27).

For women who experience unanticipated events such as sexual assault, or whose prevention needs are anticipated but intermittent, future MPT product concepts might include combinations of emergency contraception plus post-exposure prophylaxis (PEP), or on-demand contraception plus risk-informed PrEP. On-demand contraceptive options have been found to be safe, acceptable, and feasible for use by women in resource-limited settings (28), and studies suggest demand for such products could be substantial (29).

Multiple preference studies with young women, their partners, and authority figures such as matriarchs suggest that the vast majority who wish to avoid pregnancy, HIV, and STIs would prefer MPTs over single-indication prevention products (30–33). Using the discrete choice experiment (DCE) method, Minnis et al. analyzed the preferences of over 500 young women in jurisdictions of Kenya and South Africa with high HIV prevalence and found that 92% would prefer an MPT for PrEP and contraception over a PrEP-only product (30). Friedland et al. found that 82% of women responding to an online survey from multiple countries, over half of whom were from sub-Saharan Africa, expressed preference for an MPT over a PrEP-only product (33). Wagner et al. found that male partners, too, tended to prefer MPTs, with a particular preference for injection over rings or oral tablets for privacy and convenience (34). Among adolescent girls and young women in South Africa, forecasts of future HIV PrEP uptake (oral, vaginal ring, injectable) increased 4-fold if products also provided pregnancy protection (35).

MPTs may offer the additional benefit of circumventing PrEP stigma, a major barrier to effective PrEP use (36–38). Many societies attach less stigma to contraception use than to PrEP use (27), allowing the contraceptive function of MPTs to serve as a proverbial "fig leaf" to divert attention away from PrEP stigma

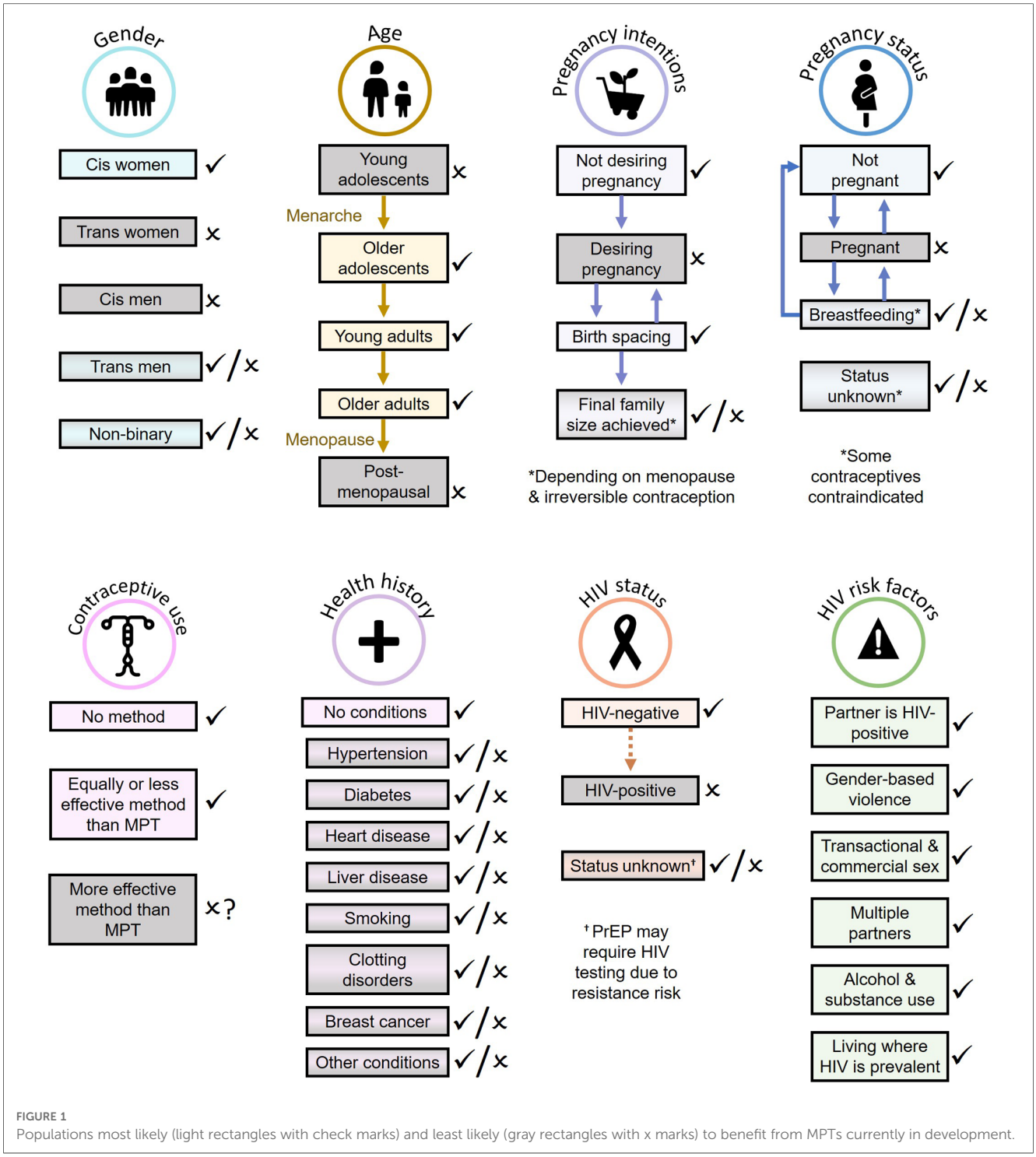

FIGURE 1
Populations most likely (light rectangles with check marks) and least likely (gray rectangles with x marks) to benefit from MPTs currently in development.

(39). A "fig leaf" could help to alleviate multiple challenges that have impeded PrEP scale-up, including internalized stigma, disapproval from partners or authority figures, the need to conceal PrEP, and fear of gender-based violence (40–42). It could also offer new opportunities to market PrEP-containing products in a broader manner than just PrEP, e.g., as a general wellness product (27, 43).

Despite these potential benefits, there remain several important challenges and barriers for effective MPTs in women not wanting to get pregnant. Contraception remains highly stigmatized in many settings, especially among adolescents and young women (44), which could erase or even reverse the "fig leaf" effect. In addition, for some, HIV prevention needs may not fully align with periods of risk for unintended pregnancy, producing unnecessary costs and side effects when only one form of prevention is needed, and potentially increasing burden on health providers due to greater need for product switching.

Product switching could also have deleterious effects on MPT cost-effectiveness, i.e., quantity of benefit per expenditure of

resources when compared to other potential uses of these resources. Prior modeling studies have found that oral PrEP cost-effectiveness among most women in sub-Saharan Africa is reliant on aligning PrEP use with time periods of heightened risk (45–48). For longer-acting MPTs such as implants, changes in prevention needs or intolerable side effects from any one component of an MPT may require premature removal. For shorter-acting products, some MPTs could offer less flexibility to optimally time product use, e.g., focusing use during periods of condomless sex with a partner potentially able to transmit HIV and/or an STI, due to mismatches in timing of when PrEP and contraception can be paused and resumed while remaining safe and effective.

As no MPTs are currently licensed and many are early in the product development pipeline, MPTs are likely to cover a narrower range of product formats than single-indication products for the next several years. The daily oral Dual Prevention Pill (DPP), which co-formulates oral tenofovir/emtricitabine HIV PrEP with oral estrogen/progestin contraception, is likely to be the first MPT to be licensed. While its introduction will represent a tremendous milestone in MPTs, it will be just one initial step toward fulfilling the need for MPTs, considering that long-acting contraceptive methods are the fastest-growing segment of method mix in sub-Saharan Africa (49). Long-acting contraceptives (50) and long-acting injectable PrEP (51) have been observed to be more effective than short-acting alternatives. Long-acting products may also facilitate more effective use. For example, in a clinical crossover study of vaginally inserted PrEP products, women tried placebo versions of four products for 1 month each, and adherence was such that the long-acting monthly ring offered significantly greater PrEP coverage over time than any short-acting vaginal product (vaginal film, tablet insert, or gel) (52). Initially introducing only short-acting MPT formats could force women to choose between MPTs that are less effective for prevention, versus separate products that are, individually, more effective for prevention. A modeling study based on a DCE in South Africa suggests that adding pregnancy prevention to HIV PrEP—and, to a lesser extent, adding STI prevention—would be strongly preferred and increase PrEP use much more among adolescent girls, compared to increasing the efficacy of PrEP (35).

While women who want to prevent unintended pregnancy have been the focus of a majority of MPTs under development, gaps remain, and additional innovations are under consideration: for example, an oral MPT that does not use estrogen, thereby avoiding cardiovascular and other contraindications (53). Parallel innovations in HIV PrEP, such as a 6-monthly subcutaneous injectable method currently in development (54), could enable safer, more potent, and longer-lasting MPT options with a more preferred drug delivery format. Innovations in contraceptive administration methods, such as contraceptive self-injection using the Sayana Press device (55), could offer greater agency and lesser dependence on under-resourced health systems. These and other innovations could lead to a robust and inclusive array of MPT options for women at life stages when they wish to avoid pregnancy.

Desiring pregnancy

MPTs that include contraception—the majority of those under development—clearly would not be indicated for women desiring pregnancy, as they would prevent conception. However, women desiring pregnancy still face barriers to PrEP and STI prevention, and could benefit from the "fig leaf" effect of MPTs—the more so because the pre-conception, conception, and pregnancy periods carry biologically elevated HIV risk (56–58) and because women desiring pregnancy would not be able to rely on condoms for HIV/STI prevention. For women who relied on MPTs to circumvent PrEP stigma, the "fig leaf" will be snatched away for each successive pregnancy. For those at sustained risk of HIV, MPTs that can only be used during life stages when a woman wishes to avoid pregnancy would result in gaps in MPT eligibility over the lifecourse, potentially postponing rather than preventing HIV infection.

For continuity of MPT benefits into the pre-conception period, product development would need to span a broader set of reproductive and health-related dimensions. Long-acting implants could emphasize switchable MPT product concepts, such as devices that could pause contraception while women desire or experience pregnancy (59, 60), thereby reducing removals and re-implantations. One long-acting reversible contraceptive implant has been designed to use an wireless controller to switch contraception on and off through the skin (61), though product developers have yet to incorporate an HIV or STI prevention component into such device concepts.

While most research on MPTs for women has focused on combined HIV prevention and contraception options, research suggests that women also place a high value on products that provide simultaneous protection from HIV and other STIs (62). Several products are currently under development, including three vaginal rings (63–65), one vaginal gel (66), and several product formats for rectal application (67–70). A modeling analysis estimating uptake of various MPTs and HIV prevention products based on DCE data from South Africa found that uptake of HIV prevention among women increased by an additional 30% if products also provided STI prevention (35). The combination of HIV and STI protection may be particularly appealing for women desiring pregnancy to avoid the risk of infertility associated with untreated STIs, as previous research has found that STIs are a leading cause of infertility in Africa (71, 72). Further research is needed to explore the preferences and motivations of this particular sub-group to inform development and prioritization of MPTs to meet their health needs.

Pregnancy

Pregnant women bring unique opportunities and challenges for MPT development. Pregnancy is associated with heightened HIV risk (73), and maternal HIV and STI infections can cause risks to the fetus, making this time period an important opportunity to avert SRH-related health burdens across generations. Pregnancy is

also time when most women have reliable contact with the healthcare system, and for some may be a first opportunity for HIV and STI screening and access to prevention services. For women testing HIV-negative in antenatal care, initiation of a life-stage-appropriate MPT could serve as a gateway to future MPT use. On the other hand, pregnancy is a time when some MPTs, including the DPP, would be contraindicated. Pregnancy also creates numerous new demands on women, including symptoms such as nausea and fatigue, increased nutritional needs, medical visits, and planning for labor, delivery, and caregiving. MPTs could allow women to integrate HIV and STI prevention into activities for other prevention needs so that HIV and STI prevention does not add further burden during this demanding life stage.

One potential MPT product concept for pregnant women could combine HIV and STI prophylaxis with a prenatal vitamin and mineral supplement, which is widely recommended from pre-conception through pregnancy and lactation. Such product carry relatively little stigma and could provide a "fig leaf" to circumvent PrEP stigma, while also avoiding adding to product burden given that prenatal supplements are universally recommended.

Postpartum period and breastfeeding

As with pregnancy, the postpartum period is associated with heightened HIV risk (73). The postpartum and breastfeeding period is also extremely demanding on women's time and resources, and is a time when some MPTs under development, including the DPP, would be contraindicated.

It is recommended that women continue to take prenatal micronutrient supplements over the postpartum and breastfeeding period to support recovery and lactation. Thus, a micronutrient MPT could be suitable for this life stage.

In addition, postpartum and breastfeeding women may wish to reduce their risk of becoming pregnant again, either to accomplish spacing between pregnancies, or because their final family size has been achieved. Some, but not all, contraceptive-containing MPTs may be appropriate for such women. While two versions of the DPP are currently under development, both formulations contain combined hormonal contraception with estrogen, which is contraindicated for women during the first weeks after birth. MPTs that combine PrEP with contraception options that can be used immediately after birth (implants, injections, progestogen-only pills) could help meet the needs of postpartum women who are looking to delay or avoid subsequent pregnancies.

Menopause

Peri-menopause and menopause are associated with a range of health risks in women, including cardiovascular disease, metabolic syndrome, musculoskeletal disorders, cognitive decline, depression, vasomotor symptoms, sleep disturbances, and migraine (74). Moreover, globally, an estimated 110,000 new HIV infections occurred in women aged 50 years and over, demonstrating an ongoing need for products that prevent HIV and other STIs (75).

Menopause is often associated with vaginal dryness. MPTs that combine lubrication with prevention of HIV and/or STIs could be a beneficial prevention method in this age group.

Additionally, some research suggests that estrogen therapy decreases coronary heart disease and all-cause mortality for health women aged 50–59 years (76). As a result, for women in menopause who remain at risk for HIV and other STIs, MPTs that combine estrogen therapy with STI and/or HIV prevention may provide an option for dual protection. However, treatments and health risks associated with menopause and hormone replacement remain critically understudied globally and warrant further research.

Discussion

While MPTs offer promising opportunities to meet the health needs and preferences of women not desiring pregnancy, development of MPTs directed toward other stages of the reproductive lifecourse remains limited. We have identified a number of potentially novel product concepts (**Table 1**), which illustrate the opportunities for offering women continuity of MPT benefits across the reproductive lifecourse. Ultimately, product concepts should be co-created with patients, providers, and other stakeholders using a framework combining innovation, impact, and equity goals. Implementation frameworks such as the Health Equity Implementation Framework (19) and the CFIR Innovation Outcomes Addendum (20) can help guide the synthesis of patient, provider, and decision-maker factors in the context of their healthcare, sociopolitical, societal, and economic contexts toward equitable population impact. Using these frameworks, and building on the momentum of recent MPT innovations, developers and funders should evaluate MPT options that more effectively span a woman's reproductive life, particularly in vulnerable and underserved life stages such as pre-conception, pregnancy, lactation, and menopause.

Beyond development and licensure, many steps remain to realize the benefits of MPTs. Once licensed, MPTs will necessitate co-delivery of multiple SRH services, which in low-resource settings often operate under separate funding sources, vertically-designed infrastructure, and siloed administrative entities (77–79). The World Health Organization (WHO) recently issued conditional recommendations to integrate HIV and family planning services (80)—an important step toward implementation—but a catalyst such as MPT introduction could accelerate action, analogous to how COVID-19 lockdowns accelerated the implementation of HIV treatment multi-month dispensation guidelines (81). Done right, MPT implementation could increase health system efficiencies by consolidating clinical visits and pharmacy dispensations.

Despite their tremendous promise, MPT introduction is likely to force difficult trade-offs in resource-limited healthcare settings. Financially, if MPTs were less cost-effective than currently available options, there is a risk that they could divert funds from other, more cost-effective health services, leading to a net detriment to population health. Similarly, given severe constraints on the number of healthcare providers in low-resource settings, if MPTs were to divert limited provider time

TABLE 1 Challenges and opportunities for MPT product concepts across the reproductive lifespan.

Reproductive life stage	Challenges with MPT pipeline	Potential new product concepts
Not desiring pregnancy	• Unexpected prevention needs • Intermittent prevention needs • Contraindications • Side effects	• Emergency contraception + PEP • On-demand contraception + on-demand PrEP • Non-estrogen and non-hormonal
Desiring pregnancy	• Most MPTs in development include contraception	• Long-lasting switchable implants • Prenatal supplements + PrEP
Pregnancy	• Some MPTs contraindicated • Demanding life stage	• Long-lasting switchable implants • Prenatal supplements + PrEP
Postpartum/breastfeeding	• Some MPTs contraindicated • Demanding life stage • Shifting reproductive intentions, e.g., wishing to delay next pregnancy	• Long-lasting switchable implants • Prenatal supplements + PrEP • Non-estrogen and non-hormonal (if wishing to delay next pregnancy)
Menopause	• Shifting health needs and priorities	• Lubricant-based MPTs • Hormone replacement + PrEP

away from other activities, potential harms would need to be weighed against potential benefits at the systems level. Interviews with Kenyan and South African healthcare providers have highlighted how MPT introduction could increase provider workload, e.g., by complicating counseling or requiring more frequent product switching (82). Providers have also raised concerns about the readiness of inventory controls to accommodate MPTs (82). Given persistent challenges with product stock-outs in low-resource settings, it is vital that MPTs not displace other product options in manners that reduce access or detriment health overall.

Licensure of the DPP—the first MPT since the condom—is likely to spark new ideas among innovators globally, including MPT users themselves. Human-centered design, co-creation, and the composition of R&D leadership should tap into the motivation and lived experiences of those most in need of MPTs. Sub-Saharan Africa should become a hub for women-led MPT innovation, as it is home to 15% of the world's women of reproductive age, 24% of women with unmet need for contraception (83), and 93% of the world's women living with HIV (84).

Although challenges and opportunities remain, women and their partners, care providers, and community leaders have expressed strong enthusiasm for MPTs already in the development pipeline. The potential benefits of these products could work across multiple levels—greater motivation at the user level, fewer product administration events at the user or provider level, accelerated delivery integration at the health systems level, and opportunities to circumvent stigma at the societal level—which could synergize to support greater access, effective use, and improved health and quality of life. The opportunity to tackle two of the leading causes of death among women of reproductive age, while honoring women's preferences and supporting intergenerational health and equity, makes MPTs one of the most promising global health frontiers of our time.

Author contributions

All authors conceptualized and critically revised and edited the review. AB wrote the initial draft and was responsible for the decision to submit the article. 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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Synthesis of end-user research to inform future multipurpose prevention technologies in sub-Saharan Africa: a scoping review

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Introduction: Women in sub-Saharan Africa (SSA) experience disproportionately high rates of HIV infection and unintended pregnancy compared to their age-matched counterparts in other regions of the world. Multipurpose prevention technologies (MPTs) that offer protection against HIV and unintended pregnancy in a single product stand to address these dual sexual and reproductive health needs simultaneously. The aim of this scoping review is to identify factors that are important for optimizing the likelihood of MPT adoption by end users in SSA.
Methods: Study inclusion criteria included MPT research (HIV and pregnancy prevention dual indication) published or presented in English from 2000 to 2022 and conducted in SSA amongst end-users (women aged 15–44), male partners, health care providers, and community stakeholders. References were identified by searching peer reviewed literature, grey literature, conference presentations (2015–2022), grant databases, and outreach to MPT subject matter experts. Of 115 references identified, 37 references met inclusion criteria and were extracted for analysis. A narrative synthesis approach was used to summarize findings within and across MPT products.
Results: Studies were identified from six countries in SSA and a substantial proportion included a South African ($n = 27$) and/or Kenyan ($n = 16$) study site. Most studies utilized a qualitative study design ($n = 22$) and evaluated MPT acceptability and preferences by presenting hypothetical products through images or a list of product attributes ($n = 21$). The vaginal ring ($n = 20$), oral tablet ($n = 20$), and injection ($n = 15$) were examined most frequently. Across studies, there was high acceptability and demand for an HIV and pregnancy prevention MPT. End users valued choice in prevention product type as well as discreetness and long-acting options. Provider counseling and community sensitization were reported as essential for future introduction of novel MPT delivery forms.
Conclusion: Recognizing the heterogeneity of women's preferences and changing reproductive and sexual health needs over the life course, choice is important in the delivery of pregnancy and HIV prevention products as well as amongst MPT products with distinct product profiles. End user research with active MPTs, vs. hypothetical or placebo MPTs, is necessary to advance understanding of end-user preferences and acceptability of future products.

KEYWORDS

multipurpose prevention technologies, HIV, contraception, pregnancy, end-users, review

1. Introduction

In sub-Saharan Africa (SSA), adolescent girls and young women (AGYW) ages 15–24 account for nearly 32% of all new HIV infections, and 40%–65% report an unintended pregnancy before the age of 25. This sexual and reproductive health burden among AGYW in the SSA region is disproportionally high compared to their age-matched counterparts in other regions of the world (1, 2) and persists despite significant progress in HIV and unintended pregnancy prevention over the last decade, including increased availability of and access to contraceptive options, opt-out HIV testing and counseling, voluntary medical male circumcision, treatment for HIV-positive individuals, and pre-exposure prophylaxis (PrEP) available in oral tablet, and, most recently, vaginal ring and injectable formulations (3).

Multipurpose prevention technologies (MPTs) that offer protection against HIV and unintended pregnancy in a single product stand to address these dual sexual and reproductive health needs simultaneously (4, 5). MPTs have the potential for increased acceptability and use relative to single-indication products for numerous reasons (6–8). First, improved access, consistent use, and health system efficiencies could be achieved through offering an integrated product that requires fewer clinic visits and reduces provider burden. Second, reductions in stigma related to HIV prevention product use could be achieved by developing discreet MPT products and integrating MPTs into family planning delivery systems and messaging. Third, increased uptake could be achieved by ease of MPT use and expanded choice in the available method mix (6, 7, 9). Male and female condoms, however, are the only approved MPTs available.

The existing MPT research and development pipeline includes a diverse range of delivery forms, mechanisms of action, and indications (10–12). Vaginal rings, which contain both antiretroviral and contraceptive agents, offer 1- or 3-month continuous use and constitute the delivery form with the greatest number of products in development, including both nonhormonal and hormonal rings (11, 13). The co-formulated dual prevention pill (DPP) is anticipated to be the first MPT to move to market since female and male condoms; the pharmacokinetic profile of a co-formulated DPP is being assessed in a bioequivalence trial. Acceptability of an over-encapsulated DPP is also being evaluated through two studies in Zimbabwe and South Africa (14, 15). Vaginally delivered products comprise a core focus of the future MPT pipeline, with both on-demand forms used prior to intercourse (such as fast-dissolving inserts) and, more recently, longer-acting formulations (such as monthly films) in preclinical development and planned early clinical trials. Other long-acting MPT delivery forms, such as an implant and a microneedle applicator patch, are also in preclinical development (12).

While active MPT products are largely in the design and research phase, there have been studies conducted to explore MPT acceptability by presenting women with hypothetical MPT products through images and product attribute lists or providing women with placebo MPT products for use. This review synthesizes what is known about end user preferences for MPTs for HIV and pregnancy prevention in the existing literature and identifies gaps in the evidence base. This information is essential to inform the development of new MPTs for prevention of unintended pregnancy and HIV. The overarching goal of this scoping review is to identify what product attribute factors and social factors are important for optimizing the likelihood of MPT adoption and use by end users. Thus, we examine the existing evidence on MPT preferences and acceptability amongst end users and how they are viewed and influenced by male partners, health care providers, and other community stakeholders in SSA.

2. Methods

2.1. Scoping review

We conducted a scoping review, which enables researchers to map the current state of research and identify gaps in knowledge. Unlike systematic reviews, scoping reviews are intended to explore multiple research questions without restrictions on a particular study design and readily allows for inclusion of conference abstracts and unpublished reports (16). Scoping reviews are often precursors to systematic reviews and meta-analyses because they can be used to confirm the relevance of inclusion criteria and research questions for future research and synthesis efforts.

2.2. Search terms and inclusion criteria

The conceptual model used for the present review (**Figure 1**) informed our selection of search terms and synthesis of resulting articles. The conceptual model was refined drawing on two existing frameworks [Mensch et al. (17); Friedland et al. (14)] that were developed to be HIV PrEP or MPT product specific. The Mensch et.al., framework suggests that influencing factors and acceptability factors impact product preference and adherence (17), which in this review applies to use of future products. Influencing factors are based on the socio-ecological model, whereas acceptability factors are based on product-specific attributes and perceptions. The Friedland et al. framework suggests that provider factors and product factors inform an individual's HIV and pregnancy prevention choices and ultimately their intention to use future MPTs (14).

Search terms were also informed by our inclusion criteria. Study inclusion criteria included research published or presented between January 1, 2000 and November 30, 2022, in English and with a geographic location in one or more sub-Saharan African location. We included original research regardless of study design, research encompassing all delivery forms in peer-reviewed literature or the MPT development pipeline, and specifically focused on MPTs designed to combine HIV and pregnancy prevention. We excluded research that reported on condoms only as an MPT and peer-reviewed publications that reported modeling studies, reviews, commentaries, and editorials. A list of search terms is included in **Supplementary Table S1**.

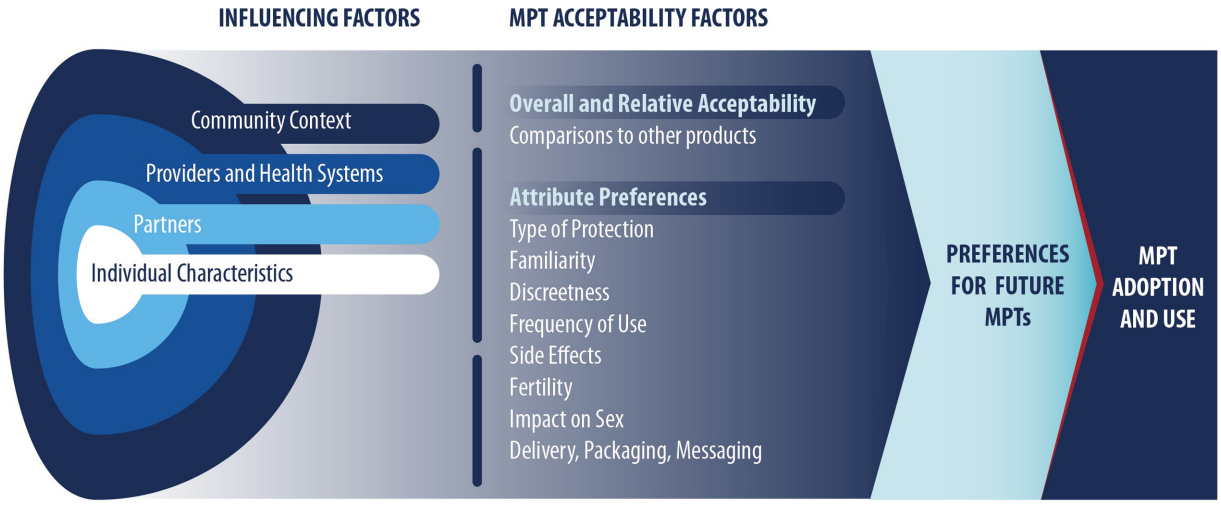

FIGURE 1
Conceptual model.

2.3. Reference identification

The study team used multiple search modalities to identify relevant references. To comprehensively search the peer-reviewed literature, the study team worked with a research librarian to develop a structured search strategy for articles indexed on PubMed, Embase, and Web of Science. The study team then conducted extensive hand-searching to identify relevant conference abstracts, grey literature reports, and manuscripts under review not available in the above databases. Hand-searching included a comprehensive search of MPT and HIV prevention websites (i.e., AVAC, IMPT, PrEP Watch), a search of HIV prevention and family planning conferences [i.e., International AIDS Conference (AIDS), IAS Conference on HIV Science (IAS), HIV Research for Prevention Conference (HIVR4P), Conference on Retroviruses and Opportunistic Infections (CROI), Population Association of America Annual Meeting (PAA), International Conference on Family Planning (ICFP)] held between 2015 and 2022, and a review of the reference lists of the included articles. To orient the scoping review to MPT products in the development pipeline and ongoing MPT-related research, we conducted a search of NIH RePORTER and Grants.gov and reached out to investigators with current funded research and known MPT subject matter experts regarding their ongoing and future work.

2.4. Synthesis approach

All references identified in the search process were uploaded to Covidence, an online review software. Two study team members independently reviewed each reference by title and abstract, and then by full text, applying specified inclusion criteria. Structured forms were used to extract information from the resulting set of included references. Team members met to discuss differences when individual determinations did not align to reach consensus at each stage. A narrative synthesis approach was then used to summarize findings within and across products. Narrative synthesis is an appropriate strategy in scoping and other reviews when variability across study designs and outcomes assessed preclude our ability to use meta-analytic techniques. For this review, we read through all extracted text and identified relevant thematic categories that appeared frequently in extracted text (e.g., familiarity, discreetness) through discussion with one another and consultation with our conceptual framework. After reaching consensus on these themes, we created product-specific summaries that pulled together all end-user data for a specific MPT product type and narratively summarized available data on each theme, noting gaps in the available literature and any studies that stratified results by region or sociodemographic characteristics. Finally, we compared findings across these product-specific summaries and created cross-product syntheses, which draw upon common findings identified across products for the same theme and highlighted distinctions and gaps in the evidence. This process was similar to a qualitative data analysis through coding and memo-writing. The larger research team held meetings to discuss overall emerging themes and to identify gaps in the evidence that warranted further exploration.

3. Results

3.1. Overview of studies

As shown in Figure 2, the team identified 113 unique references and 37 were included in the review, with reasons for exclusion noted. A summary of key characteristics of included references presented in Table 1 with a full list of references is available in Table 2. Most references came from the peer-reviewed literature ($n = 21$) followed by conference findings

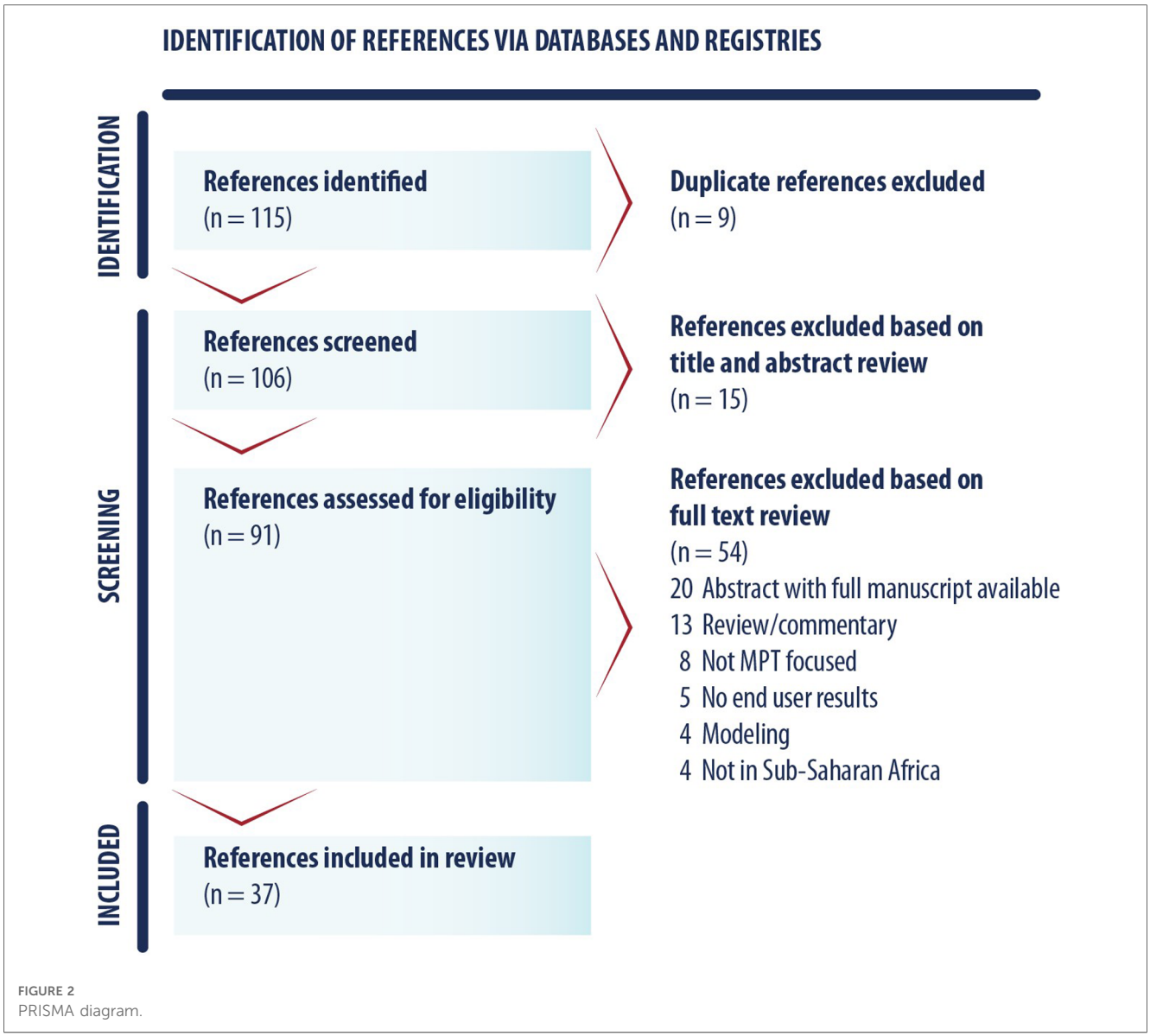

FIGURE 2
PRISMA diagram.

($n = 10$), and grey literature ($n = 6$). The most frequently used study design was qualitative ($n = 22$), followed by a variety of quantitative approaches (i.e., discrete choice experiment (DCE; $n = 6$) and randomized cross-over ($n = 3$), mixed methods ($n = 3$), and human-centered design workshops ($n = 2$). Study sites spanned six countries in sub-Saharan Africa: South Africa, Kenya, Zimbabwe, Uganda, Nigeria, and Malawi. A substantial proportion of studies included a South African study site ($n = 27$) and/or a Kenyan study site ($n = 16$), reflective of many articles that included data from the Tablets, Ring, and Injectables as Options (TRIO) study, which examined acceptability of placebo versions of these three delivery forms for an MPT indication ($n = 11$) (53).

Given the diversity in type of study design, sample sizes ranged from 15 participants to 2,165 participants; however, most studies included fewer than 200 participants. Additionally, most references included end users aged 15–24. Although AGYW perspectives therefore predominate, the literature also included perspectives from health care providers ($n = 7$), men and male partners ($n = 12$), and community stakeholders ($n = 5$). Most references evaluated MPT acceptability and preferences by presenting potential future products ($n = 21$) where participant interaction with MPT candidates was limited to seeing images of candidate products in the pipeline and/or seeing a list of potential product attributes ($n = 20$). The vaginal ring ($n = 20$), oral tablet ($n = 20$), and injectable ($n = 15$) were most frequently examined as drug delivery platforms for MPTs; other delivery forms examined are noted in Tables 1, 2, 3.

3.2. Product attribute factors

3.2.1. Interest in MPTs for HIV and pregnancy prevention

Nearly every study assessed end users' preference for an MPT compared with single-indication products for HIV or pregnancy

TABLE 1 Reference characteristics ($N = 37$).

	n	%
Publication Type		
Peer-Review Article	21	57%
Conference Findings	10	27%
Grey Literature	6	16%
Country[a]		
South Africa	27	73%
Kenya	16	43%
Zimbabwe	12	32%
Uganda	9	24%
Nigeria	1	3%
Malawi	1	3%
Years		
2013–2017	6	16%
2018	7	19%
2019	5	14%
2020	2	5%
2021	5	14%
2022	11	30%
Study Design		
Qualitative	22	59%
Discrete Choice Experiment	6	16%
Randomized Cross-Over	3	8%
Mixed Methods	4	11%
HCD Workshops	2	5%
Other Influential Populations[a]		
Providers	7	19%
Male Partners and Men	12	32%
Community Stakeholders	5	14%
Number of Participants		
Not reported	4	11%
<100	15	41%
100–500	10	27%
>500	8	22%
Hypothetical or Actual Products		
Placebo MPT Products	14	38%
Hypothetical Products	21	57%
Active MPT Products	2	5%
Participant Interaction with MPTs[a]		
Used product(s)	11	30%
Did Not Use: Saw Pictures	21	57%
Did Not Use: Touched Products	6	16%
Product Type[a]		
Vaginal Ring	20	54%
Oral Tablet	20	54%
Injectable	15	41%
Vaginal Microbicide Gel	7	19%
Diaphragm	5	14%
Vaginal Film	5	14%
Subcutaneous Implant	5	14%
Vaginal Insert	3	8%
Hypothetical Vaginal MPT	2	5%
Vaginal Fabric[b]	1	3%
Microarray Patch	3	8%
Parent Study		
TRIO	11	30%
QUATRO	2	5%
MTN-045/CUPID	3	8%
Fabric Study	1	3%
HPTN-035 and Duet	1	3%
SCHEILD	2	5%
UPTAKE	1	3%
Kisumu Combined Ring Study	1	3%
Not named	16	43%

[a]Totals greater than 100% due to category overlap.
[b]The vaginal fabric is a novel dosage form for intravaginal drug delivery made of drug-eluting nanofibers.

prevention. This yielded evidence of strong interest among reproductive-aged women for an MPT that simultaneously addresses HIV and pregnancy prevention (range across multi-country quantitative studies of 86%–93%). Participants also viewed MPTs as a product for improved sexual and reproductive health protection and reported that an MPT's overall purpose was more important than product-specific attributes (20, 23, 31, 34, 40, 46, 47, 52). Few studies reported reasons for not preferring MPTs; however, those that did noted the primary reason was a desire to conceive, retaining the option for flexibility, or concerns with drug toxicity (42, 45, 47, 52).

Preferences for the type of protection afforded by a dual-indication MPT product were mixed across studies. When TRIO participants were asked to select the one product attribute that most influenced their acceptability, almost half selected pregnancy prevention (44%) ahead of other factors. In other studies, participants placed more importance on HIV protection than pregnancy protection (20, 31, 39, 46, 47). Furthermore, across studies, participants noted the importance of having an HIV-only prevention option so that women would be able to continue protecting themselves against HIV when they want to have a child and would need to discontinue use of the MPT (44, 47, 52).

3.2.2. Familiarity

Familiarity was an important acceptability factor across most studies that examined and compared specific delivery forms. Known and used delivery forms such as injectables and tablets were initially preferred and ranked higher than newer delivery forms such as the ring and implant (6, 18, 38, 40, 43, 44, 47, 50, 51). Reasons for preferring familiar products included decreased hesitation about side effects due to the ability to stop product use quickly, confidence in how to use the product discreetly, and ease of explanation to partners, family, peers, and community members (6, 18, 25, 38, 45, 50). However, initial concerns about unfamiliar products and unfamiliar product attributes could be overcome through learning about products and using products. For example, initial concerns over tablet color and size, and ring insertion and comfort, decreased after the opportunity to use placebo versions of these delivery forms. Similarly, concerns over vaginal insertion of a nanofiber fabric decreased after participants watched the product dissolve (6, 18, 31, 35, 38, 40, 51). Additionally, ratings and concerns for known and used products

TABLE 2 References reporting MPT acceptability and preferences.

Author, Year	Reference Type	Country	Study/Trial Name	Study Design	Population	Sample Size	Product Type(s)	Product Use
Agot, 2019 (18)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	277	Ring; Oral tablet; Injectable	Placebo Products
Agot, 2020 (19)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	165	Ring; Oral tablet; Injectable	Placebo Products
AVAC, 2021 (20)	Grey Literature	South Africa; Zimbabwe	None	Human Centered Design Workshops	Women (age 18+)	25	Oral tablet	Hypothetical Products
Barker, 2021 (21)	Conference Findings	South Africa; Zimbabwe	None	Qualitative Study	Adolescent and Adult Women and Men (age 16–40)	Not Reported	Oral tablet	Hypothetical Products
Bayigga, 2018 (22)	Conference Findings	Uganda	DREAM Trial	Qualitative Study	Community Stakeholders	1,076	Ring	Hypothetical Products
Beksinska, 2018 (23)	Peer-Reviewed Article	South Africa	None	Randomized Cross-Over Study	Women (age 18–45)	115	Gel; Diaphragm	Placebo Products
Bhushan, 2022 (24)	Peer-Reviewed Article	Uganda; Zimbabwe	MTN-045/ CUPID	Qualitative Study	Couples (Women (age 18–40), Men (age 18+)	78 (39 couples)	Ring; Oral tablet	Hypothetical Products
Bowen, 2017 (25)	Grey Literature	South Africa	None	Qualitative Study	Adolescent Girls, Adolescent Boys, Women, Men (age 16–34)	28	Ring	Hypothetical Products
Browne, 2020 (26)	Peer-Reviewed Article	South Africa; Zimbabwe	QUATRO	Discrete Choice Experiment	Women (age 18–30)	395	Vaginally Delivered MPT	Hypothetical Products
Gachigua, 2022 (27)	Conference Findings	Kenya	None	Qualitative Study	Adolescent Girls and Young Women (age 15–24), Female Sex Workers, male partners of AGYW/FSW, Stakeholders	Not Reported	Microarray Patch	Placebo Products
Gachigua, unpublished (28)	Conference Findings	Kenya	None	Qualitative Study	Adolescent Girls and Young Women (age 15–24), Female Sex Workers, male partners of AGYW/FSW, Stakeholders	Not Reported	Microarray Patch	Placebo Products
Ipsos, 2014 (29)	Grey Literature	Nigeria; South Africa; Uganda	None	Mixed Methods Study	Women (age 15–35), Men (age 18+)	2,165 (Qualitative Sample: 443; Quantitative Sample: 1,722)	Ring; Implant; Injectable; Film	Hypothetical Products
Kilbourne-Brook, 2021 (30)	Conference Findings	South Africa; Uganda	None	Qualitative Study	Women (ages 18–24 years), Female Sex Workers, Heterosexual men, MSM, Stakeholders	Not Reported	Microarray Patch	Hypothetical Products
Laborde, 2018 (31)	Peer-Reviewed Article	South Africa; Uganda; Zimbabwe	Fabric Study	Qualitative Study	Women (age 18–49)	55	Gel; Film; Fabric	Placebo Products
Lunani, 2022 (32)	Conference Findings	Kenya; Uganda	UPTAKE	Qualitative Study	Adolescent Girls and Women (age 15–24)	30	Injectable	Hypothetical Products
Lutnick, 2019 (33)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	24	Ring; Oral tablet; Injectable; Implant	Placebo Products
MatCH Research, 2016 (34)	Grey Literature	South Africa	None	Qualitative Study	Women (age 18–49), Men (age 18+)	24	Gel; Diaphragm	Hypothetical Products
McLellan-Lemal, 2022 (35)	Peer-Reviewed Article	Kenya	Kisumu Combined Ring Study	Qualitative Study	Women (age 18–34)	25	Ring	Active Product
Mgodi, 2022 (36)	Conference Findings	Kenya; South Africa; Zimbabwe	None	Human Centered Design Workshops	Not Reported	Not Reported	Oral tablet	Hypothetical Products
Milford, 2014 (37)	Conference Findings	South Africa	None	Qualitative Study	Women and Stakeholders	24	Diaphragm	Hypothetical Products
Minnis, 2018 (38)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Mixed Methods Study	Women (age 18–30)	277	Ring; Oral tablet; Injectable	Placebo Products

(*Continued*)

TABLE 2 Continued

Author, Year	Reference Type	Country	Study/Trial Name	Study Design	Population	Sample Size	Product Type(s)	Product Use
Minnis, 2019a (39)	Peer-Reviewed Article	Kenya; South Africa; Zimbabwe	TRIO; QUATRO	Mixed Methods Study	Women (age 18–30)	419	Ring; Oral tablet; Gel; Injectable; Film; Insert	Placebo Products
Minnis, 2019b (41)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Discrete Choice Experiment	Women (age 18–30)	536	Ring; Oral tablet; Injectable	Placebo Products; Hypothetical Products
Minnis, 2021 (6)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	88	Ring; Oral tablet; Injectable	Placebo Products
Minnis, 2022 (42)	Peer-Reviewed Article	Uganda; Zimbabwe	MTN-045/ CUPID	Discrete Choice Experiment	Couples (Women (age 18–40), Men (age 18+))	800 (400 couples)	Ring; Oral tablet; Film; Inserts	Hypothetical Products
Namukwaya, 2022 (43)	Conference Findings	Uganda	None	Qualitative Study	Adolescent Girls and Adult Women Sex Workers (age 15–45)	15	Oral tablet; Implant; Injectable; Hypothetical Vaginal Product	Hypothetical Products
Nkomo, 2021 (44)	Conference Findings	South Africa; Zimbabwe	SCHEILD Study	Qualitative Study	Women (age 18–30)	110	Implant	Hypothetical Products
Nkomo, Under Review (45)	Grey Literature	South Africa; Zimbabwe	SCHIELD	Qualitative Study	Women (age 18–30)	110	Implant	Hypothetical Products
Quaife, 2018 (46)	Peer-Reviewed Article	South Africa	None	Discrete Choice Experiment	Adolescent Girls (age 16–17), Women and Men (age 18–49), Female Sex Workers	661	Ring; Oral tablet; Gel; Injectable; Diaphragm	Hypothetical Products
Routes2Results, 2017 (47)	Grey Literature	South Africa	None	Mixed Methods Study	Women (age 18–21)	1,457 (Qualitive Sample: 216, Quantitative Sample: 1,241)	Ring; Oral tablet	Hypothetical Products
Shapley-Quinn, 2019 (40)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	88	Ring; Oral tablet; Injectable	Placebo Products
Stoner, 2022 (48)	Peer-Reviewed Article	Uganda; Zimbabwe	MTN-045/ CUPID	Discrete Choice Experiment	Couples (Women (age 18–40), Men (age 18+))	790 (395 couples)	Ring; Oral tablet; Film; Insert	Hypothetical Products
Terris-Prestholt, 2013 (49)	Peer-Reviewed Article	South Africa	None	Discrete Choice Experiment	Women (age 18–45)	1,017	Microbicide	Hypothetical Products
Wagner, 2022 (51)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Qualitative Study	Women (age 18–30)	127	Ring; Oral tablet; Injectable	Placebo Products
Weinrib, 2018 (50)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Randomized Cross-Over Study	Women (age 18–30)	277	Ring; Oral tablet; Injectable	Placebo Products
Woodsong, 2014 (52)	Peer-Reviewed Article	Zimbabwe; Malawi	HPTN 035A, Duet Acceptability Study	Qualitative Study	Women (age 18+)	231	Gel; Diaphragm	Active Product
van der Straten, 2018 (53)	Peer-Reviewed Article	Kenya; South Africa	TRIO	Randomized Cross-Over Study	Women (age 18–30)	277	Ring; Oral tablet; Injectable	Placebo Products

such as injectables and tablets changed minimally after demonstrations, educational videos, or actual use (6, 18, 38, 51), whereas increased exposure to and experience with novel delivery forms increased acceptability ratings and comfort (38, 39).

Participants' previous experience or lack of experience with family planning products also shaped preferences for MPT delivery forms (18, 29, 38–40, 43, 46, 50). For example, women who had previously used contraceptive implants or an IUD expressed a higher preference for the ring, women who had previously used birth control pills expressed a higher preference for the tablet, and women with only condom experience expressed a higher preference for films, inserts, and diaphragms (39, 50). Lastly, TRIO participants cited a lack of familiarity with new biomedical technologies as an important consideration with MPT introduction (42).

3.2.3. Discreetness

Having the option to use a product discreetly was a key component of product acceptability among end users (6, 18, 27, 28, 30, 37, 38, 49, 52), some of whom described that their preferences for discreet products were driven primarily by concerns about a partner's inadvertent discovery of product use (40, 51) and potential disapproval (37). End users frequently noted that ideally they would like to talk to their partners about using an MPT (21) but that having the option of discreet use was essential because navigating discreet use or disclosing use to a partner was something unique to each individual and relationship (6, 25). Anticipated difficulties with discreet use were viewed as a substantial disadvantage (38, 40). Similarly, perceived ease of discreet use was a substantial driver of product preference (18, 29, 38, 40, 51). In one study, end users initially expressed

TABLE 3 Summary of findings by delivery form, product attributes, and social factors.

Products and number of references	Vaginal administration  Vaginal ring ($n = 20$), Gel ($n = 7$) with Diaphragm ($n = 5$), Film ($n = 5$), Other ($n = 6$)[a]	Oral administration  Oral tablet ($n = 20$)	Injectable, implant, and microarray patch  Injectable ($n = 15$), implant ($n = 5$), patch ($n = 3$)
Product Attributes			
Type of Protection	Dual HIV and pregnancy prevention preferred for diaphragm with gel (23, 34).	When compared, greater importance was placed on HIV prevention efficacy vs. contraception efficacy (40, 46, 47)	Independently retrievable rods in an MPT implant was an appealing feature for end users, with some variation by site (45). End users preferred dual indication patches (27, 30, 28)
Familiarity	Unfamiliarity with vaginal dosing often led to initial hesitations (25, 31, 38, 40, 43, 47), which were overcome by counseling, information, and product use experience (18, 23, 31, 35).	Familiarity with tablets as a dosing form contributed to preference for MPT tablets (40, 43, 47, 51); among those with initial fears about tablets' size or color, concerns decreased with product use experience (6, 38, 51).	Familiarity with injectables and implants as dosing forms contributed to preference (6, 18, 40, 43, 51) (45), although end users who had negative experiences with other injectables preferred non-injectable MPTs (40). Notably, the patch was an unfamiliar dosing form for all end users.
Discreetness	Hesitations about discreet use (38, 40) were overcome when end users found discreet use possible (35, 38) and made decisions around product use disclosure to partners (25, 38). Some viewed vaginal MPTs, particularly films and fabrics, as "woman initiated" and discreet (29, 31, 37, 39).	Although some felt tablets could be used without a partner's knowledge (20, 21), discreet use was challenging due to a lack of privacy in the home to store and take pills and some expressed concerns that others would discover the pill bottle or raise concerns due to visual similarity between MPT tablet and ARVs (36, 38, 40, 50, 51).	Injectables were often preferred due to their heightened discreetness and ability to be used without partner detection (18, 38, 40, 51). The placement, flexibility/palpability, and biodegradability of an implant are important enablers of discreet use (45). High interest in the patch related to its potential for self-administration and discreet use (27, 28).
Frequency of Use	Opinions were varied on the acceptability of leaving a vaginal ring inserted for a month or longer (6, 35, 38, 40, 50, 51), as were preferences on dosing frequency and reasons for selecting other vaginally MPTs (29, 31, 39, 42).	Daily adherence was typically viewed as burdensome, particularly when taken at the same time each day, as were frequent clinic visits for tablet refills (6, 21, 40, 47, 50, 51). End users who valued lower frequency of use had lower preference for an MPT tablet (6, 39, 40, 50, 51).	Non-daily dosing was a positive attribute of injectable MPTs (18, 19, 38, 50, 51), implants (45) and patches (27, 28), although preferences for the ideal dosing interval varied widely (implants and injectables: 1 month–5 years; patch: 1–3 + months) (6, 18, 19, 27, 28, 30, 38, 40, 43, 45, 50, 51).
Side Effects	Side effects associated with an active MPT ring were assessed in one study (35) and with a placebo MPT ring in TRIO (6), as were concerns about side effects of a fabric MPT (31). Not discussed for diaphragms plus gel.	Despite some concerns about possible side effects (40, 47, 50, 51), tablets were typically perceived to have limited side effects and to be a safer delivery form because they could be stopped at any time (6, 18, 40, 50).	Although some end users expressed concerns about fear, pain, and side effects of injections (6, 38, 40, 50), these subsided after use experience (40). Similarly end users had concerns about pain with implant placement and removal (43, 45). End users wanted more information about patch side effects (30).
Fertility	Fertility was explored in one study of an active MPT ring, where end users expressed concerns about infertility caused by the ring that were related to rumors circulating in the community (35) Not discussed for other delivery forms.	Not discussed.	The potential for a separate, independently-removable contraceptive rod was highly salient for end users and return to fertility while maintaining HIV protection was of great interest (45).
Impact on Sex	Overwhelming preference for no change to the vaginal environment or interference with sex (31, 35, 37, 49, 51); specific preferences around changes to the vagina (e.g. wetness) were varied (26, 31, 39). End users that used rings and diaphragms during sex found them generally acceptable and rarely reported negative impacts (6, 23, 34, 35, 38, 51).	An MPT tablet's lack of interference with the sexual experience is an appealing feature to some end users (51).	The injectable MPT's lack of interference with sex was viewed as a positive feature for both women and their male partners (29, 51).
Delivery, Packaging, Messaging	End users desired marketing that emphasizes vaginal MPTs' potential to empower women and enhance the sexual experience (6, 29, 34) but had mixed opinions on where diaphragm should be marketed (HIV vs. family planning) (31).	End users desired MPT tablets to be visually distinct from ARVs and had discreet, non-medical packaging (6, 20, 47). Potential channels of information for messaging included healthcare, traditional media, social media, and influencers (20).	End users and providers supported messaging that emphasizes both contraception and HIV indications, and that counseling at facilities should be augmented by community-level education and communication activities such as media and community-based awareness raising (45).
Social Factors			
Partners	Although partner-related social harms related to discovery of vaginal MPT use were minimal where reported (50), end users both anticipated and experienced resistance from male partners related to use of vaginal products (18, 31, 34, 35).	End users anticipated resistance and negative reactions from male partners if they discovered covert use of an MPT tablet, which could be mistaken for ARVs and/or indicate infidelity (20, 21, 36, 40, 51). Some felt that an MPT tablet could be an easier delivery form to "explain away" to a male partner compared to other forms (18, 40).	Male partners indicated that the increased discreetness of an MPT injectable and the dissimilarities with ARVs could be advantages for women with unsupportive or resistant partners (51). Similarly, implants placed in the same location as contraceptive implants could avoid partner detection as MPTs (45).

(*Continued*)

TABLE 3 Continued

Products and number of references	Vaginal administration Vaginal ring ($n = 20$), Gel ($n = 7$) with Diaphragm ($n = 5$), Film ($n = 5$), Other ($n = 6$)[a]	Oral administration Oral tablet ($n = 20$)	Injectable, implant, and microarray patch Injectable ($n = 15$), implant ($n = 5$), patch ($n = 3$)
Healthcare Providers	End users expressed a strong desire for MPT ring and diaphragm counseling from providers and "testimonials" from other end users to support method uptake and use (23, 25, 47).	Health care providers saw both the potential benefits and implementation challenges of MPT tablets (21).	Health care providers may be critical and salient sources of information for education MPTs, although provider attitudes towards end users could influence uptake and use (29, 45). For implants, providers expressed preference for biodegrade, less flexible, palpable implants that were placed in the upper arm (45). Providers also supported the idea of independently retrievable rods for HIV protection during conception (45). Providers viewed patches as innovative with the potential to overcome issues related to daily adherence (27).
Community	Community members expressed and expected demand and support for MPT rings (22, 35), but end users anticipated community resistance related to norms around sex and contraception (31, 35).	End users anticipated stigma and judgment from the community due to presumptions that MPT tablet use indicated sexual promiscuity and mistaking MPT tablets for ARVs (6, 20, 21, 47, 51).	Policymakers felt that patches, like other MPTs, could address multiple sexual and reproductive health needs, and could alleviate workload in facilities with integrated service delivery (27, 28).

[a]Other vaginally-administered products included insert ($n = 3$), hypothetical vaginal MPT ($n = 2$), and fabric ($n = 1$).

concerns about partner detection of product use but later reported that this happened infrequently (38). Importantly, the physical delivery form of a product played a role in what discreet use could or might look like, with specific discretion-related considerations for each product; for example, physical location on the body and palpability of an implant (45). In a DCE with end users in South Africa, the importance of being able to use a product discreetly was rated with greater importance among end users who reported ever having difficulties negotiating condom use compared to those without condom negotiation difficulties (49).

3.2.4. Frequency of administration and product duration

Frequency of administration or duration of use was a salient aspect of product acceptability for end users, and, when assessed, for their partners (26–28, 30, 40, 42, 51). Across studies and products, end users expressed a range of preferences for an ideal dosing frequency that most often ranged from 1 month to 1 year, with the ideal target duration varying by delivery form, study population, and location (6, 18, 19, 27, 28, 30, 32, 38, 40–43, 46, 50, 51). Preferences for ideal product duration were also often based on experience with HIV prevention or contraceptive products. For example, women who previously used long-acting contraceptives (i.e., implants and IUDs) often preferred long-acting MPTs, and women who previously used short-acting products (i.e., condoms) often preferred on-demand MPTs (39, 50).

Some end users described daily dosing regimens as burdensome or stressful and emphasized nondaily administration as a favorable attribute offering peace of mind and longer intervals of feeling "worry free" (18, 19, 38, 40, 50, 51). They also noted potential adherence challenges with daily dosing regimens, describing that daily stressors or unexpected events could interfere with routines (40, 51). Other end users raised concerns about long-acting products with infrequent dosing such as forgetting to re-administer products at the appropriate time, particularly user-controlled methods that required vaginal insertion monthly (6), and unknown health impact of long-acting product use (6, 51). A smaller proportion of end users noted that event-driven dosing was an appealing option for people who engaged in infrequent sexual activity (29, 42). End users who engaged in vaginal sex more frequently had lower preference for a product administered before sex, whereas end users who engaged in less frequent sex had lower preference for a product administered daily (26).

3.2.5. Side effects

End user perceptions of, and experiences with, side effects such as pain and menstruation were varied. The available data indicated that although some end users had concerns about side effects of potential active MPTs, most end users discussed pain and discomfort with product administration more frequently and saliently than drug-related side effects. For example, end users discussed fear of painful MPT placement or administration within research about injectables, implants, and rings (6, 30, 43, 45).

Overwhelmingly, end users preferred products that did not alter their menstrual cycles (6, 29, 35, 40, 42), although some preferred lighter menses (39). Additionally, end users had mixed opinions about using a vaginally-administered product during menstruation, with some noting a dislike of the idea of inserting a product while menstruating; others had concerns about product displacement or reduced efficacy during menstruation (25, 31). Additionally, end user concerns about drug-related side effects were minimal but were mentioned by end users in research related to tablets and the microarray patch (30, 51). In a market research study with women in Uganda, Nigeria, and

South Africa, country-level differences were found in tolerance of side effects, with more participants in Uganda finding a wide range of side effects (e.g., migraines, menstrual irregularities, nausea) to be unacceptable compared with participants in South Africa and Nigeria (29).

3.2.6. Fertility

Effects of MPT use on fertility and product-related preferences to facilitate return to fertility were explored infrequently in the reviewed articles. This topic was largely examined within studies on nanofiber fabric and implants and constituted one of the attributes included in MTN 045/CUPID, which included vaginal film/inserts, vaginal ring, and oral tablets (24, 29, 31, 42, 45). Some end users expressed preferences for MPT products that allowed for flexibility in contraception administration or similarly noted that lack of flexibility in contraception coverage was a limitation of specific methods (31, 45). For example, end users were highly interested in an MPT implant with a distinct contraceptive implant component that could be removed in the event of a desire to return to fertility. Some end users expressed concerns about long-term MPT use affecting fertility and fetal development (52). Overall, a range of preferences (immediate, 3 months, 6 months) regarding return to fertility following product discontinuation were found in MTN 045/CUPID, with this attribute not significantly influencing product choices. Zimbabwean women preferred a more immediate return to fertility as compared with Ugandan women who regarded a longer return to fertility as an extended benefit of the product following discontinuation (42).

3.2.7. Impact on sex

Across most studies, female participants revealed a preference for products that did not interfere with sex or sexual pleasure for their male partners (6, 23, 24, 31, 34, 37, 38, 40, 51). Consequently, participants were initially disinterested in products (ring, diaphragm, fabric) that would be inserted into the vagina, could potentially change vaginal dryness or wetness, or become dislodged during sex. However, acceptability and ratings for vaginally inserted products increased after participants had the opportunity to learn more about the product or try the product (6, 23, 24, 31, 42, 51). Lack of interference with sex was described as a positive attribute for products (injectable, tablet) that could be taken before an encounter as they would make participants feel prepared and limit the opportunity for partners to notice or stop product use (29, 51). The effects of an MPT product on the sexual experience was explored extensively in studies where women used study products serving as MPT proxies, such as placebo versions in TRIO, and in research on the diaphragm and gel (23, 34). The impact on sex was explored minimally in relation to the nanofiber fabric and in non-TRIO general MPT research.

Overwhelmingly, end users preferred products that improved the sexual experience, did not alter the vaginal environment, or did not interfere with sex (6, 31), a sentiment echoed among end users' male partners (24, 51). Similarly, the expected or actual interference with sex was described as a barrier to product acceptability and use (37), whereas perceiving a product to have a limited influence on sex was associated with more favorable overall acceptability ratings (34, 38). However, some variations in preferences were found by country setting. For example, MTN-045/CUPID found that while participants in Zimbabwe preferred products that did not influence the vaginal environment, participants in Uganda preferred a product that increased vaginal wetness during sex (42).

3.2.8. Delivery, packaging, messaging

Few studies examined end user's preferences for MPT distribution and delivery. In studies that did examine this question, women generally indicated a preference for receiving MPT products through a government health facility or with an official prescription (25, 32). Additionally, when asked to select the one attribute that most influenced acceptability in research with former TRIO participants and product-naïve end users, almost one-quarter of participants selected distribution location (40). Participants reported that over-the-counter availability would increase MPT acceptability and uptake and that education and information on MPT product options should be readily available at health clinics to be integrated into contraceptive and HIV prevention decisions (29, 45). In qualitative research with TRIO participants, end users emphasized the importance of community sensitization and dispelling misperceptions about MPTs as essential components of MPT introduction (6). End users also called for opportunities to try MPT delivery forms, particularly those that may be novel, before deciding to use a particular product (6).

Among studies reporting on design and packing preferences for MPTs, participants suggested "feminine" or "sexy" packaging to make MPTs look appealing, similar to existing branding approaches for menstrual products (6). A few studies stressed the importance of packaging being discreet, small, and nonmedical, such as face powder, chocolate box, lip gloss tube, or snuff boxes (6, 20, 47). The nonmedical preference was particularly important for tablets because participants wanted to avoid the stigma of MPT tablets being confused with ARV tablets (6, 20, 47). Opinions were mixed on whether MPTs should equally emphasize pregnancy and HIV prevention in their packaging, rather than only one indication. Some participants believed that emphasizing only pregnancy prevention might be more discreet, amenable for wary male partners, and a way to avoid HIV-related stigma or assumptions of infidelity (20, 24, 45, 47).

Participants suggested several MPT benefits to emphasize in future MPT messaging, including dual protection, women's empowerment, enhanced sexual pleasure, and increased safety and control over sexual and reproductive health for women (6, 20, 29, 47). Community sensitization was reported as essential for the rollout of any future MPT product to dispel misperceptions about MPTs and for individuals to ask questions (6, 18, 20, 45). One study specifically noted that for an MPT to be acceptable in the community and within relationships, it must be available for everyone, and it must be extremely public, which is similar to the rollout of voluntary male medical circumcision (20).

3.3. Social factors findings

3.3.1. Partners

Women's views of male partner MPT acceptability varied across studies. In some studies, participants were hesitant to use MPTs because of potential negative reactions from male partners and the potential impact on men's sexual pleasure. Expectations of negative reactions were based on previous negative experiences in disclosure of HIV prevention or contraceptive use and a preference to avoid conversations about HIV prevention. In some instances, male partners were distrustful of their partners for concealing or delaying disclosure of study participation or they assumed that using HIV prevention methods meant the female partner was promiscuous and engaging in other sexual relationships (6, 20, 21, 24, 36, 40, 50, 51). Participants also were wary that male partners would not approve of vaginally inserted products or products that interrupted the sexual encounter because they might change the vaginal environment and decrease sexual pleasure for men (6, 24, 31, 39–42). Some participants indicated that negotiating MPT use with male partners may be easier than negotiating use of separate HIV and pregnancy prevention methods, particularly if they could omit the HIV prevention benefits component with MPTs (24, 52). Additionally, participants noted that it would be easier to explain away MPTs with known delivery forms such as a tablet or injectable, as compared with novel MPT delivery forms, such as the ring, implant, fabric, or insert (18, 40). Despite these concerns regarding disclosure, and a preference for a product that a partner would not notice during sex, women commonly indicated that they would tell a primary partner they were using a product even if it could be used without partner detection; as found, for example, among two-thirds of women in Zimbabwe and South Africa participating in the Quatro study (26).

Male partner's views on MPT acceptability also varied across studies. Some male partners could acknowledge the benefits of MPTs for HIV and pregnancy protection but were concerned with limiting potential MPT side effects that impacted sexual pleasure (such as vaginally inserted products and changes in menstruation and wetness) and female partners using products discreetly (24, 42, 51). Other male partners were supportive of women using MPTs and acknowledged the personal benefits of MPTs to them, expressed concern about product adherence, and had more positive views of products that women could more easily use with consistency (24, 51). Participants enrolled in a couples MPT study described that the process of discussing and selecting a hypothetical ideal product together as a couple resulted in greater satisfaction with their chosen product because it built trust and communication and allowed individuals to focus on the interests of the couple over that of the individual (24, 42).

3.3.2. Healthcare providers

End user perspectives on healthcare provider impact on MPT acceptability was infrequently assessed. Health care providers were generally seen as an important and trusted source of information, although there were some region-level differences in these perspectives (29). For novel or unfamiliar products, end users expressed a strong desire for counseling from health care providers to ensure they received adequate support on product administration and use (25, 47). For products designed to be user-controlled or that could be self-administered, such as the microarray patch, women considered self-administration acceptable and expressed a desire to first receive instruction from a health care provider (30). Some end users expressed concerns about health care providers' stigmatizing attitudes toward those who used MPTs, particularly young women and married people (21, 25, 45).

Health care provider perspectives on MPT products were frequently product specific. However, providers generally expressed positive attitudes toward MPTs and perceived them as innovative approaches that could empower women, reduce unplanned pregnancies, and reduce new HIV infections in their communities (21, 27, 33). In considering health systems factors, health care providers noted that MPTs could provide efficiencies in reducing frequency of clinic visits and improving accessibility (21). Some providers noted advantages of reduced burden in frequency of women's interactions with the healthcare system tied to use of self-administered delivery forms like the microarray patch and long-acting delivery forms such as implants (30, 45). However, other providers noted that regulatory requirements could mean that products may only be available in regulated dispensaries, which could reduce accessibility (25).

3.3.3. Community stakeholders

Few studies examined how community stakeholders impacted MPT acceptability and uptake potential. Stakeholders and policymakers acknowledged the benefits of overall MPTs and reported that their development (such as the ring or patch) could be particularly useful for AGYW (22, 28). Some participants were wary of the potential HIV-related and sexual activity related stigma that would coincide with using an MPT product (such as a tablet or diaphragm), particularly if it looked like ARV medication or was advertised as an HIV prevention product rather than a dual-indication product or pregnancy prevention product (6, 20, 21, 34, 47, 51). Participants and providers both suggested community sensitization and provider forum sessions to decrease MPT-related fears and stigma, particularly among men (6, 18, 20, 45). In one study, some participants noted that religious prohibition of the use of contraception could be a potential barrier in their communities to fabric acceptance and uptake (31).

4. Discussion

The present scoping review synthesizes existing research on MPTs that was conducted amongst women of reproductive age in SSA and their male partners, healthcare providers, and community stakeholders. The aim of the review was to identify factors that are important for optimizing the likelihood of MPT acceptability and future adoption by end users in the region. Overall, there was a strong interest amongst women and healthcare providers for an MPT that simultaneously addresses HIV and pregnancy prevention. However, due to changing reproductive needs throughout the life course, women valued MPTs as an additional option to add to the existing (and growing) range of HIV and

pregnancy prevention options. Though women and health care providers often preferred long-acting MPTs, there was considerable variation by product familiarity and form, as well as study population. Unfamiliarity with novel delivery forms, particularly with forms that were vaginally administered, was an initial barrier across most studies but was often addressable through counseling and experience trying a product. The ability to use an MPT discreetly – through its physical design, attributes, and administration—was one of the most salient topics for end users and was more frequently examined in the existing literature compared to other MPT factors such as side effects, fertility, and impact on sex. Importantly, current knowledge about end user preferences for MPTs is largely based on end user experience with placebo or hypothetical MPT products and there is potential for MPT acceptability, attitudes, and adoption experiences to considerably vary after end users have access to active MPT products and experience side effects tied to each indication.

The integration of HIV prevention and contraceptive services that an MPT could afford was cited by women and health care providers as a critical advantage. Healthcare providers reported that MPTs could potentially provide efficiencies in reducing clinic burden, frequency of clinic visits, and adherence challenges among women. End-users indicated a strong preference for MPTs to be available through family planning service settings to de-medicalize HIV prevention. Several studies have highlighted the importance of examining models to achieve this through dual provision of existing HIV and pregnancy prevention services such as HIV testing, PrEP, and contraception (55). However, implementation science-oriented evidence relevant to integration of MPTs into health delivery systems is sparse (e.g., training needs, cost, and effective counseling and decision-making models for end-users, the male partners, and their community members) (56). Future research to explore these domains is necessary not only for eventual MPT delivery but also for dual delivery of existing single indication prevention options.

In general, most women preferred longer-acting MPTs (one month or more, depending on delivery form), because they were perceived to reduce user dosing burden and allow for more discreet use. This finding aligns with SSA-based studies that have reported adherence challenges with daily use of oral PrEP (57, 58) and was echoed in the Share.Learn.Shape study that indicated increased interest in long-acting methods (specifically implant, ring and injection) among women in low- and middle-income countries compared with those from high-income countries (59). Providers likewise recognized advantages of longer-acting MPT options in reducing demands on the health care system; however, research with providers is limited and largely drawn from small qualitative studies. The classification of "longer-acting" was conceptualized differently depending on whether products were delivered vaginally or via implant. Yet, the longest duration examined, was often, but not always, the most preferred. In many studies there consistently remained a subset of women with an interest in on-demand MPT options that afforded user control and flexibility. The contraceptive model of providing a method mix with provider-administered longer-acting reversible contraceptives alongside user-delivered, shorter-acting methods has been important in increasing family planning product adoption and use (60). The model also offers a uniquely relevant and compelling strategy for conceptualizing development of multiple MPT options.

Familiarity with the MPT delivery form prominently influenced initial acceptability with the strongest evidence derived from DCE and placebo clinical studies. This was particularly evident in the preference for injectables among those with injectable contraceptive experience. A review of values and preferences informing contraceptive use highlighted a similar finding that familiarity was a primary factor in decision-making among contraceptive options (61). However, multiple clinical studies signaled that lack of familiarity can be addressed and, importantly remained an interest in new delivery forms across studies (29, 40, 42). Both the TRIO and Quatro MPT and HIV placebo clinical studies underscored that with increased opportunity to use and gain experience with novel vaginally-administered products, acceptability ratings for products increased over time (38, 54). User experience with placebo microneedle patch likewise increased acceptability of an otherwise unfamiliar MPT delivery form (30). Research focused exclusively on HIV prevention also reflects the influence of use experience on increasing acceptability; in the REACH Study, two-thirds of adolescent girls and young women chose to use the dapivirine vaginal ring (an initially unfamiliar product) for HIV prevention after using the ring and oral PrEP for six months each (62). Taken collectively, familiarity with delivery form may facilitate earlier adoption for many women but education and use experience can increase acceptability for novel delivery forms.

An important partner-related consideration is how an MPT may help women overcome male partners' resistance to their use of an HIV prevention product by positioning the method as a contraceptive, first and foremost, and de-emphasizing implications of sexual fidelity and risk behavior. This consideration was infrequently examined as was the degree to which the availability of a range of MPTs will increase adoption or influence use of contraceptive methods. However, women in MTN 045/CUPID noted these advantages as did health care providers in TRIO, pointing towards the importance of marketing and communications materials related to MPTs. In several other studies, women reported that MPT packaging should emphasize pregnancy prevention instead of HIV, for acceptability reasons associated with privacy and discretion to partners and other individuals in their social network (20, 45, 47). Across the MPT research, whether conducted with women alone, or those that included men and male partners, there is strong evidence of the important role that partners assume in shaping women's MPT preferences and acceptability by indirectly influencing women's perceptions of product attributes and directly influencing women's decision-making. For women coupled with casual or unsupportive partners, potential use of MPTs without a partner's detection was regarded as valuable, and products with non-daily dosing, clinic-based administration, and undetectability during sex were important as their characteristics might contribute to this goal. Including opportunities for male partner involvement in MPT development and delivery, while preserving women's agency to use products

independently, may ultimately address many of the discreetness considerations and increase MPT adoption.

Given that most MPTs in the pipeline are in pre-clinical development, most studies assessed preferences through presentation of hypothetical product descriptions, images, or product models. While the existing body of research offers important findings to inform early product development and to iterate designs, very few studies report on research in which women used placebo or active MPT products. This evidence base reflects the state of the field where few MPT products have yet been evaluated in clinical studies. Although preferences derived through DCEs have been shown in other areas of health research to correlate with choices among actual prevention options (63), the extent to which the findings synthesized in this review will ultimately reflect end users' actual use experiences and the trade-offs they may be willing to make to achieve dual protection with an active MPT product is unknown. Thus, it remains important to include robust social behavioral and end-user research as part of the MPT research agenda, particularly to conduct studies with novel placebo delivery forms to refine their design and understand user experiences and factors influential to acceptability of new MPT products, particularly related to side effects. Research with active pharmaceutical ingredients (API), be they with contraceptive or HIV prevention indications, provide strong evidence for the importance of the impact of side effects on user experience and acceptability. Side effects, whether actual or perceived, are often a primary reason for contraceptive method switching (64). For example, in a cohort study examining contraceptive discontinuation and switching among Kenyan women, lack of expected menstrual bleeding was associated with method switching and multiple side effects, including sexual side effects, irregular bleeding, weight changes, and increased rates of method discontinuation (65). Thus, although several studies included in this review provided evidence that side effects were important to women's preferences, we anticipate that side effects and implications on timing of return to fertility could emerge as more important factors when MPT products are examined in clinical trials. Likewise, given the importance of discretion, examining whether and how women are able to use products discreetly, will be critical as we move from hypothetical studies to clinical trials of MPT products and ultimately MPT introduction.

The literature synthesized for this review has several important limitations and gaps. First and foremost, the breadth and rigor of the available research on end-user preferences for single indication HIV and pregnancy prevention options are abundant, but sparse when specifically about dual indication MPTs. Despite extending our search to include conference abstracts, grey literature reports, unpublished research obtained through personal communication with subject matter experts, and research databases—our review yielded only 37 references. Furthermore, many of our references (59%) reported results of qualitative research where hypothetical or placebo MPT options were considered, and a substantial proportion of the of the articles (30%) reported data from the TRIO study. Second, the generalizability of findings must consider the heterogeneity of women in the SSA region. Most of the evidence in this review comes from end users in South Africa, Kenya, and, to a lesser extent, Zimbabwe. In addition, the majority of studies were conducted in urban or peri-urban areas and included women who would be most likely to access care in public health and research clinic settings, resulting in very limited perspectives from end users living in peri-urban and rural areas and other countries in SSA. Further, women who join research studies, and studies that cover novel biomedical methods may have different individual- and relationship-level characteristics than those who do not enroll. In addition, few studies included cross-country comparisons. The lack of diversity in research populations and settings, and limited cross-country comparisons, warrants careful consideration of the end users that have contributed to this evidence, and the broader potential populations of MPT users across sub-Saharan Africa. It also highlights the importance of conducting multisite and multi-country clinical trials and research studies for future active MPT products. Third, most of the peer-reviewed and grey literature is focused on overall acceptability of MPTs. Based on frequency of mentions in this literature, discretion and partner engagement are salient considerations to MPT acceptability, and findings echo those from HIV prevention and contraceptive choice research. Additionally, acceptability is a nuanced construct to assess in end-user research with MPTs. This is due to an array of factors including the diversity of end user experiences, lack of consensus on how to best assess acceptability, and nuanced relationships between acceptability and compliance and adherence. In a clinical trial setting, acceptability data are also subject to social desirability bias, and to complexities whereby an "acceptable" product in a trial setting may not translate to a product that end-users will prefer and use consistently in a real-world circumstance. However, there remains opportunity to further consider how to effectively engage men and couples throughout the MPT product development pipeline. MPTs' impacts on sex, including on sexual pleasure, are explored to some extent, although more research, with actual and placebo delivery forms, may be needed to understand the diversity of end user preferences. Very little research has been conducted with providers and other community stakeholders, limiting our ability to characterize their views in a rigorous and substantive manner.

5. Conclusion

The present scoping review of end-user preferences and acceptability for MPTs underscores women's strong interest in MPTs and the importance of multiple MPT options. Recognizing the heterogeneity of women's preferences, and within women, changing needs for HIV and pregnancy prevention over their reproductive life course and relationships, the central concept of "choice" should be understood and integrated in multiple ways. For example, choice includes offering MPTs within delivery of family planning and HIV prevention services, as well as choice among MPTs with distinct product profiles. However, current knowledge about end user preferences for MPTs is largely based on end user experience with existing single indication HIV prevention and

contraceptives or studies that used placebo or hypothetical MPT products. Conducting research where end user experience with active products can be evaluated stands to advance understanding of end-user preferences and acceptability for MPTs.

Author contributions

The review was led by AMM and NLB, with scientific contributions to design by ETM. NLB and KR assumed primary responsibility for reference review and data extraction. Synthesis of data and summarizing in memos was conducted by NLB, KR, and EHL. All authors (NLB, KR, EHL, TPP, ETM, and AMM) contributed to manuscript development and review. 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. The reviewer MB declared a shared affiliation with the author TPP, to the handling editor at the time of review.

Publisher's note

Supplementary material

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Commentary: Multipurpose prevention technologies—What about sexually transmitted infections?

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KEYWORDS

sexually transmitted infections, multipurpose prevention technology, gonorrhea, chlamydia, syphilis

Introduction

Over the past decade, developers have made advances in addressing sexual and reproductive health (SRH) needs through multipurpose prevention technologies (MPTs)—products designed to simultaneously prevent HIV, Sexually transmitted infections (STIs), and/or unintended pregnancy (1). Multiple studies have demonstrated users' preference for methods that prevent pregnancy alongside HIV and/or STIs rather than a single indication (2–7). While there are limitations to interpreting results from hypothetical use studies, it is intuitive that individuals would prefer a product that offers multiple benefits. By leveraging contraceptive priorities, MPTs provide a potential solution to known challenges such as ongoing low uptake of HIV pre-exposure prophylaxis (PReP) (8) while reducing the stigma of prevention (5, 9–11).

The majority of MPTs under development incorporate HIV prevention (**Figure 1**) (12) consistent with stakeholder prioritization and funding allocation. U.S. government research funding for HIV/AIDS totaled $1.4 billion dollars in 2018, dwarfing funding for all other STIs and contraception combined (**Table 1**) (13). This heavy focus on HIV has been appropriate given the large global costs and burden. Global HIV infection causes 47.63 million DALYs in 2019, compared to an estimated 8.58 billion global DALYs accounted by non-HIV STIs (14). With recent promising advances in HIV treatment and prevention, MPT initiatives and appropriate funding must now shift to advance more products preventing non-HIV STIs to curb the growing STI epidemic.

Why do we need to care about STIs?

Non-HIV STIs account for 98% of all prevalent STIs worldwide (15, 16). In 2016, the World Health Organization (WHO) estimated there were 376 million new infections of four curable STIs: chlamydia (127 million), gonorrhea (87 million), syphilis (6 million), and trichomoniasis (156 million) (15). Viral STIs such as genital herpes simplex virus (HSV) and human papilloma virus (HPV) also have notably been increasing in prevalence (15). In the U.S. alone, 2.4 million new cases of chlamydia, gonorrhea, and syphilis were reported in 2020 despite underreporting and reduced access to screening during the COVID pandemic (17). Despite global efforts to combat STIs, infections are at an all-time high and cost $2 billion in treatment annually (18, 19). Untreated, STIs have

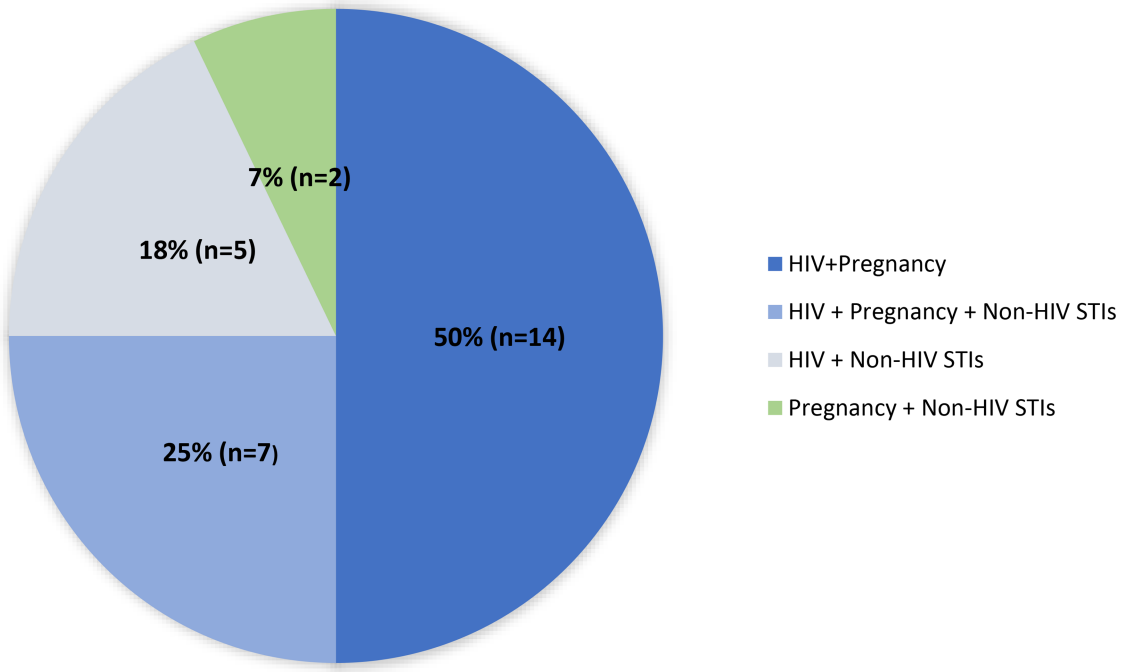

FIGURE 1
Multipurpose prevention technologies by indication (n = 28). Adapted from "MPT Pipeline by Indication Combination" by MPT 101, 2023 (https://mpts101.org/wp/wp-content/uploads/2023/01/MPT-Pipeline-Table_The-IMPT-Dec-2022_Indication-Combination.pdf). Copyright by IMPT for Reproductive Health. [Accessed January 29, 2023].

TABLE 1 Sexual and reproductive health research & development funding (US$ million) (2018).

Health issue	Funding (US$ million)
HIV/AIDS	1,442
STIs—excluding HPV	71
Contraception	64
Multipurpose prevention technologies	48

Source: G-finder global investment survey, 2020. Policy cures research. (https://gfinder.policycuresresearch.org/). [Accessed January 29, 2023].

broad-reaching health impacts ranging from increased risk of HIV acquisition, cancer, chronic pelvic pain, infertility, preterm delivery, and neonatal morbidity and mortality (15). Many infections may be asymptomatic and go undiagnosed. Even when identified, treatment may be complicated by challenges such as medication shortages, emerging antibiotic resistance, and reinfection after inadequate partner treatment (20–23). Adverse health impacts and barriers to diagnosis and treatment make renewed dedication to STI prevention strategies critical.

Non-HIV STIs are inextricably linked to HIV and contraception. Infection with some STIs such as HSV, chlamydia and gonorrhea may increase the risk of HIV acquisition (24, 25). Use of certain contraceptives may be associated with increased acquisition of chlamydia and HSV (26, 27). While some of these findings may be linked to more frequent access of diagnostic services, biological plausible mechanisms for altered risk exist (28, 29). As the linkages expand beyond epidemiologic and behavioral sexual risk factors, developers have an enhanced imperative to develop overlapping prevention tools.

Current and emerging tools for STI prevention

While not universally available, the global market for HIV prevention includes medications taken pre- or post-exposure with different formulations including daily pill, long-acting injectables and vaginal rings (30–32). Prevention for other STIs still largely relies on promoting healthy sexual behaviors and barrier method use—traditional approaches that have been inadequate in curbing rise in infections (33). The current STI prevention pipeline leans heavily on vaccine development. While there are only two vaccines currently on the market, both of which act against viral STIs (Hepatitis B and HPV) (21), several vaccines in development offer hope for broader protection. Several MPTs are integrating non-vaccine prevention methods, however these are mostly in the preclinical stages. Promising options currently being explored for STI prevention include the recently FDA approved on-demand vaginal pH modulator (VPM) Phexxi® (34) and doxycycline as a possible pre- or post-exposure bacterial STI prophylaxis (35, 36).

Triple protection MPTs with broad pregnancy, non-HIV STIs, and HIV prevention make up about a quarter of all MPTs in development (**Figure 1**) (12). Advancing triple-indication products would align with the overlapping risks faced by many people around the world (37) and simultaneously confront concerns of risk compensation. Risk compensation theorizes that individuals who use STI prevention methods might engage in high-risk sexual behavior such as condomless sex and increased number of sexual partners. Although it is unclear to what extent risk compensation occurs, this potential raises concern that use

BOX 1 Recommendations for future MPT product development.

Resources
• Continue to escalate investments for MPTs indicated for non-HIV STIs
• Engage legislators, policymakers, and investors who are interested in non-HIV STI prevention given the large potential market in developed countries, but who have not yet partnered with MPT development
• Seek non-traditional funding sources such as from impact investors and Corporate Social Responsibility
Research
• Expand STI prevention toolbox to diversify biomedical modalities beyond vaccines
• Strengthen research on current lagging topics such as nonviral STIs, antibiotic resistance and medication shortages
• Connect researchers working on non-HIV STI prevention with those working on contraception and/or HIV prevention
• Ensure MPTs under development represent a breadth of options to suit the needs of diverse users (e.g., with and without pregnancy prevention, hormonal and non-hormonal, ARV and non-ARV, on-demand, short acting, and long acting, user-controlled and provider initiated).
• Conduct studies to determine market size for non-HIV STI prevention in developed countries to support the business case for investment
Regulation
• Develop streamlined processes for regulatory approval of products with multiple benefits
• Ensure surveillance systems are in place to monitor the impact of new prevention technologies on STIs

of a prevention method for one STI might contribute to increasing rates of other STIs (38). Monitoring MPTs' impact on other STIs is critical as newer methods enter the market. As it is unlikely there will be one method that protects against all STIs, a diverse range of MPTs must be developed to enable individuals to prioritize STIs that are highly prevalent in their community.

Discussion: a call to action

Efforts to counter the STI epidemic through MPTs rely on several key actions listed in Box 1. Exciting novel MPTs indicated for non-HIV STIs are already making their way through the development pipeline. Critical to success in the fight against STIs is momentum in R&D activities. This requires engaging researchers who are already focused on non-HIV STI projects as well as funders and impact investors who may be interested given their large potential market in developed countries, but who have not yet partnered with MPT developers. A key challenge to advancing these products is also ensuring that the regulatory environment facilitates approval of multipurpose prevention. The development of regulatory processes tailored specifically for the approval of MPTs will accelerate expansion of the STI prevention toolbox. With the traditional regulatory framework, multiple costly Phase 3 trials can be a barrier to advancing some indications, leading to the potential risk of secondary benefits not obtaining regulatory approval. As products advance, acknowledging that users value product characteristics other than effectiveness may open avenues for a broader array of options that address users' needs. Ultimately, advancing MPTs indicated for non-HIV STIs will allow more individuals to achieve their sexual and reproductive health goals.

Author contributions

AL and LH: jointly drafted the manuscript and equally contributed to the writing and review. 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.

Publisher's note

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Randomized controlled phase IIa clinical trial of safety, pharmacokinetics and pharmacodynamics of tenofovir and tenofovir plus levonorgestrel releasing intravaginal rings used by women in Kenya

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Introduction: Globally, many young women face the overlapping burden of HIV infection and unintended pregnancy. Protection against both may benefit from safe and effective multipurpose prevention technologies.
Methods: Healthy women ages 18–34 years, not pregnant, seronegative for HIV and hepatitis B surface antigen, not using hormonal contraception, and at low risk for HIV were randomized 2:2:1 to continuous use of a tenofovir/levonorgestrel (TFV/LNG), TFV, or placebo intravaginal ring (IVR). In addition to assessing genital and systemic safety, we determined TFV concentrations in plasma and cervicovaginal fluid (CVF) and LNG levels in serum using tandem liquid chromatography-mass spectrometry. We further evaluated TFV pharmacodynamics (PD) through *ex vivo* CVF activity against both human immunodeficiency virus (HIV)-1 and herpes simplex virus (HSV)-2, and LNG PD using cervical mucus quality markers and serum progesterone for ovulation inhibition.

Results: Among 312 women screened, 27 were randomized to use one of the following IVRs: TFV/LNG ($n = 11$); TFV-only ($n = 11$); or placebo ($n = 5$). Most screening failures were due to vaginal infections. The median days of IVR use was 68 [interquartile range (IQR), 36–90]. Adverse events (AEs) were distributed similarly among the three arms. There were two non-product related AEs graded >2. No visible genital lesions were observed. Steady state geometric mean amount (ssGMA) of vaginal TFV was comparable in the TFV/LNG and TFV IVR groups, 43,988 ng/swab (95% CI, 31,232, 61,954) and 30337 ng/swab (95% CI, 18,152, 50,702), respectively. Plasma TFV steady state geometric mean concentration (ssGMC) was <10 ng/ml for both TFV IVRs. *In vitro*, CVF anti-HIV-1 activity showed increased HIV inhibition over baseline following TFV-eluting IVR use, from a median of 7.1% to 84.4% in TFV/LNG, 15.0% to 89.5% in TFV-only, and −27.1% to −20.1% in placebo participants. Similarly, anti-HSV-2 activity in CVF increased >50 fold after use of TFV-containing IVRs. LNG serum ssGMC was 241 pg/ml (95% CI 185, 314) with rapid rise after TFV/LNG IVR insertion and decline 24-hours post-removal (586 pg/ml [95% CI 473, 726] and 87 pg/ml [95% CI 64, 119], respectively).
Conclusion: TFV/LNG and TFV-only IVRs were safe and well tolerated among Kenyan women. Pharmacokinetics and markers of protection against HIV-1, HSV-2, and unintended pregnancy suggest the potential for clinical efficacy of the multipurpose TFV/LNG IVR.
Clinical Trial Registration: NCT03762382 [https://clinicaltrials.gov/ct2/show/NCT03762382]

KEYWORDS

intravaginal ring, multipurpose technology, tenofovir, levonorgestrel, HIV, HSV-2, Africa

1. Introduction

Women accounted for 49% of the estimated 1.5 million new HIV infections in 2021 a majority of whom reside in sub-Saharan Africa, where girls and women represent 63% of new HIV infections (1). Globally, 64% of the estimated 0.5 billion persons infected with herpes simplex virus (HSV-2) are women (2–4). Human immunodeficiency virus-1 (HIV-1) and HSV-2 have a synergistic relationship, with a two-fold increased risk for HIV among HSV-2 infected persons (5). In sub-Saharan African countries with endemic HIV, adolescent girls and young women aged 15–24 years account for 24% of incident HIV infections although they comprise only 10% of the population (5). In the United States and other Western countries, an estimated 19% of incident HIV infections occur among women, with 85% of these attributed to heterosexual transmission (6). Concurrently, pregnancy related complications remain the leading cause of death among girls aged 15–19 years in low-income countries, with approximately 10 million unintended pregnancies each year in this age group (7). Young women face triple epidemics of HIV, unintended pregnancy and HSV-2 infection.

Multipurpose prevention technologies (MPTs) aim to simultaneously meet sexual and reproductive health needs, including prevention of unintended pregnancies, HIV infection, and other sexually transmitted infections (STIs) with a single product. Therefore, MPTs have the potential to provide significant reproductive health benefits to women globally (8). Market research has demonstrated that women in sub-Saharan Africa would prefer MPTs conferring protections against both HIV and unintended pregnancies instead of separate methods (9). Long-acting, female-controlled MPT interventions have the potential to overcome barriers that limit use of existing preexposure prophylaxis (PrEP) products, such as adherence, stigma, lack of privacy for storing products, and perception of HIV risk (10). Findings from a recent systematic review of intravaginal ring (IVR) acceptability and preference among women in low- and middle-income countries reported that women expressed a preference for accessible, long-acting products that can be used covertly without partner knowledge and with few side effects (11).

CONRAD, a non-profit biomedical research and development organization, developed two 90-day controlled-release IVRs containing tenofovir (TFV) alone (TFV-only) or TFV/levonorgestrel (LNG), which were both similar in appearance to the contraceptive NuvaRing® (12, 13). The CONRAD A13–128 trial evaluated both IVRs for safety, pharmacokinetics (PK), pharmacodynamics (PD) and drug release with 15-day use among healthy, sexually-active, low-risk women in the United States and the Dominican Republic (14). Both IVRs were found to be safe, with vaginal TVF concentrations above 100,000 ng/ml, higher than the 489 ng/swab estimated threshold for HIV prevention (15). LNG plasma concentrations among TFV/LNG IVR users were above the 240 pg/ml threshold for systemic LNG contraceptive efficacy and cervical mucus Insler score with abnormal sperm penetration (14). Building on these results, we assessed the TFV-releasing IVRs with and without LNG during up to 90-day use for safety, PK, and PD in a study among women in Western Kenya.

2. Materials and methods

CONRAD Protocol B17–144 was a single site, phase IIa randomized, partially blinded, placebo-controlled clinical trial conducted at the Jaramogi Oginga Odinga Referral Hospital,

Center for Global Health Research clinic, Kenya Medical Research Center (KEMRI), Kisumu, Kenya from December 14, 2018, to August 20, 2019. Institutional ethics review boards of KEMRI and the University of Washington reviewed and approved the study protocol. The protocol was registered in Clinicaltrials.gov (NCT03762382) and implemented in accordance with Good Participatory Practice guidelines, with engagement of a local community advisory board. Participant safety oversight was provided by a safety monitoring committee. Written informed consent was obtained from all participants prior to undertaking any study procedures.

Eligible women were aged 18–34 years; not pregnant; seronegative for HIV and hepatitis B surface antigen (HBsAg); ovulating (based on home use of an ovulation prediction kit) followed by confirmatory luteal phase serum progesterone (P4) ≥3.0 ng/ml; had a body mass index ≤30 kg/m^2; scored ≤4 on a validated HIV risk scoring tool (predicted HIV incidence <3.95/100 person-years for women in sub-Saharan Africa) (16); and were not using or desiring to use PrEP and not planning to be pregnant during the study period. Prior to enrollment, women must have stopped using oral contraceptive pills for ≥2 months, injectable contraceptives for ≥4 months, or a contraceptive implant for ≥6 months. Prior use of contraceptive was assessed through self report, serum progesterone at screening visit and LNG detection in a blood sample collected prior to IVR insertion. Eligible women were provided with non-spermicidal condoms and copper intrauterine device (IUD) for contraception. Women who chose to use copper IUD had a two month wait period between IUD insertion and study IVR randomization and insertion. Women were ineligible if they had any pelvic abnormalities or were diagnosed with an STI. Screening of participants included testing for *Chlamydia trachomatis, Neisseria gonorrhoeae, Trichomonas vaginalis*, candidiasis (based on wet mount), bacterial vaginosis (BV) diagnosed using Nugent scoring or Amsel's criteria and syphilis (17). Women diagnosed with BV received treatment and were re-assessed for eligibility.

2.1. Study schedule and randomization

Study participants had up to 13 scheduled study visits arranged outside of days with menstruation. Participants were scheduled to use the IVR for 90-days or until August 20, 2019, to coincide with the expiry date of the IVRs. IVR insertion was scheduled in the follicular phase of the menstrual cycle and confirmed by measuring luteal phase serum progesterone prior to IVR insertion at visit three. Participants were randomized 2:2:1 to continuous use of one of the following IVRs: TFV/LNG; TFV-only; or placebo [containing starch instead of active pharmaceutical ingredient (API)]. The randomization scheme was generated using permuted block randomization to ensure balanced arm assignment over the accrual period. The study investigators and clinic staff were blinded to the randomization.

The randomized study IVR was inserted and removed by the study clinician. Participants were instructed to keep the IVR in place for continuous use for the duration of the study. Demonstration of self-insertion and removal was done using a 3-D demonstration model and participants practiced self-insertion and removal using a placebo IVR so they could re-insert the study IVR if it was accidentally or intentionally removed. Adverse events (AEs) were evaluated through clinical history at all visits. At baseline before IVR insertion, post-insertion, 24- hours post-removal and all scheduled study visits in between, the study clinician visually assessed for genital AEs through speculum pelvic exam. During these visits, samples were collected for the following biomedical measurements: TFV levels in cervicovaginal fluid (CVF) collected by vaginal swab during pelvic exam by the clinician; and plasma TFV, serum LNG and serum sex hormone binding globulin (SHBG) levels for PK analyses.

Additional vaginal swabs to characterize the vaginal microbiome, secreted soluble genital tract proteins, and activity against both HIV-1 and HSV-2 (hence forward referred to as anti-HIV and anti-HSV-2 activity) were collected pre-IVR insertion and at IVR removal. Cervical mucus quality assessment using Insler score and P4 levels were done to evaluate for ovulation during the first and third menstrual cycle and timed using urinary luteinizing hormone (LH) (18). Partner involvement and HIV testing for partners was encouraged but not required. Participants were asked to refrain from sexual activities 24 h prior to IVR insertion visit and 48 h prior to the ovulatory assessments.

2.2. Study product

CONRAD developed the two IVRs, which release TFV with or without LNG in a controlled and sustained manner for at least 90 days; pre-clinical product development and initial clinical evaluation have been previously reported (12, 13). The API TFV was supplied by Gilead Sciences, Inc. (USA) and the API LNG was acquired from Industriale Chimica s.r.l. (Italy). Particle Sciences (Bethlehem, PA, USA) manufactured under good manufacturing practice (GMP) conditions and shipped clinical study products (IVRs) to the clinical site packaged in individual re-sealable foil pouches, ready to use. The rings were stored at room temperature (15°–30°C) since they did not require cold chain storage. Each study participant received an IVR containing either 1.15 g of TFV plus 6.0 mg of LNG (estimated daily release doses of 8–10 mg of TFV and 20 µg of LNG), 1.41 g TFV (estimated daily release dose of 8–10 mg of TFV), or a non-eluting placebo IVR. The TFV IVR consisted of a single segment of polyurethane tubing filled with a white TFV-containing paste. The TFV/LNG IVR appearance was similar to that of the TFV IVR except it contained a 2 cm-long solid hydrophobic polyurethane reservoir segment loaded with 6 mg LNG, capped by 2 mm-wide hydrophobic polyurethane spacers welded to the TFV segment. The placebo IVR had the same dimensions and configuration as the TFV/LNG IVR in which the TFV API is replaced by modified starch (that is non-eluting from the reservoir) to provide a similar white filled tube appearance and the short segment consists of solid polyurethane without LNG.

2.3. Safety outcomes

Grade 2 or higher genital and systemic treatment emergent AEs were primary study safety outcomes, including cervicovaginal ulcerations, abrasions, edema, or findings as assessed by naked eye visualization of the cervicovaginal epithelium, including at IVR removal. AEs were also defined by abnormal safety laboratory measurements. AEs were graded and assessed for relationship with use of study product and/or procedures by the study physician. A safety monitoring committee met every two weeks to review AEs. Each adverse event was graded for severity using the July 2017 update of the Division of AIDS (DAIDS) table (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).

2.4. TFV and LNG pharmacokinetic assessment

TFV concentrations were quantified from plasma samples collected at IVR insertion and each visit until 24 h post-IVR removal. A Dacron swab was used to collect genital fluid from the lateral vaginal wall to quantify amount of TFV in genital fluid at baseline before ring insertion and at every visit following IVR insertion. TFV concentrations in plasma and amount on vaginal swabs were determined *via* protein precipitation followed by tandem mass spectrometry (LC-MS/MS) analysis as previously described (19, 20). The lower limit of quantification (LLOQ) of TFV for this study was 10 ng/ml for plasma and 1 ng/swab for vaginal swabs. Assay-specific results with concentrations below the lower limits of quantification were imputed as 1/2*LLOQ. Serum LNG concentrations were measured by the Endocrine Technologies Core at the Oregon National Primate Research Center (ETC ONPRC) with a Shimadzu Nexera-LCMS-8050 liquid chromatography-tandem triple quadrupole mass spectrometry (LC-MS/MS) platform (Shimadzu Scientific, Kyoto, Japan) using a previously published method (21). Briefly, LNG was extracted from samples using supported liquid extraction and LNG concentrations were then determined by LC-MS/MS across two assays. The assay range was 20 pg/ml–10 ng/ml; intra- and inter-assay coefficients of variation were <10%. Free LNG index was computed as the ratio of LNG nmol/L to SHBG nmol/L after converting LNG to nmol/L per molar mass of 312.446 g.

2.5. Pharmacodynamic (PD) assessments

2.5.1. Levonorgestrel PD assessment

We modeled the potential contraceptive efficacy of LNG by assessing several surrogates, including ovulation during IVR use, defined as a serum P4 ≥3.0 ng/ml at months 1, 2, and 3; at IVR removal; and 24 h after IVR removal. Study participants started checking for LH surge on day 10 of the menstrual cycle (after IVR insertion) at home using ovulation prediction kits (OPK) and presented within 12–24 h post LH surge. To evaluate local micro-dose LNG effects, at least two examiners assessed the cervical mucus Insler score on a scale of 0–3 for each factor (Spinnbarkeit, volume, viscosity, cellularity and ferning) with a combined score of 10 or more indicating normal, ovulatory, mid cycle mucus receptive to sperm penetration (18).

2.5.2. Anti-HIV-1 & anti-HSV-2 PD assessment in cervicovaginal fluid

2.5.2.1. Activity against HIV

For CVF activity against HIV-1 (PD), CVF was collected from the lateral vaginal wall using Dacron swabs, which were then frozen until analysis. Testing was performed at the CONRAD Intramural Laboratory at Eastern Virginia Medical School (Norfolk, VA, USA) using the TZM-bl cell line (ATCC: The Global Bioresource Center | ATCC)) as previously reported (22). Briefly, TZM-bl cells were plated and CVF (1:5 or 1:10 final dilution in DMEM/10% FBS/1% penicillin/streptomycin) was applied to the appropriate wells. For toxicity testing, 100 µl of medium with or without CVF were added to each well for 48 h. For antiviral evaluation, Bright-Glo Luciferase Assay System (Promega, Madison, WI, USA) was used following the manufacturer's instructions. Briefly, 100 µl of medium, with or without CVF, containing HIV-1BaL (5×10^3 TCID50) were added to each well. After 48 h, the cells were lysed with 100 µl of Glo Lysis buffer. Lysates (50 µl) were then transferred to a 96 well black microtiter plate and 50 µl of Bright-Glo assay reagent added before luminescence was measured in a BioTeK microplate reader. The average percent inhibition of HIV-1BaL growth in wells exposed to CVF was determined based on deviations from HIV-1 only control. Within the same participant, antiviral activity was further assessed comparing HIV-1 infection in the presence of CVF collected at IVR removal to infection in the presence of baseline CVF.

2.5.2.2. Activity against HSV-2

Using Starplex™ Scientific Starswab II™, CVF was collected from the lateral vaginal wall, frozen and stored at −80°C until processing. Thawed swabs were placed in 300 µl of HEC1A media for 5–10 min, then placed in SpinX insert (MIDSCI, M850003) and centrifuged at 370 g force for 5 min at 4°C to remove all secretions from the swab. To assess the activity of the swab eluent against HSV-2, HEC1A cells (ATCC: The Global Bioresource Center | ATCC) were plated at 200,000/well in a 48 well plate containing McCoy's 5A medium with penicillin/streptomycin. The following day 70 µl of the swab extract were added to the well for a total of 6 h and in the last hour, each well was infected with 200 PFU HSV-2 in 30 µl of media. The treatment/inoculum was removed and 200 µl of fresh media were added. Real-time polymerase chain reaction (PCR) was done on Day 5 using the supernatant to detect HSV-2 DNA and compared to untreated control.

2.5.3. Soluble immune mediators in cervicovaginal secretions

Soluble markers were eluted from CVF collected with Dacron swabs (14). Cytokines interleukin (IL)-1β, IL-6, IL-8, IL-10,

tumor necrosis factor-alpha (TNFα), granulocyte macrophage colony-stimulating factor (GM-CSF), regulated upon activation, normal T cell expressed and secreted (RANTES), interferon-γ-inducible protein 10 (IP-10), macrophage inflammatory protein 1a (MIP-1α), and IL-1 receptor agonist (IL-1 RA) were measured in swab eluents using Luminex technology (25 µl of sample) (Millipore, Billerica, MA, USA). Secretory leukocyte protease inhibitor (SLPI) (R&D Systems, Inc., Minneapolis, MN, USA) and human β defensins 1, 2, and 3 (Alpha Diagnostics, San Antonio, TX, USA) were quantified by commercial enzyme-linked immunosorbent assay and read using a Varioskan LUX multimode microplate reader (ThermoFisher Scientific, Waltham, MA, USA). Soluble markers were reported as concentration per swab.

2.5.4. Residual drug assessments and estimated in vivo drug release rates

Details on analysis of the LNG IVR segment have been previously described (12–14). Used IVRs containing TFV with or without LNG were stored in individual sealed foil packages at −80°C until shipped on dry ice to Lubrizol Health Services (Bethlehem, PA, USA) for evaluation of residual drug (14). IVRs containing LNG segments were cut at the joint between the LNG segment end cap and the end of the sealed TFV segment to isolate the LNG segment.

Analysis of LNG by LC-MS/MS was conducted similar to methods previously described (21, 23). IVR release rates were estimated by subtracting the recovered API concentration result from the average control API recovery and dividing by the number of days of reported use. Serum LNG concentrations were measured by the Endocrine Technologies Core at the Oregon National Primate Research Center (ETC ONPRC) with a Shimadzu Nexera-LCMS-8050 liquid chromatography-tandem triple quadrupole mass spectrometry (LC-MS/MS) platform (Shimadzu Scientific, Kyoto, Japan) using a previously published method (21). The assay range was 20 pg/ml–10 ng/ml; intra- and inter-assay coefficient of variation were <10%. The IVR release rates were estimated by subtracting the recovered API concentration from the reference standard and dividing by the number of days of reported use. In an exploratory descriptive analysis (with a small sample size per group) we examined potential effects of BV-associated microbiota on TFV released and estimated release rates.

2.5.5. Placebo IVR assessment

CONRAD Intramural laboratories assessed placebo IVRs for visual appearance as well as glycerin content to determine duration of use. At the time the IVR is inserted in the vagina, glycerin, an excipient in the TFV paste contained within the ring, is released in a time-dependent manner until most of its content is exhausted. Residual glycerin content, therefore, may be used as a marker indicating lack of use or low adherence (23).

2.5.6. SHBG assessment

Plasma samples for SHBG assessment were collected at IVR insertion and each visit until 24 h post-IVR removal. SHBG levels were measured by the ETC ONPRC using a Roche cobas e411 automatic immunoassay (Roche Diagnostics, Indianapolis, IN, USA). The assay range for SHBG is 0.033–19 µg/ml; intra- and inter-assay coefficient of variation ($n = 2$ assays) were <2.8%.

2.5.7. Assessment of vaginal microbiota

A lateral vaginal wall swab was collected, and a Gram stain performed to assess Nugent score prior to IVR insertion and at IVR removal visits (17). Absolute abundance of bacteria per swab was determined by quantitative PCR of the 16S region to determine the microbial composition of the female genital tract. The vaginal microbiota assessment was done at the Seattle Children's Hospital laboratories (Seattle, Washington, USA), as described in a separate publication (24).

2.6. Demographic, behavioral, and other participant characteristics

Demographic data and perceptions of sexual partner attitudes, as well as behavioral data on sexual behaviors and IVR acceptability were collected *via* audio computer-assisted personal interview. IVR adherence and tolerability data were collected *via* electronic case report forms.

2.7. Sample size and statistical analyses

The participant sample size was planned to be 50 based on feasibility, similarly sized phase I studies, and study timelines rather than statistical criteria.

2.8. Statistical analysis

Safety was evaluated by clinical review of descriptive statistics of AEs by randomization group. For the evaluation of PK endpoints, plasma TFV, vaginal swab CVF, and serum LNG were used to calculate the following, planned PK parameters: maximum concentration (C_{max}), concentration steady state (C_{SS}), percent of steady state achieved 24 h after IVR insertion, concentration 24 h after the IVR removal visit; and the area under the curve (ln/linear trapezoidal method). Geometric means and 95% confidence intervals (CI) for PK parameters were calculated assuming a log-normal distribution. To evaluate the effect, if any, of the TFV/LNG product combination, transformed TFV concentrations were compared between participants randomized to the TFV-only IVR vs. the TFV/LNG IVR. TFV concentrations were compared using mixed log linear models, with treatment group as fixed effect and time (visit) as a repeated measure. Since the trial was not powered to find statistically significant group differences in primary or secondary endpoints, inferences based on statistical significance (or lack thereof) are made cautiously. Changes in soluble markers and anti-HSV-2 and anti-HIV-1 activity over time using IVR was assessed statistically by comparing paired measurements from pre-IVR insertion visit and IVR removal visit, using the Wilcoxon Signed Rank test.

3. Results

The first study IVR was inserted on January 31, 2019, and the study concluded in September 2019. As summarized in Figure 1, 312 women completed clinic screening visits and 27 eligible women were randomized to IVR insertion. The most common reasons for screening failures were bacterial vaginosis (BV) (32.6%) and positive STI test results (HIV, syphilis, *Neisseria gonorrhoeae, Chlamydia trachomatis* or hepatitis B virus) (27.4%). Less prevalent reasons included Grade 2+ laboratory abnormalities and inability to confirm ovulatory cycles (Supplementary Table S1). Eleven women were randomized to TFV/LNG, 11 to TFV-only and five to a placebo IVR use. The mean age of enrolled women was 24 years (SD 4.7), 24 (88.9%) had some secondary school education and 13 (48%) had been previously pregnant (Table 1).

3.1. Duration of IVR use

The median duration of IVR use was 68 days [interquartile range (IQR) 36–90]; 46 days (IQR 21–89) among women randomized to the TFV/LNG, 90 days (IQR 40–91) for the TFV-only, and 68 days (IQR 67–90) for the placebo group. No study participant was lost to follow up and only one scheduled study visit was missed. Six (22%) women had unplanned early IVR removal. Among the TFV/LNG IVR group, four women had early IVR removal at day 21, 34, 36 and

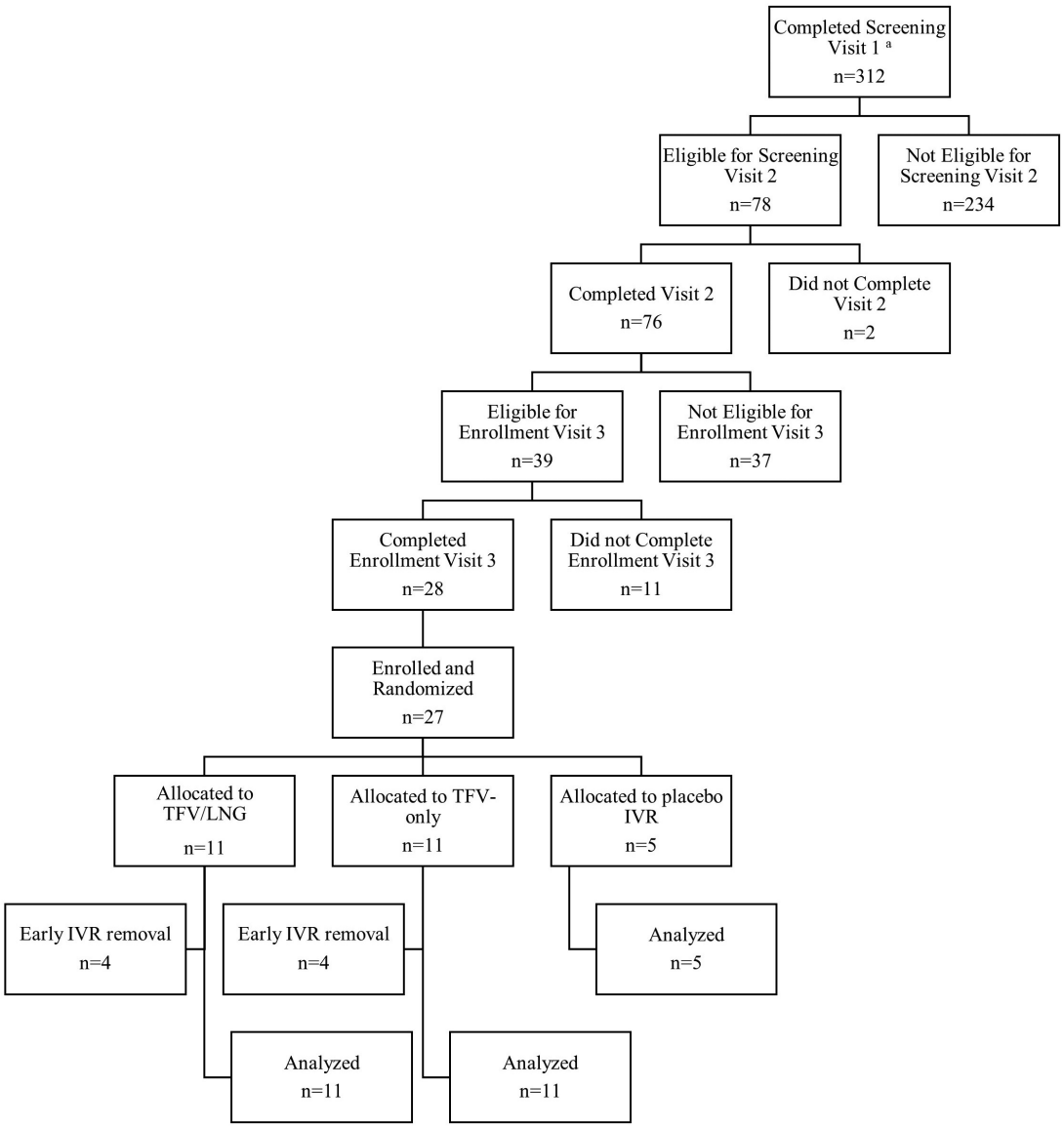

FIGURE 1
CONRAD Protocol B17-144 screening and enrollment flow chart, Kisumu, Kenya, 2019. [a]Provided written informed consent including data and sample collection and storage for study screening and enrollment.

TABLE 1 Participant demographic and sexual health characteristics by treatment group, Kisumu, Kenya, 2019.

Characteristics	Treatment group			
	TFV/LNG IVR ($n = 11$)	TFV-only IVR ($n = 11$)	Placebo IVR ($n = 5$)	Overall ($n = 27$)
Age, mean (SD)[a]	22.09 (2.88)	25.91 (5.74)	23.80 (4.76)	23.96 (4.74)
BMI, mean (SD)[b]	21.83 (3.78)	23.38 (3.10)	23.03 (3.45)	22.69 (3.40)
Menstrual cycle length[a,c], mean (SD)	31.14 (4.15)	29.29 (4.20)	31.00 (4.54)	30.42 (4.12)
Previously pregnant[a]	4 (36.4%)	6 (54.5%)	3 (60.0%)	13 (48.1%)
Education[a]				
At least some primary school	0 (0.0%)	1 (9.1%)	2 (40.0%)	3 (11.1%)
At least some secondary school	9 (81.8%)	8 (72.7%)	2 (40.0%)	19 (70.4%)
Completed college/university	2 (18.2%)	2 (18.2%)	1 (20.0%)	5 (18.5%)
Marital status				
Single	8 (72.7%)	7 (63.6%)	4 (80.0%)	19 (70.4%)
Married	3 (27.3%)	3 (27.3%)	1 (20.0%)	7 (25.9%)
Divorced/separated	0 (0.0%)	1 (9.1%)	0 (0.0%)	1 (3.7%)
Sexually active in past 3 months ($n = 20$)[a]				
Yes	8 (88.9%)	7 (100.0%)	3 (75.0%)	18 (90.0%)
No	1 (11.1%)	0 (0.0%)	1 (25.0%)	2 (10.0%)
Contraceptive use in past 6 months[a,d]				
None	1 (9.1%)	2 (18.2%)	1 (20.0%)	4 (14.8%)
Oral contraceptives	2 (18.2%)	2 (18.2%)	0 (0.0%)	4 (14.8%)
Male condom	9 (81.8%)	8 (72.7%)	4 (80.0%)	21 (77.8%)
Intrauterine device	1 (9.1%)	1 (9.1%)	0 (0.0%)	2 (7.4%)
Nugent score				
Nugent score at IVR insertion[b], median (IQR)	0.00 (0.00–5.00)	0.00 (0.00–0.00)	0.00 (0.00–7.00)	0.00 (0.00–5.00)
Positive for BV[e] at screening[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Positive for BV[e] at IVR insertion[b]	1 (9.1%)	1 (9.1%)	2 (40.0%)	4 (14.8%)

TFV, tenofovir; LNG, levonorgestrel; IVR, intravaginal ring; SD, standard deviation; BMI, body mass index; IQR, interquartile range; BV, bacterial vaginosis.
[a]Data collected at screening visit where participants were allowed to skip the question.
[b]Data collected just preceding (at time of) IVR insertion (baseline, Visit 3).
[c]Menstrual cycle length estimated from dates recorded on a Screening Menstrual Bleeding Electronic Case Report Form. The average of 2 cycles was taken for women who provided 3 dates, otherwise cycle length is computed from 2 dates. Eight women had just one menstrual period start date recorded and therefore are not included in computation of cycle length.
[d]A participant could report more than 1 type of contraception.
[e]Nugent score ≥7 was interpreted as positive for BV. Nugent score assessment occurred at both screening visit and IVR insertion visit (baseline, Visit 3).

46 of IVR use for the following reasons: one due to menorrhagia, two due to symptomatic BV, and one due to vulvovaginitis and recurrent IVR dislodgement. In the TFV IVR group, two women had early removal due to pregnancy confirmed at day 16 and 63 of IVR use; there were no early removals in the placebo IVR group.

3.2. Safety

A total of 110 AEs occurred in 26 women across the intervention and control arms, 58 (53%) grade 1 and 50 (45%) grade 2, one grade 3 and one grade 4 but only 7 (6%) were determined to be related to the study product. The grade 4 and grade 3 AEs were determined to be unrelated to the study intervention. AEs were similarly distributed among the three groups of IVR users (Table 2 and Supplementary Table S2).

Among the 27 enrolled women, the most reported AEs were BV in 12 (44.4%) women with 12 events, headache in 10 (37%) with 13 events, and upper respiratory tract infections (URTIs) in seven (25.9%) women with seven events, with similar distribution across study groups (Supplementary Table S2). Among the diverse etiologies of grade 2 AEs, the most common was URTI in six (22%) participants, BV in five (19%), reduced estimated glomerular filtration rate (eGFR) in five (19%), vulvovaginitis in four (15%) and headache in four (15%) (Supplementary Table S2). Additional AE data is summarized in Table 2 and Supplementary Table S2.

3.2.1. Systemic adverse events

There were five reported grade 2 AEs, with reduced eGFR compared to baseline in five (18.5%) women, one of which followed acute malaria and another a complete abortion; three women were in the TFV/LNG and two in TFV-only group. Decreases in eGFR from baseline values were limited to a range of 10.0% to <30.0% change, and all eGFR remained >90 ml/min/1.73 m^2, within normal parameters and assessed to not have clinical significance. One participant in the TFV only group, who experienced a complete abortion after the IVR removal visit also had grade 3 AE with reduced sodium reported at the final visit.

TABLE 2 Adverse events* by treatment group, Kisumu, Kenya, 2019.

	TFV/LNG IVR *n* (%)	TFV-only IVR *n* (%)	Placebo IVR *n* (%)	Overall *n* (%)
Adverse events (AEs)[a]				
Total AEs (any grade)	47 (42.7%)	47 (42.7%)	16 (14.5%)	110 (100.0%)
Serious AEs	0 (0%)	1 (100.0%)	0 (0%)	1 (100.0%)
Participants reporting at least one AE				
AE (any grade)	11 (100.0%)	10 (90.9%)	5 (100.0%)	26 (96.3%)
Severity of AE[b]				
Grade 1: Mild	0 (0%)	1 (10%)	1 (20%)	2 (8%)
Grade 2: Moderate	11 (100%)	8 (80%)	4 (80%)	23 (88%)
Grade 3: Severe	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Grade 4: Potentially life-threatening	0 (0%)	1 (10%)	0 (0%)	1 (4%)
Grade 5: Death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Relationship of AE to IVR use[c]				
Any related AE	6 (55%)	1 (10%)	0 (0%)	7 (27%)
No related AE	5 (45%)	9 (90%)	5 (100%)	19 (73%)

TFV, tenofovir; LNG, levonorgestrel; IVR, intravaginal ring; AE, adverse event(s).
*July 2017 update of the Division of AIDS (DAIDS) table (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf).
[a]Events reported. More than one event may have been reported per participant. Percentages given are among total events reported and represent a row percent.
[b]Participants reporting more than one AE were counted only once using the highest severity of AE reported.
[c]Participants reporting more than one AE were counted only once using the closest relationship to IVR use reported (i.e., "related" or "not related").

3.2.2. Genitourinary (GU) tract adverse events

Menstrual cycle changes with IVR use were observed in all three groups. Most AEs associated with menstrual changes were in the TFV/LNG group, in which five women reported intermenstrual bleeding, one had prolonged bleeding that led to IVR removal, and one had heavy menstrual bleeding. In the TFV group, one woman reported a grade 1 menstrual change AE with increased menstrual bleeding; none of the placebo IVR users had changes reported as AEs. Only one of these AEs was grade 2 and presented with prolonged light bleeding for 20 days, was assessed as product-related and led to product discontinuation. The other three GU AEs that led to product discontinuation were grade 2 BV and vulvovaginitis. Among 11 women in the TFV-only group, there were 17 GU AEs, with five grade 2AEs, and one grade 1 AE related to menstrual disorder. Among the placebo group, there were three GU AEs, two due to BV (grade 1 & 2) and one to genital pruritus (grade 1). There were no product discontinuations related to GU AEs in the TFV-only and placebo groups.

BV was the most common GU AE, with seven grade 1 and five grade 2 diagnosed in 12 women after IVR insertion—four (36.4%) women in the TFV/LNG, six (54.5%) in the TFV-only and two (40%) in the placebo IVR group. There was one visible small nodular vaginal lesion in the genitalia noted after IVR insertion in the TFV/LNG group, which was not product use related.

3.3. Acceptability and adherence

Women expressed concerns about using the IVR prior to use, but most concerns diminished with use. At the study screening visit, 73% of participants expressed some concern about the IVR but after IVR use only one woman in the TFV/LNG group expressed physical discomfort once or twice with IVR use and no one had difficulty with removal. Two women in the TFV-only IVR group reported removing the IVR for less than 2 h and had no difficulty with re-insertion. One woman in the TFV/LNG group had IVR displacement in the vagina which she easily repositioned. There were no IVR expulsions. Three women in the TFV/LNG group expressed concern with bleeding irregularities. At exit, 60% stated they would use an IVR for HIV prevention alone, all would use an IVR for both pregnancy and HIV prevention and all would recommend the IVR to their community.

Residual glycerin content, assessed only in the placebo IVRs, was high in the IVRs of two women, suggesting low adherence to use. All women in the placebo group stated they did not remove the IVR, did not feel any discomfort and did not feel it inside the vagina. Residual TFV and LNG assessed in women using TFV containing rings was consistent with IVR use and demonstrated steady depletion with each additional day of reported use (**Supplementary Figures S1A, S1B**).

3.4. Tenofovir and levonorgestrel pharmacokinetics assessment

3.4.1. Tenofovir in cervicovaginal fluid

In both TFV-containing IVR treatment groups, there was a rapid increase in TFV levels in vaginal fluid following insertion (**Figure 2A**). At 6 h post-IVR insertion, median vaginal fluid TFV was 1,300 ng/swab (IQR 638–3,520) in the TFV/LNG group and 837 ng/swab (IQR 419–1,290) in the TFV-only IVR group. At the 24-hour sampling, the geometric mean amount (GMA) of TFV was 16,141 ng/swab (95% CI

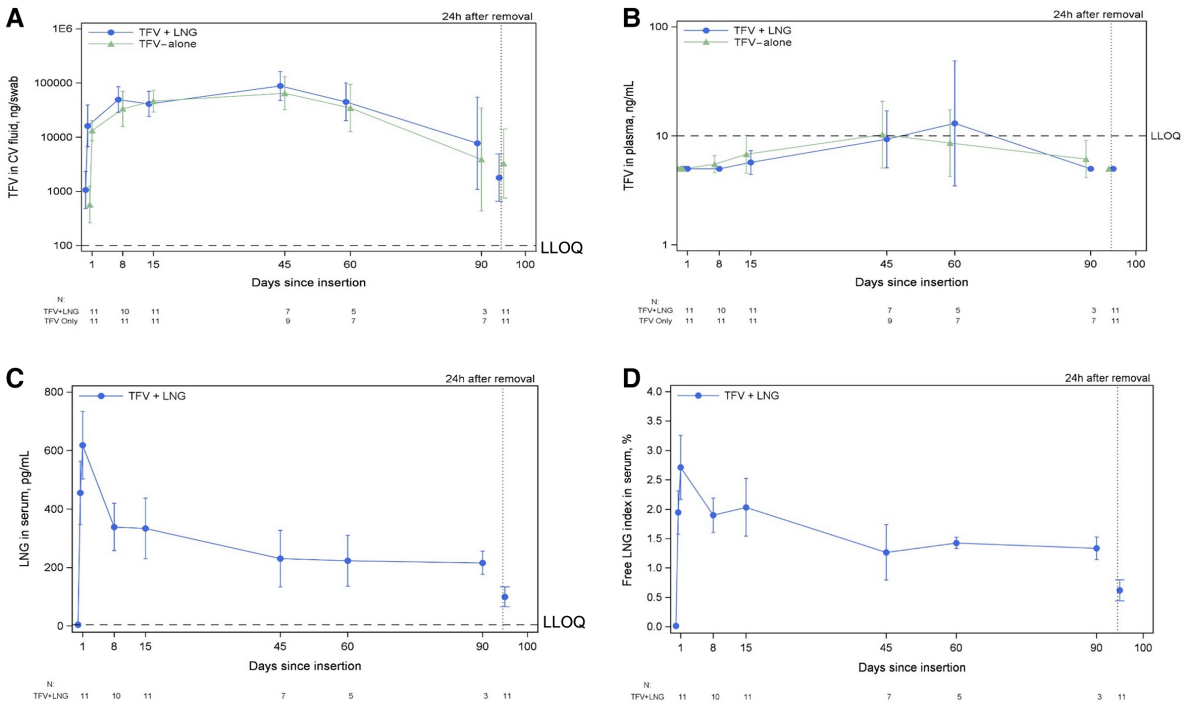

FIGURE 2
Tenofovir (TFV) levels among TFV/LNG and TFV-only intravaginal ring (IVR) users, and LNG levels among TFV/LNG IVR users, Kisumu, Kenya, 2019. 2A: TFV concentration in cervicovaginal (CV) fluid from IVR insertion through 24 hours (24h) after IVR removal; 2B: Plasma TFV concentration from IVR insertion through 24h after IVR removal; 2C: Serum LNG concentration from IVR insertion through 24h after IVR removal; 2D: Serum free LNG index from IVR insertion through 24h after IVR removal. LLOQ, lower limit of quantification.

6,549, 39,784) in the TFV/LNG group and 13,208 ng/swab (95% CI 8,532, 20,446) in the TFV-only IVR group, and at steady state, 43,988 ng/swab (95% CI 31,232, 61,954) in the TFV/LNG group and 30,337 ng/swab (95% CI 18,152, 50,702) in the TFV-only IVR group. Time to maximum (T_{max}) TFV GMA in cervicovaginal swabs was similar in the two treatment groups. For the TFV/LNG IVR group, T_{max} was 26.1 days (95% CI 16.1, 36.1), and for the TFV-only IVR group, T_{max} was 34.4 days (95% CI 17.6, 51.1). There was immediate decline in TFV vaginal amounts within 24 h of IVR removal, with GMA of 1,789 ng/swab (95% CI 645, 4,958) in the TFV/LNG group and 3,261 ng/swab (95% CI 745, 14,276) in the TFV-only IVR group. TFV GMA at 24 h post-insertion, during steady state, and at 24 h post-removal, as well as T_{max} or C_{max}, were similar in both treatment groups (Figure 2A).

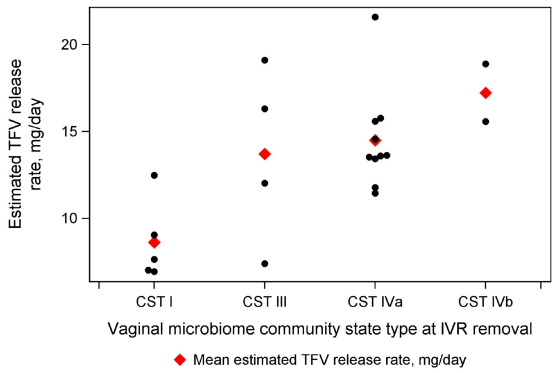

FIGURE 3
Estimated tenofovir (TFV) release rate, by vaginal microbiome community state type (CST) at intravaginal ring (IVR) removal visit. Kisumu, Kenya 2019.

3.4.2. Daily tenofovir release rates from IVRs

Among the TFV/LNG and the TFV-only IVR groups, the estimated TFV release rate was similar at 12.3 mg/day (SD 4.2) and 14.0 mg/day (SD 3.8), respectively. The potential effect of BV-associated microbiota on TFV release was assessed on a smaller sample size per treatment group (24). The estimated daily release rate was 8.6 mg (SD 2.3) among women with *Lactobacillis crispatus*-dominant community state type (CST I), 13.7 mg (SD 5.1) among *Lactobacillus iners*-dominant community state type (CST III), and 14.5 (SD 2.9) among non-*Lactobacillus*-dominant state types (CST IV). Tenofovir release increased with increased bacterial diversity and BV-associated bacteria (Figure 3).

3.4.3. Tenofovir in plasma

At 6 h prior to IVR insertion, 24 h post-insertion and throughout IVR use (with one exception at day 60), the steady state plasma concentration of TFV remained below the level of quantification (BLQ) (<10 ng/ml) for both TFV-containing IVR treatment groups), (Figure 2B).

3.4.4. Levonorgestrel in serum

Mean serum LNG levels were BLQ (<7 pg/ml) prior to TFV/LNG IVR insertion with T_{max} of one day and exceeding 400 pg/ml within 6 h. LNG concentrations (GMC) were 586 pg/ml (95% CI 473, 726) 24 h after insertion, 241 pg/ml (95% CI 185, 314) during steady state, and 87 pg/ml (95% CI 64, 119) at 24 h after IVR removal (Figure 2C). Geometric mean serum free LNG index was 2.6% (95% CI 2.1%, 3.2%) at 24 h after insertion, 1.5% (95% CI 1.2%, 1.9%) during steady state, and 0.6% (95% CI 0.4%, 0.8%) at 24 h after IVR removal (Figure 2D).

3.4.5. Daily levonorgestrel release rates from IVRs

Among the TFV/LNG IVR group, the estimated LNG release rate was 25.2 µg/day (SD 6.4).

3.5. Pharmacodynamics of tenofovir in cervicovaginal fluid

Activity against HIV-1 in CVF demonstrated a median of 7.1% inhibition at baseline, increasing markedly to a median of 84.4% at IVR removal ($p = 0.05$) for the TFV/LNG group. In the TFV-only IVR group median activity against HIV-1 also increased markedly from 15.0% inhibition at baseline to 89.5% at IVR removal ($p = 0.15$) (Table 3). In the placebo IVR group, the median activity against HIV-1 was similar at baseline and end of IVR use, −27.1% and −20.1% inhibition, respectively (Table 3). The TFV-only IVR group includes a few outliers displaying low/no inhibitory activity similar to that of the placebo group (Figure 4A). Among the TFV IVR groups, six of 17 women for whom CVF could be evaluated at IVR removal exhibited low HIV inhibition. Four of these had used the IVR for 90 days, had high estimated average TFV release rates and, at IVR removal, low levels of intravaginal TFV, low residual IVR TFV content and BV-associated microbiota (CST IV). The other two women had the IVR removed at 20–34 days and, at IVR removal, had high CVF TFV concentrations and IVR TFV content and showed CST III or IV (one each) microbiota. Regarding CVF activity against HSV-2, the median $\log_{10}$ fold-change reduction in HSV-2 levels at baseline and IVR removal was 8.8 and 563.7, respectively, in the TFV/LNG group ($p = 0.008$), and 1.8 vs. 185.9, respectively, in the TFV-only group ($p = 0.006$). In the placebo group, there was little change in HSV−2 levels from a baseline $\log_{10}$ fold−change median of 102.2 (IQR 2.4–711.5) to 119.3 (IQR 2.3–177.3) at IVR removal (Table 3 and Figure 4B), indicating no increase in CVF anti-HSV-2 activity due to placebo IVR use.

3.6. Pharmacodynamics of levonorgestrel

3.6.1. P4 and sex hormone binding globulin (SHBG)

All study participants had a luteal phase serum progesterone (P4) ≥3.0 ng/ml prior to IVR insertion. Serum P4 measurements with IVR use relative to pre-IVR insertion were consistently lower in the TFV/LNG group and were not substantially different in the TFV-only and placebo groups (Table 4a). At day 20–25 of the first menstrual cycle, only four (36.4%) women in the TFV/LNG group had P4 ≥3.0 ng/ml, indicating ovulatory cycles, while nine (81.8%) in the TFV-only and five (100.0%) in the placebo group showed values above 3.0 ng/ml. This trend continued to be seen at day 20–25 of the second menstrual cycle and at the IVR removal visit. One woman in the TFV-only group had detectable LNG pre-IVR, and at 6- and 24-hours post IVR insertion. SHBG levels in serum declined by 68% from baseline levels to IVR removal in the TFV/

TABLE 3 HIV-1 and herpes simplex, type 2 (HSV-2) inhibition activities in cervicovaginal fluid, by randomized treatment group and visit type, Kisumu, Kenya, 2019.

	Treatment group		
	TFV/LNG IVR ($n = 11$)	TFV-only IVR ($n = 11$)	Placebo IVR ($n = 5$)
Activity against HIV-1, % inhibition			
Pre-IVR insertion (n)	11	11	5
Median (IQR)	7.10 (−35.4–31.70)	15.00 (−6.90–37.30)	−27.10 (−140–−22.9)
At IVR removal (n[a])	9	8	5
Median (IQR)	84.40 (24.50–95.30)	89.45 (5.45–98.10)	−20.10 (−91.80–19.90)
p-value change from pre-IVR insertion[b]	0.05	0.15	0.06
Activity against HSV−2, fold change[c,d]			
Pre-IVR insertion, (n[c])	9	10	4
Median (IQR)	8.77 (2.49–44.14)	1.80 (1.35–5.82)	102.2 (2.36–711.5)
At IVR removal (n[c])	10	10	3
Median (IQR)	563.7 (43.22–983.3)	185.9 (61.15–1,558)	119.3 (2.33–177.3)
p-value change from pre-IVR insertion[b]	0.0008	0.006	1.000

HIV-1, human immunodeficiency virus, type 1; HSV-2, herpes simplex virus, type 2; TFV, tenofovir; LNG, levonorgestrel; IVR, intravaginal ring; IQR, interquartile range.
[a]Five participants samples were contaminated and are not included in the results.
[b]p-values for comparison of differences from IVR pre-insertion to end of treatment using Wilcoxon signed-rank test for paired values.
[c]Results of 4 specimens were not conclusive due to contamination or cytotoxicity and are not included in the results.
[d]Inhibition fold change = 1/fold change between log10 quantity by PCR in control (medium−only) sample, and log10 quantity by PCR in tested sample where CVF is included.

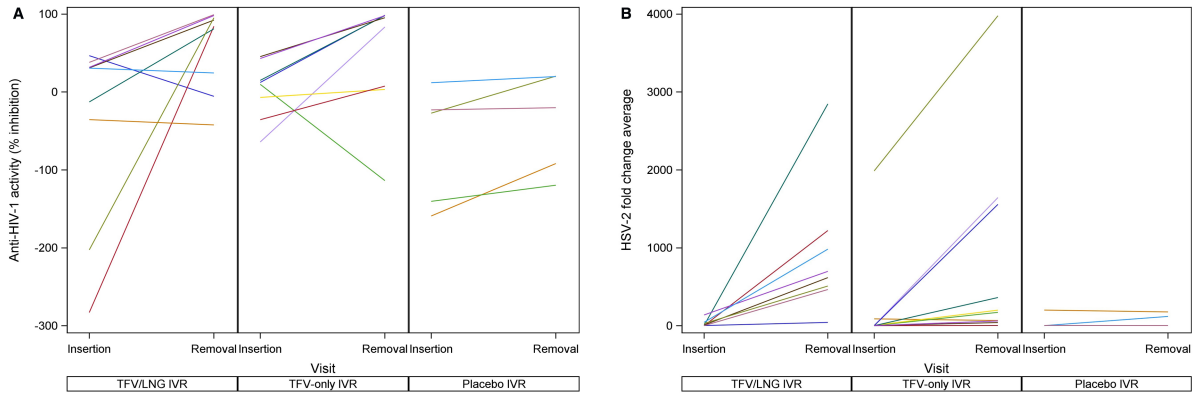

FIGURE 4
Cervicovaginal fluid (CVF) in-vitro human immunodeficiency virus, type 1 (HIV-1) and herpes simplex virus, type 2 (HSV-2) inhibition with tenofovir (TFV)/levonorgestrel (LNG), TFV-only, and placebo intravaginal ring (IVR) study groups. 4A: CVF in-vitro HIV-1 inhibition[a]; 4B: CVF in-vitro HSV-2 inhibition[a]. [a]Note, the y axes in figures 4A and 4B start at different cut off points.

LNG group but remained similar to baseline levels in the TFV-only and placebo groups through IVR use.

3.6.2. Cervical mucus assessment

The overall mean length of the menstrual cycle was 30 days (SD 4.1) across the three study groups. The mean length was 31 days (SD 4.1) in the TFV/LNG group, 29 days (SD 4.2) in TFV-only and 30 days (SD 4.5) in the placebo group. At day 14 of the first menstrual cycle after IVR insertion, six (60.0%) women in the TFV/LNG group, three (27.3%) in the TFV IVR group and one (20.0%) in the placebo group had an Insler cervical mucus score <7, reflecting poor cervical mucus (17). Similar findings were observed around day 14 (ovulatory) of the second cycle (Table 4b). The median cervical mucus score during the first menstrual cycle was 6 (IQR 5–8) for the TFV/LNG group, 9 (IQR 6–11) for the TFV-only group and 9 (IQR 9–10) for the placebo group.

TABLE 4a Surrogates of contraceptive efficacy: Serum progesterone (P4) levels at intravaginal ring (IVR) removal, randomized by treatment group and visit, Kisumu, Kenya, 2019.

P4 (ng/ml)	Treatment group		
	TFV/LNG IVR ($n = 11$)	TFV-only IVR ($n = 11$)	Placebo IVR ($n = 5$)
Visit 6: day 20–25 of 1st menstrual cycle			
Participants with P4 assessment	11	11	5
≥3	4 (36.4%)	9 (81.8%)	5 (100.0%)
<3	7 (63.6%)	2 (18.2%)	0 (0.0%)
Visit 7: day 20–25 of 2nd menstrual cycle[a]			
Participants with P4 assessment	7	9	5
≥3	3 (42.9%)	8 (88.9%)	4 (80.0%)
<3	4 (57.1%)	1 (11.1%)	1 (20.0%)
Day 90 end of treatment (EOT) visit, pre-IVR removal[b]			
Participants with P4 assessment	3	6	2
≥3	1 (33.3%)	3 (50.0%)	2 (100.0%)
<3	2 (66.7%)	3 (50.0%)	0 (0.0%)

P4, progesterone; IVR, intravaginal ring; TFV, tenofovir; LNG, levonorgestrel; EOT, end of treatment.
[a]One participant is missing P4 at Visit 7; five participants discontinued IVR use prior to Visit 7.
[b]One participant is missing P4 at Visit 9; 15 participants discontinued IVR use prior to 90 days.

3.7. Soluble immune markers

Evaluation of 11 soluble immune mediators in CVF demonstrated an increase of five mediators in the TFV/LNG and five in the TFV-only group between pre- and post-insertion compared to three in the placebo group, although most of these changes were not statistically significant. The TFV-only group

TABLE 4b Cervical mucus score (Insler Score, 0–15), simplified slide test, Kisumu, Kenya, 2019.

	Treatment group		
	TFV/LNG IVR ($n = 11$)	TFV-only IVR ($n = 11$)	Placebo IVR ($n = 5$)
Visit 5: Day 14 of 1st menstrual cycle[a]			
Observations	10	11	5
<7	6 (60.0%)	3 (27.3%)	1 (20.0%)
7–10	3 (30.0%)	5 (45.5%)	4 (80.0%)
Good (>10)	1 (10.0%)	3 (27.3%)	0 (0.0%)
Median (IQR)	6.0 (5.0–8.0)	9.0 (6.0–11.0)	9.0 (9.0–10.0)
Visit 8: Day 14 of 3rd menstrual cycle[b,c]			
Observations	5	7	4
<7	2 (40.0%)	1 (14.3%)	2 (50.0%)
7–10	3 (60.0%)	6 (85.7%)	1 (25.0%)
Good (>10)	0 (0.0%)	0 (0.0%)	1 (25.0%)
Median (IQR)	7.0 (6.0–8.0)	9.0 (7.0–10.0)	6.5 (5.5–10.0)

TFV, tenofovir; LNG, levonorgestrel; IVR, intravaginal ring; IQR, interquartile range.
[a]One woman did not attend Visit 5; percentages are based on 26 participants.
[b]Eleven women did not attend Visit 8; percentages are based on 16 participants.
[c]Visit 8 for this table includes 12 women attending Visit 8, which was prior to end of treatment (EOT) IVR removal and 4 who attended Visit 9 (EOT IVR removal) at the time of Visit 8 visit window.

showed an increase in median IL-1a from 159 to 462 pg/ml ($p < 0.001$) and reduction in median secretory leucocyte protease inhibitor SLPI from 430,355 to 71598 pg/ml ($p = 0.03$) (**Supplementary Table S3**).

4. Discussion

In this study, IVRs releasing TFV only and TFV/LNG used continuously for up to 90 days (median duration 68 days) were safe and well tolerated by young, sexually active Kenyan women assessed to be at low risk for HIV infection. These findings are consistent with those from two trials conducted in the USA and the Dominican Republic using the same IVRs (14, 25). Median vaginal steady state TFV amounts over 1,000 ng/swab correlate well with the estimated threshold for HIV prevention (15, 26, 27). Furthermore, CVF from participants using TFV-based IVRs had evidence of *in-vitro* inhibitory activity against HIV-1 and HSV-2. Data from four of six TFV-containing ring users whose CVF did not exhibit HIV inhibition is consistent with depletion of TFV in the ring by the time the IVR was removed, as reported in the MTN-038 study (27). In the CAPRISA 004 effectiveness study, which evaluated event-driven pre- and post-coital TFV vaginal gel use, cervicovaginal aspirate TFV concentrations ≥1,000 ng/ml correlated with 76% HIV protection (28). In our study we assessed TFV in CVF per swab, as a more accurate way to present and compare cervicovaginal TFV levels. TFV concentration in cervicovaginal aspirates and swabs were found to correlate well in a prior study (14). Based on these findings, we propose that the CVF TFV concentrations observed in this study have potential to confer protection from HIV infection. High cervicovaginal TFV concentrations, both in fluid and tissues, and TFV-diphosphate, the active metabolite, in tissues, as well as high CVF viral inhibitory activity, were also reported in previous studies in populations of women from different parts of the United States and the Dominican Republic (21, 25, 27, 29).

Plasma TFV concentrations were BLQ throughout IVR use. This finding of low systemic absorption of tenofovir is similar across TFV-based microbicide studies (30–32) and previous TFV IVR studies (14, 15). The low plasma TFV concentration likely explains the lack of product-related systemic AEs with similar distribution between TFV-containing IVRs compared to placebo IVR users.

This study found no statistically significant changes in CVF soluble markers of immune activation and inflammation between IVR insertion and removal, except for a significant decrease in SLPI, an immune mediator previously shown to block HIV infection, and an increase in the inflammatory cytokine IL-1α (33, 34) in the TFV only group. The clinical significance of these two isolated findings, however, is unclear. In a phase I study of an unrelated tenofovir disoproxil fumarate (TDF) IVR, which raised safety concerns and stopped early due to several findings of grade 1 genital ulceration, the vaginal fluid of the TDF arm had multiple increased soluble inflammatory markers among users of the active TDF ring but not the placebo IVR (32). The mechanism of transport of TDF (a prodrug to TFV) differs from TFV (our study intervention product) and exposure of vaginal cells to equimolar concentrations of TDF compared to TFV has been shown to result in a ∼40-fold higher levels of the active metabolite, tenofovir diphosphate (35). It is also possible that products of cleavage/degradation of the prodrug TDF delivered to a highly localized area of the mucosal might have contributed to its epithelial toxicity. The TFV rings tested in this study, collectively, have safety data from four studies assessing safety and PK of the rings used for up to 90 days, and in each of these studies, there was no evidence of vaginal ulcerations or vaginal inflammatory changes (14, 21, 36, 37).

Women diagnosed with BV at the screening visit in this study were not enrolled., During follow-up, however, BV was the most commonly identified AE and about 15% of women randomized to IVR use had asymptomatic BV. We observed a shift towards a healthier, less diverse vaginal microbiome with use of the TFV/LNG and placebo IVR and a slight shift towards more diverse community state with TFV-only IVR. These data have been reported separately (24). TFV degradation by BV-associated bacteria has been suggested as possible cause for the reported reduction in vaginal drug concentrations and TFV gel efficacy in the CAPRISA 004 study (26, 38). Contrary to this observation, in our study, TFV release rates were found to increase with vaginal bacterial diversity and BV-associated microbiota. The increased TFV release observed in the presence of BV or BV-associated microbiota, possibly linked to increased vaginal pH and its effect on TFV solubility, may have helped maintain TFV levels in the cervicovaginal compartment, at least for the median duration of use (68 days) and until the IVR content was exhausted (13). This unexpected change in IVR release kinetics may counter the postulated TFV luminal degradation and its deleterious effect on efficacy. Future follow up studies should further assess these changes and their impact on HIV prevention potential.

Changes in menstrual bleeding patterns were the only product-related AEs identified and were almost all in the TFV/LNG group. Among women using LNG hormonal contraceptive methods, irregular menstrual bleeding is common and may lead to contraceptive discontinuation (39). Changes in menstrual patterns with progestin only contraceptives however have not diminished their overall acceptability and share of the market. The TFV/LNG evaluated in this study delivers a microdose of LNG (∼20 μg/day), reducing anovulation and its associated menstrual changes and potentially increasing acceptability. The release rate of about 20 μg of LNG per day from the IVR is comparable to the LNG-intrauterine device, and lower than the two-rod Jadelle® contraceptive implant with an estimated *in vivo* LNG release of 100 μg per day (40). The lower LNG dose released by the TFV/LNG IVR was intended to reduce frequency of irregular bleeding while retaining contraceptive efficacy (41). Most of the TFV/LNG users in the CONRAD A15-138 study using similarly low dose of LNG in the IVR did not experience changes in menstrual bleeding (37). Serum LNG concentrations among TFV/LNG IVR users were above the estimated threshold of 200 pg/ml for effective contraception among systemic LNG users, suggesting contraceptive potential for this multipurpose prevention IVR (40, 42). This was further supported by mean serum LNG concentration of 400 pg/ml within 6-hour and T_{max}

within 24-hours of use, meeting the standard minimum threshold of LNG serum concentration for contraception determined in early LNG contraceptive implant studies, from which concentrations of LNG above 210 pg/ml are held to infer contraceptive effectiveness (40). The threshold for serum LNG levels for contraceptive effectiveness with IVR LNG use, however, has not been determined. In our study, markers of fertility such as ovulation and cervical mucus quality suggest contraceptive potential for the TFV/LNG ring. Furthermore, there were no pregnancies in that group, while two pregnancies were registered among women using the TFV-only IVR.

In this study, steady state LNG GMC remained above the standard threshold of 200 pg/ml, with a quick drop to 87 pg/ml within 24 h of IVR removal, providing the basis for quick return to fertility. However, this rapid decline can also leave women unprotected if they delay insertion of a new IVR or re-insertion after self-removal. On the other hand, TFV-diphosphate in tissue remains high after removal for several days, endowing the IVR with a longer forgiveness for HIV protection (14).

LNG implants and intrauterine systems act to prevent pregnancy through suppression of ovulation, suppression of endometrial lining maturation and thickening of cervical mucus (43–45). In long term implant studies, while more than 50% of women resume ovulation and cycling, they still remain protected against pregnancy, presumably due to local effects on the female genital tract (45, 46). In this study, TFV/LNG IVR users predominantly had low cervical mucus Insler score, indicative of cervical mucus that is impenetrable by sperm. Furthermore, 57%–67% of these women had anovulatory cycles.

The small sample size is a major limitation of this study and did not allow us to characterize detailed changes in vaginal microbiota or immune soluble markers and their effect on TFV release rates. Other limitations include the need to limit duration of IVR use in some participants due to product expiration date, the fact that we did not take genital biopsies for PK or histology to avoid increasing the risk of acquiring genital infections, such as HIV, and the use of the glycerin-based adherence assay only in the placebo arm. The duration of ring use was different in the two arms of the study; however this cannot be attributed to AEs or other product related differences.

This is the first study conducted among women in Africa to evaluate two IVRs releasing TFV and TFV/LNG. Data showed the IVRs were acceptable, safe and well tolerated in this small sample of selected Kenyan women. High vaginal TFV and serum LNG concentrations for the median duration of use and consistent PK profile and surrogates of protection against HIV-1, HSV-2 and pregnancy suggest good potential for these vaginal rings as multipurpose prevention technologies, expanding choice and prevention tools among adolescent girls and women.

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/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Kenya Medical Research Institute Scientific Ethics Review Committee and the University of Washington Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

The authors contributed to protocol development, study implementation, laboratory analysis and manuscript writing. The contents of this article are the sole responsibility of the authors and do not necessarily reflect the official positions or views of the investigators' institutions, CDC, USAID, PEPFAR and/or the United States Government. All authors contributed to the article and approved the submitted version.

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Conflict of interest

Jared M Baeten is an employee of Gilead Sciences, outside of the present work. Nina Isoherrranen has consultancy agreements with Boehringer-Ingelheim, Johnson and Johnson and Xenon Pharmaceuticals. The remaining 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1118030/full#supplementary-material.

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Strategic actions to advance multipurpose prevention technologies in low- and middle-income countries

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Background: HIV, other sexually transmitted infections (STIs) and unintended pregnancies are critical and interlinked health risks for millions of women of reproductive age worldwide. Multipurpose prevention technologies (MPTs) offer an innovative approach for expanding combined pregnancy and/or disease prevention. So far, MPT development efforts have focused mostly on HIV prevention, but about half of product candidates comprise compounds active against non-HIV STIs as well. This review aims to provide a framework that promotes the efficient advancement of the most promising preclinical products through the development pathway and into the hands of end-users, with a focus on women in low- and middle-income countries (L/MICs).
Methods: This mini review provides a summary of the current landscape of the MPT field. It comprises a landscape assessment of MPTs in development, complemented by a series of 28 in-depth, semi-structured key informant interviews (KIIs) with experts representing different L/MIC perspectives.
Main results: We identified six primary action strategies to advance MPTs for L/MICs, including identification of key research gaps and priorities. For each action strategy, progress to date and key recommendations are included.
Conclusions: To realize the life-saving potential of MPTs and maximize the momentum made to date, a strategic, collaborative and well-funded response to the gaps and next steps outlined in this paper is critical. A coordinated response can add rigor and efficiency to the development process, to successfully advance the most promising MPT products to the hands of end-users.

KEYWORDS
multipurpose prevention technologies, MPTs, HIV, LMICs (low and middle income countries), contraception, STIs

1. Introduction

For millions of women of reproductive age worldwide, HIV, other sexually transmitted infections (STIs) and unintended pregnancies are critical and interlinked health risks. Adolescent girls and young women (AGYW) from sub-Saharan Africa (SSA), aged 15–24, are at particular risk of HIV, representing 63% of all new HIV infections in 2021 (1). STIs are on the rise globally, leading to severe health consequences for women and their children, including pelvic inflammatory disease, infertility, ectopic pregnancy, chronic

pelvic pain, and neonatal and infant infections (2). According to the World Health Organization (WHO), more than 1 million STIs are acquired every day globally (2, 3). Concurrently, an estimated 830 women die from preventable causes related to pregnancy and childbirth each day worldwide (4). More than 160 million women have an unmet need for contraception (5). Simultaneously, HIV stigma and other socio-structural barriers often discourage women from accessing biomedical HIV prevention strategies, such as pre-exposure prophylaxis (PrEP) (6).

Multipurpose prevention technologies (MPTs) are designed to deliver multifaceted prevention to address two or more of these health risks with a single product (7). Condoms are the only commercially available MPT; indeed, the majority of MPTs are in early stages of development. The MPT pipeline has grown over the past decade, primarily focused on combining anti-HIV drugs with hormonal contraceptive drugs into a single product (7). Given finite funding and technical challenges for the MPT field, the objective of this review is to provide a framework that promotes the most promising preclinical products through the development pathway and into the hands of end-users, with a focus on women in low- and middle-income countries (L/MICs).

2. Methodology

This review provides a summary of the previously published 60+ page landscape of MPT product candidates in all stages of preclinical and clinical development (6). The search strategy included three principal avenues: product developer surveys, key informant interviews, and a desk review. Data collection was implemented between May and September 2021, with an update to the desk review in November–December 2022. The product developer surveys consisted of 18 questions about each MPT candidate included as part of the Initiative for MPT's (IMPT) annual MPT product development pipeline update process. The research team surveyed 18 product developer organizations, with an 83% response rate ($n = 15$). A desk review was then conducted, reviewing MPTs in all stages of development—both those already in the MPT Database and those identified through a supplementary literature review to ensure all new or emerging MPT candidates were reflected. A series of 28 in-depth semi-structured key informant interviews (KIIs) were then conducted with technical experts representing a vast array of HIV and STI prevention and contraception expertise. They included product developers, regulatory experts, program implementers, civil society leaders, policy makers, and donors/supporting agencies, among others. Respondents brought L/MIC perspectives from sub-Saharan Africa, Latin America, and the Asia Pacific Region. A pre-KII self-administered form and a KII interview guide were used to explore key informant input on missing/outdated research in the product developer surveys and desk review and other additional details on new or ongoing MPT research and development (R&D), as well as insights around priority MPT approaches and indications, key gaps and challenges, and recommendations for the field. Following the interviews, the research team aggregated and reviewed the interview notes to identify key themes (6).

3. Results

From the process described above, we propose six primary action strategies to advance MPTs for L/MICs, including identification of key research gaps and priorities.

3.1. Action area 1: technical challenges and opportunities

3.1.1. Overview

The two basic design strategies for MPTs are: (1) formulation of a single drug capable of addressing two distinct indications, and (2) separate, independent drugs co-formulated into a single formulation. Details on different Active Pharmaceutical Ingredients (API) and delivery forms are summarized elsewhere (6–8).

Although antiviral drugs are the most common APIs used specifically for HIV prevention in MPTs, other single drug options are being evaluated for dual indications (9). Whereas established antiretroviral (ARV) drugs offer no protection against unintended pregnancy, some non-ARV drug products in development have dual indications (e.g., contraception + STIs) (7, 10). To date, the majority of the MPTs in development with a contraceptive indication are hormonal contraceptives, with expanding interest in non-hormonal contraceptive approaches (11). Aside from achieving an effective multiple API delivery system, it is equally critical that the MPT product configuration is also consistent with end-user preferences. Data from end-user studies have shown end-user dislike of daily dosing, and preference for longer-acting products (e.g., injectables, implants) (12), although on-demand products are of interests to some end-users too (13, 14). Importantly, evidence suggests that long-acting products are best aligned with end-user interest and adherence behaviors, which translate to better protection, consistent with findings from contraception research (15). However, ensuring the full suite of options is available to end users to enable choice is critical to meet the needs of diverse target populations with varied lifestyles and preferences. Other less familiar delivery types, including intravaginal rings (IVRs), gels, films, and non-daily oral tablets will likely expand the set of choices even further.

3.1.2. Progress to date

3.1.2.1. Status of MPT product pipeline

The MPT pipeline is dynamic, with over two dozen MPTs encompassing eight delivery types, as shown in **Figure 1** (7, 15–17). As of December 2022, more than half of the product candidates combined HIV prevention with contraception, and a third provided prevention against HIV and other STIs but without contraception.

Despite these advances, innovations in product design have remained conventional, resulting in redundancy of delivery forms. Half of the MPT pipeline is made up of IVRs, yet, many preference studies for potential MPTs highlight interest for provider-administered long-acting approaches, such as injectables

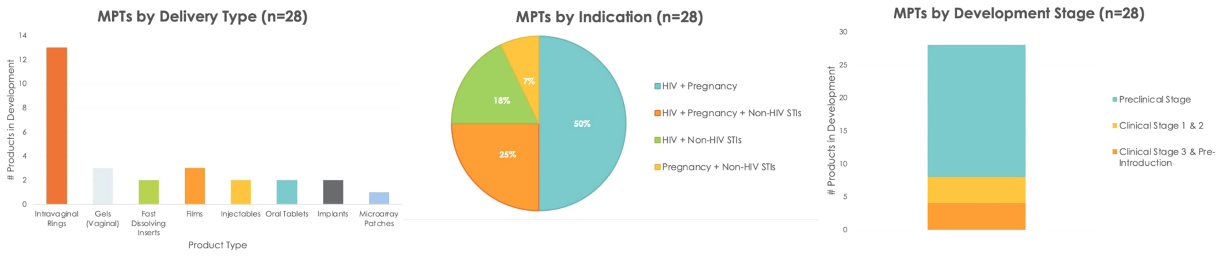

FIGURE 1
MPT product candidates by delivery type, indication and stage of development (as of December 2022) (6, 7).

and implants (18–20). Given the technical complexity of developing long-acting multi-drug formulations, few long-acting MPT approaches—aside from IVRs—are currently in the pipeline.

An important new trend is the expansion of APIs for MPTs. Since preventing HIV and unintended pregnancy was considered the initial MPT fieldwide priority, it evolved primarily from hormonal contraceptive and ARVs. This approach used drugs that were well-established (separately) for contraception and HIV treatment or prevention. Today, a number of alternative APIs are being evaluated in MPTs, including lectins, monoclonal antibodies (mAbs), and non-hormonal contraceptives (6).

3.1.2.2. Status of end-user research

The preference for MPTs over single indication products is evident across diverse populations and geographies (19, 21). Lessons learned from the contraceptive field have shown that increasing available options to users improves overall method uptake and persistence, along with population-level coverage and beneficial health impact (22–24). Similarly, expert opinions, along with evidence from empirical studies, suggest that expanding PrEP and MPT options will improve prevention coverage and impact (25–27). Key preferences for end-users included ease of access, long(er)-acting delivery, discretion (i.e., use without partner knowledge), no impact on sex, and minimal side effects. Users also expressed preference for strategies that can easily gain partner approval, are de-medicalized, discreetly stored and transported, and packaged in visually appealing ways (19, 25–27). MPT acceptability research has mostly involved hypothetical preference and/or placebo studies. This acceptability gap is being filled with phase I trials assessing MPT rings (7), and more trials underway, including the oral dual prevention pill (DPP), after appropriate bioequivalence with individual doses of each drug is demonstrated (28).

3.1.2.3. Recommended next steps

1. **Define criteria to evaluate MPT** product development efforts. This includes criteria to achieve an early "kill" on products with high risk and low probabilities of technical success or public health impact to optimize limited resources.
2. **Identify more potent APIs** to address all indications of relevance for MPTs and preferred delivery forms.
3. Expand **acceptability research with active MPT** products in the relevant female populations, (e.g., L/MICs at high risk, including AGYW).

3.2. Action area 2: addressing L/MIC regulatory pathways

3.2.1. Overview

There is limited experience in multi-indication product development for MPTs. Regulatory standards for single indication products also apply to MPTs (e.g., safety, purity, stability, effectiveness, etc.). These standards will likely need to be achieved through experimental design that include combinations of APIs in the product (29).

In most L/MICs, navigating the local regulatory requirements governing registration of medicines including Chemistry, Manufacturing and Controls (CMC) is an ongoing challenge. Many product developers rely on the WHO Prequalification Program (PQ) to facilitate National Regulatory Authority (NRA) approvals in L/MICS (30). Additionally, Stringent Regulatory Authority (SRA) approvals can sometimes be leveraged, but LMICs may still need to complete their own regulatory reviews as well (31).

3.2.2. Progress to date

In January 2022, the US FDA provided a guidance document for combination products (29). Several regulatory reviews, including their applicability to MPTs have highlighted areas to address (32–34). Single indication prevention products (e.g., dapivirine ring and oral PrEP) have gone through the regulatory process successfully and could serve as models to inform MPTs (35).

It remains unclear if the FDA Tentative Approval process, which was crucial for achieving affordable generic treatments for HIV, would apply to an MPT.

3.2.2.1. Recommended next steps

1. MPT product development teams should be required by funders to include **appropriate regulatory expertise.**
2. With appropriate expertise in place, product developers should interact with **Stringent Regulatory Agencies (SRAs)** for input on product development strategies and plans.

3. MPT developers should request meetings and consultations with **in-country drug authority regulators** in L/MICs, to strengthen their capacity of independent review of dossiers, through regional meetings and consultations.

3.3. Action area 3: advancing MPTs from preclinical to clinical development

3.3.1. Overview

MPT progression from preclinical to clinical development is similar to a single indication product. Data from studies relevant to CMC, safety studies in animal models, dose determination, pharmacokinetics (PK), and pharmacodynamics (PD) will be required. Additionally, determination of drug-drug interaction with an MPT will be needed. The FDA provides guidance on combination products, which should also be referenced (29). These guidance documents are relevant for cost estimations, cost effectiveness calculations, and risk reduction strategies.

Although early-stage funding exists for MPTs, support for promising MPT candidates beyond essential phase I studies is unclear. Most MPT candidates are in pre-clinical stages or phase 1 trials, largely supported by the National Institutes of Health (NIH) and United States Agency for International Development (USAID), and by small biotechnology companies. The pharmaceutical industry traditionally avoids acquiring and funding products until after phase II clinical development stages have been successfully completed to help "de-risk" their investment (36).

Furthermore, conducting randomized control trials (RCTs) of MPTs adds methodological complexity. Current standards for contraceptive and HIV prevention trial design differ widely, notably with the contraceptive Pearl Index approach (37) vs. the placebo or comparator product approach used for HIV. Needing to adequately power study arms to meet both may require large sample sizes.

3.3.2. Progress to date

While the majority of MPTs in development are in pre-clinical development, several MPT candidates have progressed to phase I/ II, and two have progressed to phase 3 trials (**Figure 1** and **Table 1**). R&D for long-acting MPT candidates was initiated, consistent with end-user preference data.

3.3.2.1. Recommended Next Steps

1. Assess the **technical and regulatory/development risks** for MPT products in the target populations which is largely achievable via International Council for Harmonization (ICH) Guidance on Risk Assessment and Resolution Strategies (38).
2. **Ensure that technical development is aligned with pre-defined milestones** for cost-effectiveness and end-user preferences.
3. Apply data from milestone steps 1&2 (above) to **justify continuation or termination of investments** during development.
4. Encourage open **collaboration between active funders** to assure complementary and appropriate investment in "best" MPT candidates. This process can be informed by existing funder collaborations (39–44).
5. Collaborate with scientists, researchers and regulators on **novel clinical trial designs** that can affordably evaluate multiple indication products in drug-device combinations.

3.4. Action area 4: cost and market potential

3.4.1. Overview

Assessing product-market fit is essential for evaluating market potential and attracting investment for a novel MPT. Beyond establishing clinical efficacy, designing an MPT with attributes that are *affordable* to the eventual payers, *feasible* to deliver in the intended context and *attractive* to end users will increase the likelihood of finding a suitable market potential for investors. Assessing affordability ideally takes into account budgetary constraints, training needs for providers and cadres of staff for delivery/administration of the product, and the product's effectiveness.

3.4.2. Progress to date

As noted above, there is a significant and growing body of literature on end user preferences that suggest significant market potential for MPTs. Discrete choice experiments have found preferences in a selection of sub-Saharan African countries for monthly injections over pills and rings (26, 27), which aligns with women's contraceptive familiarity and preferences (45).

Opportunities and challenges in costing products have also been identified (6) including the challenges of forecasting cost-of-goods (COGS) for large-scale manufacturing from pilot-scale prototypes, which has often then limited the ability to gain market traction. The importance of evaluating both cost and benefit from the perspective of the payers has also been identified (6). Health economics modelling on MPTs suggests that they will have the potential to be impactful and cost-effective, but such models are limited without real-world products (46–48). Procurement data from insurers and donors on family planning, HIV and STI products as well as end user willingness to pay studies can serve as an important benchmark for cost structure and potential pricing in different markets.

3.4.2.1. Recommended next steps

1. Ensure that **target product profile criteria and standards** for MPTs are informed by evidence on willingness to purchase, ease of administration in L/MICs and end user preferences.
2. Expand and integrate **socio-behavioral & market research** into MPT R&D and introduction strategies, including from L/MICs.
3. **Optimize industry involvement** in MPT R&D to achieve scalability of products.
4. **Develop a path for MPT investment and introduction** that is relevant to public sector funders, private sector investors, and a range of markets.

3.5. Action area 5: market access

3.5.1. Overview

Without early consideration and intervention, emerging MPTs will face challenges that impede timely uptake in L/MICs where many of the primary target populations live. Given the variety and complexity of MPTs, such as long-acting mechanisms and hybrid products, there will be additional market barriers to ensure equitable access. Affordability, supply capacity, intellectual property, regulatory pathways, adaptability, and usability are all key elements to be addressed in a timely manner to ensure delivery at scale.

3.5.2. Progress to date

Initial efforts have established the investment case for MPTs (49) and MPT Target Population Identification Mapping Tool (50). These high-level advocacy tools are increasingly being bolstered by efforts to understand potential health and financial impact of specific technologies, such as the cost-effectiveness model for the DPP that is adaptable to other technologies (51).

To support early market access where prices are likely to be higher than desired, companies can pursue potential funders of market shaping financial mechanisms that can support manufacturing scale-up and faster price reductions, such as the Implant Volume Guarantee (52). Mechanisms developed in other health areas to support early identification of development and commercialization partners, as well as to enable voluntary licensing for generic manufacturing through entities like the Medicines Patent Pool (MPP), can also be leveraged (48).

3.5.2.1. Recommended next steps

1. **Establish objective scientific and target product profile (TPP)-driven criteria and standards** to serve as benchmarks for MPT candidates that can foster supporting agency collaboration (52).
2. **Leverage co-sourced funding** within the public and private sectors to advance promising MPT candidates through the product development pipeline and to support manufacturing scale-up.

3.6. Action area 6: product introduction and rollout

3.6.1. Overview

As no MPT has been launched in L/MICs since the male and female condoms, achieving successful market launch and scale will rely on close collaboration with a wide range of stakeholders to demonstrate the added benefits of a multi-indication product and to determine how best to integrate the product into the platforms available in family planning, sexual health and/or HIV. At a country level, national market authorization, inclusion in national treatment policies, and funding to implement rollout through national programs are essential to drive demand and support introduction (6). Transparent and affordable pricing is therefore crucial, as evidenced by the challenges currently faced with gaining local market authorizations and scale-up plans for long-acting injectable cabotegravir given its current higher cost than existing PrEP options (53).

Another potential challenge with MPTs is establishing the appropriate service delivery strategy. Currently, PrEP products are primarily serviced with end-users in primary health clinics and contraceptive products are managed via family planning clinics. Many countries in SSA are gradually integrating HIV testing and prevention into family planning clinics for efficient HIV testing, delivery of ARVs and contraception.

3.6.2. Progress to date

The strategy for the launch of the DPP provides a roadmap to launch an MPT, inspired by similar efforts for other HIV and contraceptive products (48, 52, 54–57). However, several initial challenges that will affect the roll-out of MPTs exist, such as decision on who funds procurement and which supply chain is used. The USAID funded MOSAIC consortium, tasked with preparing for successful introduction of diverse PrEP options, could be leveraged (58).

Creating the enabling policy environment for MPTs is critical for success, and will benefit from growing efforts since the ECHO trial, to provide policy fora for the integration of HIV and family planning service delivery (59) Integrated SRH visits, using multi-service clinic facilities, and delivering products where a target market congregates are among the key approaches (6).

An MPT developer can benefit from strong architecture for product launches in both the family planning and the HIV space. Entities like the WHO, the Reproductive Health Supplies Commission, SEMA Reproductive Health, MOSAIC, and the ARV Procurement Working Group play important roles including guidelines development, market coordination and procurement forecasting. A wealth of in-country partners and platforms are available to support governments with training, demand generation and service delivery, such as MSI Reproductive Choices, DKT, the Global Fund and PEPFAR implementers.

3.6.2.1. Recommended next steps

1. **Support implementation research and demonstration studies** which could provide important evidence to inform market authorization and offer insight into practicalities for end-users.
2. **Plan early for introduction and future adoption**. MPT awareness raising, promotion and training for end-users and health care providers is needed early to help ensure end-users and key stakeholders start thinking about MPTs well before they reach the market.
3. **Simplify access and method delivery**, including through the **self-care approach** (when possible). Offering a one-stop shop for multiple prevention needs, some user-controlled MPTs (depending on the delivery system and APIs) have the potential to expand self-care options for end-users, at least in the long term.
4. **Strategically select sites for Phase II and III MPT trials** where MPTs can be introduced and rolled out should they gain approval.
5. The **IND holder/sponsor of the product should lead the development and "own" the access plan** and incorporate access to intellectual property (IP) as part of development pathway.

TABLE 1 Snapshot of MPTs in the R&D pipeline ($n = 28$).

Delivery type	# products in the pipeline	Delivery route		Administration		Advantages	Risks	Other considerations
		Systemic	Topical	Self	Provider			
Implants	2	✓			✓	Removable implants are technically simpler to develop. Yet, biodegradability may reduce healthcare provider (HCP) burden and improve user acceptability (e.g., less pain, scarring, no clinic visit required when product is spent)	Higher level of HCP training required; small surgical intervention to remove; lack of invisibility once placed	Leverage contraceptive trocars for insertion vs. developing unique insertion devices. Explore further users' preference for removability vs. biodegradation
Rings	12		✓	✓		Can be self or provider inserted; immediately reversible upon removal; high acceptability among experienced users; rings exist for other indications (e.g., contraception, menopausal symptoms)	Unfamiliarity in target populations; partner detectability during sex; low prospective acceptability must be overcome with thorough education and training for first time users	May need HCP to administer first and/or verify placement; potential for OTC delivery
Long-acting injectables	2	✓			✓	High user compliance; discreet method; familiar delivery system	PK tail; silent infections; return to fertility concerns; pain at injection site	Requires access to qualified HCP for administration
Microarray patches	1	✓		TBD	TBD	Discreet method	*De novo* product; training for proper application; unfamiliarity in target populations; wait time at clinic prior to removal may be a concern	May need HCP to administer first and/or verify placement, or direct observation if self-placed at clinic
Oral pills	2	✓		✓		Affordable; stable; manufacturing simplicity; familiar delivery system	Adherence; low forgiveness if skipping; home storage needed	Pill and bottle/packet may be linked to HIV stigma
Gels (vaginal and rectal)	2		✓	✓		On-demand; affordable; stable; manufacturing simplicity	Adherence; messy; noticeability during sex	Potential for OTC delivery; delivered with reusable or disposable applicator
Films (vaginal)	3		✓	✓		On-demand; current R&D for extended-release formulation (1 month) without need for removal	Adherence; training for proper application; may stick to finger; unfamiliarity	May need HCP to administer first; potential for OTC delivery
Fast dissolving inserts (vaginal and rectal)	4		✓	✓		On-demand; can be dual compartment, potential for PrEP or PEP	Adherence	Potential for OTC delivery

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4. Summary

This review provides a summary of the previously published 60+ page landscape of MPT product candidates in all stages of preclinical and clinical development (6). This review identifies six primary action strategies to advance MPT access in L/MICs and their progress to date. We also highlight key research gaps and priorities that can be addressed to strategically help advance the field.

Table 1 provides a snapshot of key considerations for the different MPTs currently in the pipeline. As the MPT field evolves, delivery types are expected to change. To realize the life-saving potential of MPTs, a strategic, collaborative and well-funded response to the gaps and next steps outlined in this paper is critical.

Author contributions

The manuscript is a summary of the previously developed 60+ page published landscape report of the MPT field co-authored by BY, AV, and JR. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AV was employed by ASTRA Consulting. TB was employed by Children's Investment Fund Foundation. AC, CS, and CPC were employed by UNITIAD. JR was employed by NWJ Group, LLC.

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Participant experiences with a multipurpose vaginal ring for HIV and pregnancy prevention during a phase 1 clinical trial: learning from users to improve acceptability

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Introduction: With high concurrent global rates of HIV incidence and unintended pregnancy, there is a need to provide options beyond condoms to enable users to simultaneously prevent HIV acquisition and pregnancy. Multiple vaginal rings are in development as "MPTs" (multipurpose prevention technologies) as they are shown to provide several co-occurring benefits such as discretion, convenience, reversibility and user control.
Methods: In this Phase 1 trial of a 3-month MPT ring in the U.S., 25 participants (low-risk for HIV and pregnancy) were randomized to use the study ring for 90 days continuously or in 28-day cycles with 2-day removal periods in between. All participants completed in-depth interviews at the end of their study participation.
Results: Overall, the ring was well tolerated. Participants resoundingly endorsed the concept of an extended-use, dual-purpose vaginal ring, but reported too many functional challenges and side effects to endorse this particular ring. Participants assigned to the continuous regimen reported more positive experiences with ring use than those in the cyclic group. A minority of participants who experienced minimal side effects and did not experience challenges with vaginal retention of the ring found it appealing. However, the majority of participants experienced challenges (ring slippage, expulsions, side effects, vaginal bleeding changes) with product use that outweighed the potential benefits and led them to report that – in the future – they would not be interested in using this specific version of the ring in its current form. A subset expressed interest in using the current MPT ring under certain conditions (e.g., if fewer expulsions, less bleeding, higher risk for HIV/pregnancy).
Discussion: User feedback regarding participant experiences and challenges with the study ring was continuously shared with the product developer, underscoring the value of early-stage end-user feedback in product development.

KEYWORDS

acceptability, multi-purpose prevention technologies, vaginal ring, HIV prevention, contraception, qualitative

Introduction

Globally, the risks of HIV and of unintended pregnancy remain high. Combining both indications into a single product, or a Multipurpose Prevention Technologies (MPT), is important and generally favored by women (1). MPTs have the potential to simplify use and access, be more cost effective, improve method framing (as a contraceptive rather than as disease prophylaxis), and therefore may increase product uptake and adherence (2–4). However, current MPT options are limited to male and female condoms. While condoms are highly effective under ideal conditions, consistent use is compromised by multiple socio-behavioral barriers (5–7). Prior research has suggested that a user-centric approach, built on understanding needs and desires of end-users, is essential to ultimately developing a successful and acceptable MPT product (8–10).

Previous research demonstrated that women highly value discretion, self-reliance, efficacy, and convenience in a prevention product (11, 12). The vaginal ring meets these criteria and was found globally to be highly acceptable as a single indication product for HIV prevention and separately, for contraception (3, 13, 14). Studies have repeatedly shown high acceptability among women who use the etonogestrel/ethinyl estradiol contraceptive ring that is woman-controlled, discreet, coitally independent (monthly dosage) while also being fully and quickly reversible (15–24). Studies of contraceptive vaginal rings have shown that the contraceptive ring (compared to products like oral pills and patches) was preferred by adolescent and adult women (18, 25). As an HIV prevention method, a monthly silicone vaginal ring releasing the antiretroviral dapivirine (DPV) was shown to be safe and effective in Phase III trials and open label extension studies (26–29), and was well accepted among women in sub-Saharan Africa (SSA) (30–32), as well as among women of various age groups in the U.S (33–36). The monthly DPV ring is currently recommended for use by the WHO for those at substantial risk for HIV (37), has been approved in multiple African countries, and is undergoing regulatory review in several other African countries. Longer duration (i.e., 3 month) HIV PrEP rings are also being assessed in clinical trials, and a recent U.S. study found that user-convenience drove preference for the 3-month ring vs. the 1-month ring (38).

MPTs in the form of injectables are most highly desired by women in the U.S and in SSA, though studies have shown a substantial minority of women would prefer vaginal methods – including rings - over injections (or willing to use vaginal methods if injections were not available) (12, 20, 39–41). This highlights the importance of developing different delivery forms for MPTs. Rings are suitable devices as MPTs, as they can be loaded with sufficient drug(s) for more than one indication and can provide an extended duration of protection (42). Much of the previous research on end-user opinions of an MPT vaginal ring was hypothetical, drawing from cross-sectional data collection activities, scenarios embedded in studies of HIV prevention products that include vaginal rings, or placebo studies (12, 19, 20, 39, 43–45). Results are available from few studies to date that include end-user experiences with active MPT vaginal rings (46–48). There are currently 12 different rings being developed as MPTs, most in preclinical or early clinical stages (49). As MPT vaginal rings enter and progress through the development pipeline, gaining an understanding of end-user preferences and acceptability during the early stages of product development and clinical trial evaluation will be essential to optimization (42, 50).

This paper describes the findings from in-depth interviews (IDIs), acceptability questionnaires, and text messages from study participants, and s used to assess acceptability of and adherence to an MPT ring for HIV and pregnancy prevention, used continuously or cyclically by low-risk women enrolled in a Phase I trial in Pittsburgh, Pennsylvania, USA. The in-depth interview data also describes participant perspectives on an "ideal" vaginal ring and MPTs in general, in addition to describing the favorable and unfavorable attributes of the study product used.

Methods

MTN-044/IPM 053/CCN019 was an open label, Phase 1 trial conducted in Pittsburgh, Pennsylvania, USA. Participants were randomized (1:1) to one of two usage regimens for a 3-month vaginal ring developed for prevention of unintended pregnancy and HIV: continuous use for approximately 90 days or cyclic use (3 cycles each comprised of 28 days of ring usage followed by ring removal for 2 days). While the primary objectives of the trial were safety and pharmacokinetic data for the DPV/LNG ring, two exploratory objectives were to understand participant adherence to the assigned regimens and acceptability of using this ring for a dual HIV and pregnancy prevention indication.

The study took place between July 2018 and October 2019 and enrolled 25 participants who were aged 18–45 years (inclusive); assigned female sex at birth; HIV-uninfected and in general good health; and not at risk for pregnancy, defined as consistently using an effective, non-hormonal method of contraception for the duration of study participation, abstinence, or exclusively engaging in sex with individuals assigned female sex at birth. Participants were offered male condoms at each visit. Further enrollment criteria are described elsewhere (51, 52).

Study product

This 3-month MPT vaginal ring was a silicone matrix vaginal ring measuring 57.1 millimeters in outer diameter and 7.9 millimeters in cross-sectional diameter (see **Figure 1**). It contained 200 mg of dapivirine (for HIV prevention) and 320 mg of levonorgestrel (for contraception) and was developed by the International Partnership for Microbicides (IPM).

Data collection

At enrollment [and after learning initial information about the study product – more details can be found in the Informed Consent form found in the study protocol (52) and the Study

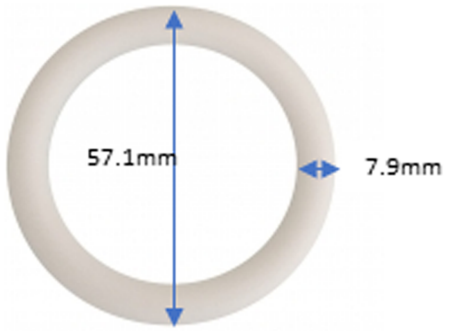

FIGURE 1
Study ring dimensions.

Specific Procedures manual (53)], all participants completed an acceptability questionnaire that included questions about prospective ring acceptability and initial concerns related to the study ring. Participants also completed an acceptability questionnaire at their Product Use End Visit (PUEV) that included questions about retrospective ring acceptability during the trial, experiences with ring use, and product preference. The questionnaire was derived from an earlier MPT ring study (54). Questions pertained to ease of use, ease of insertion, ease of removal, awareness and comfort of the ring, checking for ring presence, acceptability of changes in vaginal bleeding patterns, and how bothersome participants found any vaginal dryness or wetness from ring use. Product preference questions included preferences for HIV prevention methods, contraceptive methods, and separate vs. combined methods. The questionnaire also contained open ended questions about the participant's experience with the ring. Throughout their enrollment, participants were sent daily text messages regarding any changes in bleeding, and weekly text messages about any instances of their ring being removed or falling out (partially or fully).

All enrolled participants completed a qualitative in-depth interview (IDI) in English at PUEV, which occurred at Day 90 for all but four participants who terminated study participation early (but did complete an IDI before exiting the study). The IDI was conducted remotely using BlueJeans Video Network software by female social scientists with training in qualitative interviewing. Interviewers were based at RTI International (San Francisco and Berkeley, CA). The interviewer followed a semi-structured questionnaire guide to elicit participant experiences and opinions on study ring use, acceptability, adherence, and product preference. The interviews with 25 participants ranged from 28 to 88 min (average length of 50 min). Using notes taken during the IDI, the interviewer completed a debriefing report that summarized salient topics. The debriefing report was reviewed by another qualitative researcher and, upon finalization, shared with the protocol team. These reports provided prompt feedback and an opportunity to refine areas for probing in subsequent study interviews. Interviews were audio recorded and transcribed verbatim, and the resulting transcripts were reviewed for quality, finalized, and certified by the transcriptionist and project coordinator. Examples of questions in each of these data collection instruments are shown in Table 1.

Data analysis

The qualitative data were analyzed thematically (55). Of the three qualitative data coders on the analysis team, two had also conducted the interviews with study participants. Two interviewer-coders came from sociobehavioral public health research backgrounds, and the third coder came from a clinical

TABLE 1 Example questions from relevant data collection instruments, presented by sequence of procedures.

Baseline acceptability questionnaire (Day 0)	• How worried are you about using one vaginal ring for 3 months? ○ *Very worried, Somewhat worried, A little worried, Not at all worried* • Overall, how much do you like the ring? ○ *Dislike very much, Dislike, Like, Like very much*
Daily text message (bleeding)	• Since your last SMS survey or clinic visit, have you had any spotting or bleeding? ○ *No, Light bleeding/spotting, Moderate bleeding, Heavy bleeding*
Weekly text message (ring outage)	• Did your ring ever partially fall out? ○ *Yes, No* • Other than as instructed by study staff, was your ring ever fully out? ○ *Yes, No*
Follow-up acceptability questionnaire *Also see* Table 3 (Day 90)	• The [first/last] time you inserted the ring in your vagina, was it difficult or easy to insert? ○ *Very difficult, Difficult, Easy, Very easy, I never inserted the ring* • Overall, how did it feel to have the ring inside you every day? ○ *Very comfortable, Comfortable, Uncomfortable, Very uncomfortable*
In-depth Interview (Between Day 90 and Study Exit)	• When you first learned about the ring, what kinds of concerns did you have? • What is your opinion about wearing the ring when having sex? • Other than the specific times you were asked to remove the ring by study staff, when was your ring removed? • Given the options of having a product like the study ring that provided 2-in-1 protection and having two separate products – one for each kind of prevention – how would you decide what you prefer?

trial research background. All members of the analysis team were female and employed at an institution separate from that of the clinical trial and the product development teams. Quantitative data from the acceptability questionnaires and text messages were housed and managed at the Statistical Center for HIV/AIDS Research and Prevention (SCHARP) at Fred Hutchinson Cancer Research Center. These data, along with the IDI qualitative data, were analyzed at RTI International. The quantitative data were tabulated using Stata 17.0 (StataCorp LLC, College Station, Texas, USA).

The analysis team adapted codebooks from similar studies (MTN-036, MTN-038), incorporating constructs from the Theoretical Framework of Acceptability (56). All three coders on the analysis team applied a draft of the codebook to copies of the same study transcript to identify completeness of the codes and appropriateness of the definitions. Following this step, the codebook was updated and finalized. The coding team completed three sequential rounds of coding review, whereby each coder would review another coder's code application to a transcript. Coders met weekly to discuss questions that emerged, interesting findings, and reconcile any discrepancies identified in the coding review process. The transcripts were coded using Dedoose version 9.0.78 (SocioCultural Research Consultants, LLC, Los Angeles, CA, USA). Once coding was complete, code reports were generated to understand participants' positive and negative experiences that may have influenced adherence and their view of how acceptable the study ring was (codes included in code reports: Concern, Enabler, Future/Hypothetical, 2-in-1, Suggestions, Bleeding, Side effects/Safety, Shift/Expulsion).

All three coders contributed to writing summary memos that detailed the excerpts included in the code reports, the key messages conveyed, and themes and trends identified. The lead analyst used code reports and summary memos to develop a matrix table that documented each participant's overall assessments of the study ring, as well as salient experiences during their study participation. This matrix table was used to group women into how willing they would be to use this MPT ring in the future and analyze use experiences within those groups. This also allowed for re-categorizing participants by their assignment to the continuous or cyclic use regimen to examine any trends of use experiences within those groups.

The study protocol was approved by Advarra and the University of Pittsburgh IRBs. This study was collaboratively overseen by the Microbicide Trials Network (MTN), IPM, and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH). All participants provided written informed consent prior to any data collection activities.

Results

Participant demographics and prior use of contraceptive and vaginal products

Participants ranged in age from 21 to 43 years, with a median age of 36. The majority of participants were white, and two thirds held at least a college degree. The contraceptive methods used in the 30 days prior to study participation were male condoms ($n = 10$), non-hormonal intrauterine devices ($n = 5$), having a male partner who was sterilized ($n = 3$), fertility awareness ($n = 2$), withdrawal ($n = 1$), and/or female sterilization ($n = 1$). All participants had prior experience with vaginal insertion of a product such as a tampon, lubricant, sex toy, vaginal medication, menstrual cup, vaginal ring, or douche. Further descriptive characteristics of the study participants and their lifetime use of contraceptive methods and vaginally inserted products are provided in Table 2.

MPT ring preferences

After three months of using the study ring, participants quantitatively reported a variety of experiences with half of participants each reporting that they liked it or liked it very much ($n = 13$, compared to $n = 19$ at baseline) or disliked ($n = 12$, compared to $n = 6$ at baseline) the MPT ring. In qualitative interviews, participants generally reported positive reactions to an MPT ring in theory yet reported that this version of the MPT ring had several flawed features. When discussing the idea of an MPT ring, participants were consistently enthusiastic about the possibility of a single product providing simultaneous prevention of HIV and unintended pregnancy: this was seen as convenient and decreasing the burden on the user. The vaginal ring delivery mechanism – especially if the duration was for 90 days – was viewed to decrease user burden and the risk of user error. Having a self-inserted product was also seen as advantageous as it does not require a medical provider to administer, thereby reducing the need for repeat clinic visits. Finally, participants also appreciated that use of a vaginal ring was discreet and controlled by the user. When asked quantitatively to compare the study ring to male condoms as a method of HIV prevention or contraception, 80% of participants liked the ring at least as much as condoms. Regarding their preference to use a single or dual-purpose method for contraception and HIV prevention, an overwhelming majority (88%) preferred a combined method (Table 3).

Experiences with the study ring

Participants who reported negative experiences with use of this study ring described changes in vaginal bleeding ($n = 17$), perceived side effects ($n = 10$), and discomfort with the positioning of the ring in the vagina ($n = 21$). The impact of these challenges on their daily lives, in concert with individual willingness to navigate these challenges, led to a range of reported attitudes towards the vaginal ring. The most important challenges in determining participant views of the "real life" usability of the ring were: (1) more frequent or irregular ring-associated vaginal bleeding, (2) other perceived side effects (e.g., discharge, yeast infections, bacterial vaginosis, headaches, dizziness, acne, weight gain,

TABLE 2 Selected characteristics of study participants at enrollment.

	n = 25	%
Age in years [median (min - max)]	36	(21–43 years)
Hispanic or Latino	2	8
Race (mark all that apply)		
Asian	2	8
Black or African American	3	12
White	20	80
Highest level of education level completed		
High school graduate	4	16
Partial college	4	16
College graduate	8	32
Partial graduate school	3	12
Graduate school degree	6	24
Relationship Status		
Not in a relationship, single	10	40
In a relationship, not married	8	32
Married	6	24
Divorced	1	4
Currently has a primary sex partner	15	60
***Gender of primary sex partner* (*n* = 15)**		
Man	13	87
Woman	1	7
Transgender man	1	7
Study product assignment		
Continuous (One 90-day cycle)	12	48
Cyclic (Three 28-day cycles with two-day removals periods)	13	52
Prior use of contraceptive methods*		
Male condom	25	100
Oral contraception	15	60
Emergency contraception	11	44
Contraceptive patch	3	12
Depot medroxyprogesterone acetate	6	24
Contraceptive/hormonal vaginal ring	4	16
Spermicidal sponge, foam, cream, or jelly	4	16
Intrauterine device	8	32
Implant	2	8
Withdrawal	16	64
Fertility awareness-based methods	9	36
Female sterilization	1	4
Male sterilization	3	12
Other [spermicidal suppository, assumption of male infertility]	2	8
Prior use of non-contraceptive vaginal products		
Vaginal medication in cream or gel form	12	48
Douche/vaginally applied "hygiene" product	6	24
Tampon	24	96
Menstrual cup	10	40
Personal or sexual lubricant	17	68
Sex toys	15	60
Other [Water]	1	4

*All participants reported prior use of at least one contraceptive method. No participants reported exposure to the female or internal condom or cervical barriers.

decreased libido, vaginal odor, depression, mood swings) and (3) experiences of the ring slipping or falling out completely (partial or complete expulsions).

TABLE 3 Comparison of study ring to male condoms as reported in the 3-month follow-up acceptability questionnaire.

	n = 25	%
As a method to prevent HIV, which do you prefer to use - the ring or the male condom?		
Ring	7	28
Condom	4	16
Neither - I dislike both study products	1	4
Both - I like both study products equally	13	52
As a method OF CONTRACEPTION, which do you prefer to use - the ring or the male condom?		
Ring	10	40
Condom	4	16
Neither - I dislike both study products	1	4
Both - I like both study products equally	10	40
Would you prefer to use separate methods for contraception and HIV prevention or a combined method?		
Separate methods	0	0
A combined method	22	88
Don't know	1	4
Don't care	2	8

The 25 participants fell into three groups based on themes that emerged from this qualitative analysis. The first group consisted of a minority of participants ($n = 3$) who had minimal negative experiences with the study ring and concurrently stated they would use it in its current form. However, most participants experienced challenges in their day-to-day lives significant enough to negatively affect their willingness to use the ring. Among them, the second group ($n = 14$) found the product to be desirable in some ways and would consider using it in the future under certain conditions (i.e., fewer ring expulsions, less undesirable changes in bleeding, higher perceived individual HIV acquisition risk). The third group ($n = 8$) found that using the study ring was so problematic that they would never be interested in using it. Marital status was associated with the three groups, a demographic trend that would need to be further explored. Participants in the first group who were most willing to use the ring were all single, while being married was associated with the third group of participants unwilling to use the ring.

Willing to use the study ring (*n* = 3/25, 12%)

In qualitative in-depth interviews, 3 participants discussed interest in using this MPT vaginal ring in a "real life" situation. They did not report any perceived negative side effects associated with using the study product, and all experienced less vaginal bleeding, which was described as an unanticipated benefit of using the study ring. Light spotting was experienced by two of them and was reported as not outweighing the overall benefits of lighter/discontinued monthly periods. This group reported mixed experiences with the ring slipping and none of them experienced complete expulsion of the ring.

One of these three participants (see Figure 2A) was sexually assaulted while using the MPT ring. This participant was unique in that she experienced a transient increase in her personal risk for HIV acquisition, saying, "*it's now very real to me that this is a very real, like, condition that I can get.*" She reported that she

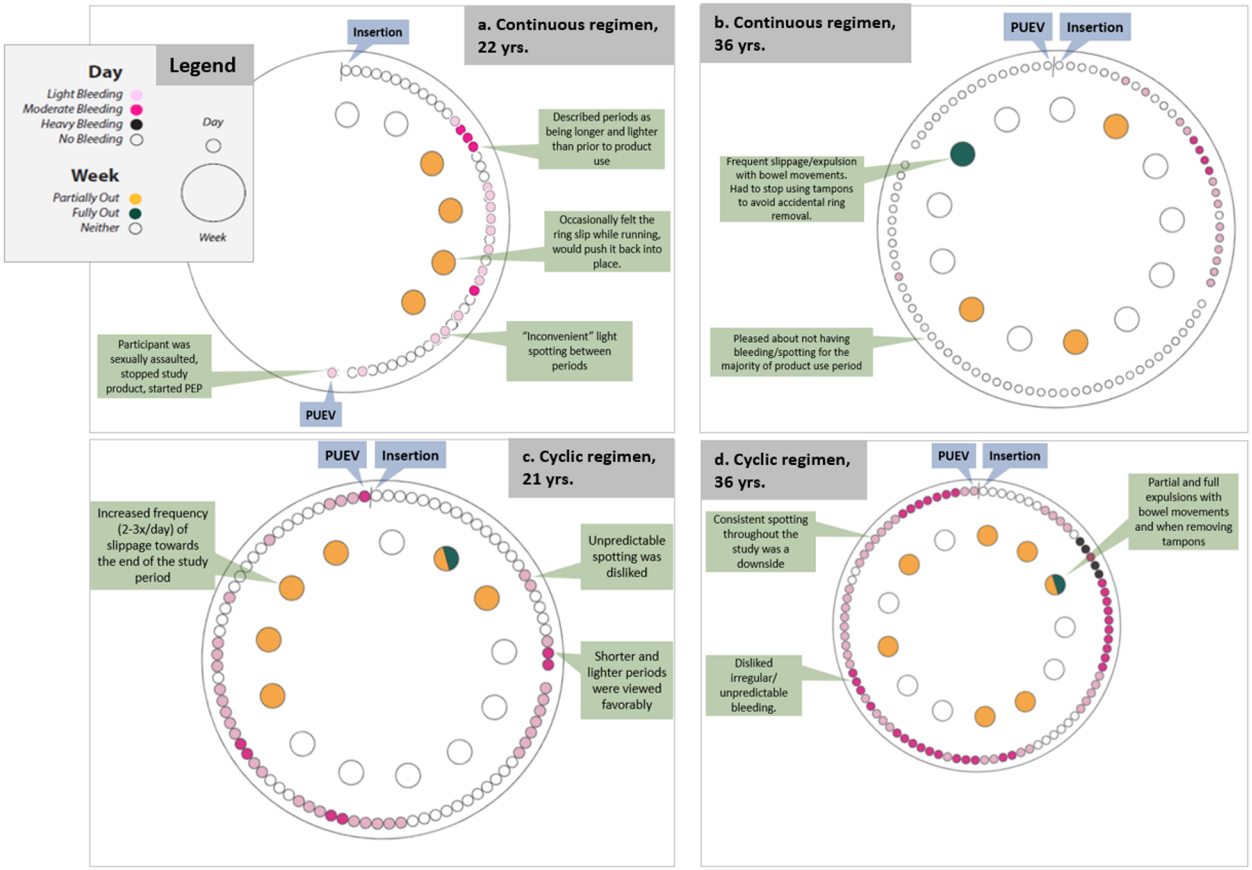

FIGURE 2
Participant reports of bleeding and slippage/expulsion: four illustrative cases using data from qualitative interviews and SMS reports.

would have liked to use the ring even if it were just a contraceptive product, but after the sexual assault, she felt that the added HIV indication was also very important. She said, "*If the ring works as like a birth control, that would be just enough for me, but the like HIV part is like huge now that I've experienced what I have*" (age: 22, regimen: continuous).

Would use the study ring, with caveats (*n* = 14/25, 56%)

Over half of the participants ($n = 14$) reported they would consider possible use of this MPT ring in the future, if improvements were made to the ring. Many of these women reported that they had significant experiences with the ring (e.g., spotting in between or instead of menses; side effects like acne, discharge, yeast infection, changes in vaginal bleeding, vaginal odor, depression and anxiety; and/or challenges with slippage and expulsion) that interfered with daily activities and that were not acceptable given their low-risk category. These participants also reported willingness to use this ring – in its current form – were they to be at higher HIV risk. A few participants noted that since this is an MPT, a person would have to perceive themselves at high risk for HIV and be highly motivated to prevent pregnancy to be willing to manage the downsides of this MPT ring.

One of these participants (see Figure 2B) reported this MPT ring as "so great," particularly the long-acting characteristic and the ability to self-administer. After insertion she experienced some bleeding which soon stopped. For the remainder of the study, she experienced no spotting or bleeding which she "loved" and none of the negative side effects she had experienced with other hormonal contraceptives (i.e., acne, changes in mood, unpredictable bleeding). However, her experience with frequent partial and full expulsions ultimately would have driven her away from using this MPT ring. She said, "*I think it's so great to have two of these products in one, and that my only, my only caveat in it would be, would be it falling out. That was just, if there's some way to tweak that I think this would be, this would be fantastic*" (age: 37, regimen: continuous).

Another participant (see Figure 2C) reported a more negative experience with use of the ring. Towards the end of the study, her ring frequently slipped out of place. She also reported the ring as unpleasant to use during sex and that she experienced unpredictable spotting and a noticeable vaginal odor with ring use. This participant also reported her perspective that someone who was at higher risk would find that the benefits of using this ring (extended duration, low opportunity for user error, shorter and lighter monthly periods) would outweigh the downsides.

Would not use the study ring (n = 8/25, 32%)

Eight participants reported that they would not use this ring, even if they were at higher HIV risk. These participants reported that either the ring itself was unusable or the ring was incompatible with their body. A subset of these participants (n = 3) hypothesized about changes to the ring that would lead them to reconsider. Though these women did not think this ring was "right" for them in its current form, many continued to like the MPT ring in theory, and thought it could be right for others who had higher HIV risk or who did not experience as many challenges.

Most of the women who said that they would not use this ring – at least in its current form - reported issues with vaginal bleeding and/or the ring staying in place. Unpredictable breakthrough bleeding, heavy and painful periods, and/or prolonged bleeding were reported among 5 of these 8 participants and were seen as unacceptably disruptive to these participants' lives. Multiple participants (7 of the 8 in this group) reported that the ring frequently slipped out of place and was on the verge of complete expulsion during bowel movements, causing the user to need to hold it in place or re-position it daily or more frequently. Participants who experienced regular sensations of ring slippage reported a mental burden associated with constant worry about expulsion and about needing to re-position the ring.

A participant (see Figure 2D) who experienced both constant bleeding and frequent slippages liked some aspects of the ring (dual indications and the fact that one could, in theory, "insert it and forget it"), though she reported that she spent mental energy worrying about the ring falling out whenever she had a bowel movement and tried to plan her day so she would be home for bowel movements rather than deal with public restrooms. Even though she typically experienced heavy flow and strong cramping during her period prior to ring use, she thought that was preferrable to the "annoying" ongoing spotting while using the ring. She also experienced three urinary tract infections during the study which was atypical for her. Together, these factors led her to state that she would not consider using this ring in the future.

Perspectives on continuous vs. cyclic regimen

Participants who were randomized to continuous ring use conveyed more positive experiences compared to those randomized to cyclic use (Table 4), with 75% of continuous users and 58% of cyclic users expressing willingness to use in the future (with or without caveats). Two of the three participants who reported willingness to use the ring in its current form were assigned to the continuous regimen, and the third participant was assigned to the cyclic regimen but appeared to view herself as a continuous user[a]. Of those who were willing to use with caveats, half were assigned to the continuous regimen. Of those who reported unwillingness to use the ring at all in its current form, a majority (5/8; 63%) were randomized to the cyclic use regimen.

TABLE 4 Willingness to use and regimen preference, by assigned use regimen (continuous vs. cyclic) as reported in the follow-up acceptability questionnaire.

	Assigned to continuous use regimen (n = 12)	Assigned to cyclic use regimen (n = 13)
Level of willingness to use in the future		
Willing to use	2	1[a]
Would use, with caveats	7	7
Would not use	3	5
Regimen preference		
Continuous use	10	6
Neutral	2	3
Cyclic use	0	4

[a]This participant was randomized to the cyclic regimen and used the ring cyclically per clinical records. However, during her interview she referred to herself as among the group of continuous users, stating that she "did have it in continuously for ninety days."

Of the 12 participants assigned to continuous use of the ring, there was a strong preference for continuous use if given the option (10 preferred continuous, 2 were neutral). When describing their motivations, participants cited a continuous use regimen as affording greater peace of mind, saying, "…*leaving it in is probably better because with any user-dependent [laughter] method, like the less thing the user has to do, the less prone to error it is*" (age: 29, regimen: continuous). These participants also thought that removing it wouldn't make any difference but had concerns about the logistics of removing and reinserting it. One participant said, "*I prefer continuous, the less I have to worry about taking things out and remembering to put it back in, the better*" (age: 36, regimen: continuous).

The 13 participants assigned to the cyclic regimen reported mixed opinions on use regimen preference. Six of them (46%) expressed a preference for continuous use, 4 (31%) favored cyclic use, and 3 (23%) were neutral. Those in the cyclic regimen who expressed interest in continuous use cited anticipated convenience, avoidance of extra health facility visits (if required for each removal/insertion), and avoidance of necessary logistics to store the ring during the 2-day removal period (i.e., refrigerating it sanitarily and at home) as reasons for their expressed preference. Of the 4 participants who preferred cyclic use, three cited having a "break" from the worry about it slipping/falling out as the predominant rationale. Other reported reasons for favoring cyclic use included a perception that the 2-day removal period may have aligned with lighter bleeding and that removing the ring would offer a scheduled opportunity to check on the ring, as one participant said: "*I don't like the idea that you're just going to forget about it for months at a time*" (age: 43, regimen: continuous).

Feedback to the product developer

Ongoing challenges with vaginal bleeding issues, recurrent ring slippage, and expulsions with this version of the MPT vaginal ring were regularly reported and discussed with IPM (the product developer) throughout the life of the study. The product

[a]This participant was randomized to the cyclic regimen and used the ring cyclically per clinical records. However, during her interview she referred to herself as among the group of continuous users, stating that she "did have it in continuously for ninety days."

developer was part of the study management team, allowing for frequent conversations where emerging themes from the qualitative data could be discussed alongside updates from the clinical trial team. This informed the design of the next iteration of the MPT ring currently being evaluated in the US (NCT05041699). The dapivirine vaginal ring has a considerably higher Shore score (with increasing Shore score reflecting increased hardness), compared to the study MPT ring used in the MTN-044 study (57). A common concern of participants in dapivirine vaginal ring clinical trials was the rigidity of the ring. For the MPT ring used in this study, the addition of levonorgestrel to the matrix ring formulation resulted in a softer ring that may have increased the rate of slippages compared to the stiffer DPV-only ring. Though the softness of this MPT ring may help to address prior user concerns about the firmness of DVRs expressed previously, the more supple quality of this MPT ring relative to other prior vaginal rings may be inadvertently at the expense of ring retention in the vagina. Due to these challenges, modifications to the product formulation have subsequently been undertaken, and the Shore score of the re-formulated ring is similar to that of other vaginal rings approved for use by regulatory authorities.

Discussion

Women in the MTN-044/IPM 053/CCN019 Phase I trial in the United States favored the concept of an MPT vaginal ring for simultaneous prevention of HIV and unintended pregnancy. Though the study ring was well-tolerated during the clinical trial based on a low rate of discontinuation (48), most participants reported that they would not want to use this version of the MPT ring due to challenges they experienced with the ring during the study. However, most participants also expressed interest in the study ring if their personal risk for HIV and/or motivation to prevent pregnancy increased in the future, or changes were made to the ring that would result in fewer expulsions or less vaginal bleeding. Participants approved of an MPT ring that would be easy and convenient to use for 3 months, thereby decreasing user burden and preventing unnecessary user error. Ideally, the ring could be initiated, administered, and controlled by the user and thus reduce repeated clinical visits with a medical provider.

However, participant views of the MPT ring used in the study were more varied, with more positive views expressed by those who experienced fewer challenges (slippages, expulsions, side effects, changes in bleeding) and those who were assigned to the continuous regimen. Compared to previous research where participant opinions of products increased after use (13, 40), it is notable that participants in this study reported liking the ring less at follow-up than at baseline. This highlights two important reflections: First, the challenges that participants encountered with using this ring dampened the original enthusiasm that the participants had (all of whom had experience with vaginally inserted products). Second, this supports the finding in other studies which suggested the positive change in attitude after exposure was a reflection of overcoming initial apprehension and finding the product more desirable than at baseline, rather than due to social desirability. These findings are useful to understand nuances of user preferences for an MPT ring, to inform future MPT study designs and reformulation of next generation MPT rings, and to encourage deeper discussion about the relationship between consumers' increasing desire for a perfect prevention product and an effective product with limitations.

Although many study participants saw how an MPT ring could be an easy-to-use, convenient, user-controlled option, the majority of the participants were not interested in using the study ring in its current form. About 1/3 of participants stated that some characteristics of the vaginal ring would have to change to make it usable for them. Dissatisfaction with the ring came from three main issues: unanticipated, heavy, or prolonged bleeding; ring slippage and expulsion; and other perceived side effects such as weight gain, acne, and changes in vaginal discharge/odor. Future MPT studies would benefit from exploring the people's willingness to manage unscheduled bleeding and other side effects as factors influencing ring acceptability.

When determining whether the ring was a good "fit" for them (or someone else), one of the prevailing caveats that women shared was the user's self-perceived risk for both HIV and unintended pregnancy. It is important to note that women in this study had – by requirement – low risk for both; thus, they often contrasted their own willingness to use this product with others who may have higher risk levels, or with hypothetical situations they judged to be riskier. Many of them hypothesized that they would use the ring if they felt more at risk for HIV infection and unintended pregnancy. To better tease out the relationship between participants' perceived risk levels and their willingness to use the ring, it is essential for future acceptability research to include women with various life contexts and needs for prevention of HIV and pregnancy.

In this trial, user perspectives reflected a preference for continuous (rather than cyclic) use: participants assigned to the continuous regimen reported more positive experiences, and most participants – regardless of study arm assignment – reported preferring a continuous ring for hypothetical future use. The smaller portion of participants who preferred cyclic use largely cited a desire to take a "break" from bleeding/slippage related challenges, rather than proactively preferring a cyclic regimen. Though the continuous regimen was preferred primarily for its convenience and less user burden, it is worth pointing out that making a choice in real life may be more complex. First, these women only used one regimen, thus lacking first-hand experience with both regimens to make a direct comparison. Therefore, if feasible, future studies may consider a crossover design to allow participants experience both regimens for individual-level comparison. Secondly, the prevention efficacy of either regimen, in addition to the ring's pros and cons, will need to be factored in decision-making. Cyclic use may represent an opportunity for user error (loss/damage, forgetting to replace, etc.) which could compromise effectiveness. Additionally, while a cyclic product has been traditonally used in contraception to allow withdrawal bleeds, the impact of periodic ring removal on

HIV prevention efficacy is not well understood. While a longer period of ring removal in a cyclic regimen may be necessary to see an improvement in bleeding patterns (58), this is constrained by the need to maintain protective dapivirine levels. This underscores the importance for future research to focus on elucidating the pharmacokinetic and pharmacodynamic ramifications of ring removals so that women can make informed decisions based on the timing of ring insertions and removals relative to sexual exposures. As indicated by the minority who preferred the cyclic regimen who appreciated the chance to take a "break" from product use, MPT ring users may appreciate the opportunity to decide if and when to do event-based ring removals (e.g., for a sexual encounter, to wash the ring, in certain cases of pregnancy ambivalence) if periodic removals do not affect efficacy.

Over decades of development for reproductive health prevention products, particularly contraceptive products for women, the bar for achieving high product acceptability has been gradually raised. The current generation of reproductive health prevention products research for all genders has a refreshing and inspiring push for products to be *desirable* – not merely tolerable, or even acceptable (59). With this evolution of standards for biomedical prevention, and with multiple options becoming a reality (beyond the current contraceptive method mix), consumers of health products rightfully have a lower tolerance for undesirable side effects and negative impacts on their day-to-day lives. The data in this study with low-risk participants suggests that women who found MPT ring use to be relatively unobtrusive (lighter bleeding, few side effects) also found the benefits of HIV and pregnancy prevention (and possibly reduced menstrual bleeding) appealing, as there were no real downsides to counterbalance them. However, for users who encountered challenges (increased bleeding, slippage, and other side effects) in their daily lives, the product would need to present very strong benefits to outweigh any negative experiences and be deemed worthwhile. Even women at higher risk for both HIV acquisition and unintended pregnancy could judge a product as acceptable in short research studies, but excessive unfavorable side effects could sway them away from continued use – despite their risks – and present a barrier to real-world uptake and/or adherence. While high perceived risk of HIV acquisition and unintended pregnancy may be a facilitator to acceptability of a MPT vaginal ring, women often underestimate their actual risk (60–62). Therefore, a particular strength and opportunity for an MPT vaginal ring may be the ability to frame it positively as a more holistic tool that helps users optimize their sexual health, rights, and pleasure, as suggested in the "triangle approach" presented by Gruskin et al. (63), rather than using risk-based messaging which can be perceived as judgmental and discriminatory.

Strengths and limitations

The MPT ring in this study is the first iteration of a dual-purpose preventive vaginal ring. As the first clinical trial in which participants compared cyclic and continuous use of a co-formulated contraceptive/HIV preventative MPT vaginal ring over 90 days, this study provides insights into factors that resulted in a wide range of acceptability related to side effects associated with the contraceptive indication, ring retention, and use of the ring cyclically (2-day removals every 28 days) vs. continuously for 90 days. These factors will help to inform future MPT ring development and acceptability research design.

An important limitation of this study is the participants' low likelihood for both pregnancy and HIV acquisition at baseline: only 13 of the 25 participants (or 52%) were sexually active with a male primary partner. Low likelihood of HIV acquisition and pregnancy was an intentional feature of the eligibility criteria for the Phase I trial, yet it limits our ability to understand how women in different circumstances relative to HIV and/or unintended pregnancy may have differed in weighing the indication-related benefits of the ring against the challenges experienced with study product use. Many study participants posited that they might have felt differently about the study ring had they been at higher risk of HIV and/or pregnancy. It will be important to pursue further acceptability research with women with varying prevention needs in next-stage clinical trials of the second generation of this MPT ring. By design, our sample size was small ($n = 25$). The sample also lacked diversity (single-site study, all participants were recruited in Pittsburgh, Pennsylvania, USA, and the study sample had relatively high levels of education and limited racial and ethnic diversity). By nature of the recruitment and enrollment process, all participants agreed to participate in a study where they knew they would be using a vaginal ring, indicating receptivity to the idea of vaginal ring usage prior to study product initiation. Additionally, all participants had prior experience with vaginally inserted products. The increase in participants reporting at follow-up (from baseline) that they disliked the ring suggests that the familiarity or comfort with vaginal product usage did not necessarily translate into comfort with this product.

Conclusion

Participants in this study had positive reactions to MPT rings in theory, yet the study MPT ring raised several concerns related to user experience and product acceptability. Though all participants understood and appreciated the benefits of a woman-initiated, longer-term, MPT product, this sample of low-risk participants found changes in vaginal bleeding, the ring slipping/falling out of place, and other side effects problematic. Importantly, these study findings contributed to development of the next generation of this MPT ring. Conducting qualitative research with participants during early-stage clinical trials can offer critical design modifications to product developers that may help to improve the future success of biomedical technologies.

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 human participants were reviewed and approved by Advarra and University of Pittsburgh IRBs. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MKSQ, EL and AvS: all contribution to the conceptualization and execution of this analysis. MKSQ: conducted qualitative data collection and contributed to the coding of the qualitative data, MKSQ and AvS contributed to the analysis of coded qualitative data, writing, and revision of the qualitative results. EL: conducted quantitative analyses and wrote and revised quantitative results. AvS: provided scientific leadership for these analyses. As protocol chair and co-chair, SA and BC (respectively) contributed scientific leadership and guidance to the study team, and provided valuable input during the development of the manuscript. MKSQ contributed significantly to drafting of the manuscript. BD, JB and DB: all provided scientific leadership and guidance to the study team. 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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Tenofovir vaginal film as a potential MPT product against HIV-1 and HSV-2 acquisition: formulation development and preclinical assessment in non-human primates

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Tenofovir (TFV) is an adenosine nucleotide analog with activity against HIV and HSV-2. Secondary analyses of clinical trials evaluating TFV gel as pre-exposure prophylaxis (PrEP) for HIV have shown that gel formulations of TFV provide significant protection against both HIV and HSV-2 acquisition in women who had evidence of use. An alternate quick-dissolving polymeric thin film, to deliver TFV (20 and 40 mg) has been developed as a potential multipurpose technology (MPT) platform. Film formulation was developed based on excipient compatibility, stability, and ability to incorporate TFV doses. Placebo, low dose (20 mg), and high dose (40 mg) films were utilized in these studies. The developed film platform efficiently incorporated the high dose of TFV (40 mg/film), released more than 50% of drug in 15 min with no *in vitro* toxicity. Pharmacological activity was confirmed in an *ex vivo* HIV-1 challenge study, which showed a reduction in HIV-1 infection with TFV films. Films were stable at both doses for at least 2 years. These films were found to be safe in macaques with repeated exposure for 2 weeks as evidenced by minimal perturbation to tissues, microbiome, neutrophil influx, and pH. Macaque sized TFV film (11.2 mg) evaluated in a pigtail macaque model showed higher vaginal tissue concentrations of TFV and active TFV diphosphate compared to a 15 mg TFV loaded gel. These studies confirm that TFV films are stable, safe and efficiently deliver the drug in cervicovaginal compartments supporting their further clinical development.

KEYWORDS

HIV prevention, genital herpes, multipurpose technology, tenofovir, vaginal film, women health

1. Introduction

Approximately 38.4 million people are currently (2021) living with human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS) (1). An additional 40.1 million people have died of AIDS-related causes since the start of the HIV pandemic. Women, especially those 15–24 years old, are at increased risk

of infection compared to men in the same age bracket. In sub-Saharan Africa (SSA), 6 in 7 new infections in the 15–19 age group are among adolescent girls and young women (1). While progress on vaccine development continues, to date no HIV vaccine is available. Therefore, the need to provide alternative prevention strategies such as topical pre-exposure prophylactic (PrEP) products for female use is paramount. Infection with herpes simplex virus-2 (HSV-2), which causes genital herpes, significantly increases the risk of HIV acquisition. Past infection by HSV-2, the leading cause of genital ulcers, is noted in more than one-third of the general population in parts of SSA (2). As per the World Health Organization, an estimated 491 million people worldwide aged 15–49 years have HSV infection (3). Women are twice as likely to contract HSV-2 infection compared to men, which is due to the efficient sexual transmission from men to women and relevant sociocultural factors. The high prevalence of HSV-2 in population vulnerable to HIV reinforces the need for combined prevention of HIV and HSV-2 using multipurpose prevention technologies (MPTs).

Topical PrEP includes products that are applied vaginally or rectally to prevent transmission of HIV and other sexually transmitted infections (STIs). Several studies have explored such products for prevention of HIV-1 acquisition (4, 5) and combined HIV-1 and HSV-2 acquisition (6). The most advanced of these products is the dapivirine intravaginal ring, which showed reduced HIV-1 infection in women in two large Phase III clinical studies (ASPIRE and the RING Study) (7, 8) and is currently recommended for use by women at substantial risk of HIV by the World Health Organization (WHO). PrEP products evaluated to date have been investigated for either coitally-dependent (on-demand) or independent (long-term) use. On-demand products provide an option for protection, which is easily reversible and provides flexibility of dosing without the risk of long-term exposure to drugs (4).

The current work provides rational development and safety testing of a tenofovir (TFV) vaginal film dosage form as an on-demand multipurpose technology (MPT) product against acquisition of HIV and HSV-2. TFV is an adenosine nucleotide analog with activity against HIV and HSV-2 (9). TFV salt forms are widely used in oral products for HIV treatment (10). TFV has been formulated into hydrogels, nanoparticles, nanoparticles-in-films, nanofibers, oral and vaginal tablets, films, and intravaginal rings (11–17). In multiple preclinical and clinical evaluations of PrEP, TFV has been shown to reduce HIV acquisition (18). Daily use of a combination oral tablet containing tenofovir disoproxil fumarate (a TFV salt form) and emtricitabine (Truvada®) was shown to protect from HIV acquisition (10, 19). Three clinical trials evaluated a TFV vaginal gel for PrEP (10, 18, 20, 21), however, inconsistent efficacy results were observed, which were partly attributed to low user adherence leading to reduced protection (22). Interestingly, a separate post-hoc analysis of one of the trials (CAPRISA 004) showed that TFV gel use reduced HSV-2 acquisition by 51% compared to placebo in women that adhered to the TFV gel product (23). Efficacy of vaginally delivered TFV in preclinical models of HSV-2 acquisition has been well established (24). Anti HSV-2 effect of oral TFV prodrugs and combination products has also been investigated in several studies with modest to no effect on HSV-2 acquisition (25, 26). High local fluid and tissue levels of TFV and TFV-diphosphate (TFV-DP), the active metabolite of TFV, will likely improve efficacy.

Some of the known problems with gels such as messiness, leakiness, and non-stealth characteristics could negatively impact user adherence, although these claims have not been proven. Nevertheless, alternate dosage forms with improved user acceptability are advantageous. Polymeric thin films have been identified as an acceptable dosage form option by users for vaginal applications in several studies (27, 28). Films are low cost, applicator-free products that can be used in a discreet manner if required. Moreover, due to their small size with low mass (<0.5 g), films are less likely to cause any undesirable effect on innate antimicrobial factors such as microbiome and glycome (29). Given these advantages, vaginal film formulations containing TFV were developed as an alternative delivery system to gel formulations.

Previous clinical studies, which evaluated the TFV gel product, utilized TFV at 1% w/v delivered in a 4 ml volume (equivalent to 40 mg TFV per dose). The goal of this work was to develop a stable and safe film dosage form that can incorporate TFV at levels equivalent to that previously used. Incorporating TFV in a vaginal film platform was met with several challenges related to physical instability. In this work, systematic and rational formulation development of TFV vaginal films as well as preclinical safety and pharmacokinetic (PK) assessment in pigtail macaques is presented. The developed platform has been evaluated in women (published elsewhere) and found to be safe (30, 31).

2. Materials and methods

2.1. Materials

Film excipients included sodium carboxymethylcellulose low viscosity (NaCMC-LV; Spectrum Chemicals, New Brunswick, NJ, USA), hydroxypropyl methylcellulose (HMCE5; Methocel E5 Premium LV and K4M, DOW chemicals, Midland, MI, USA), hydroxyethyl cellulose (HEC; Natrosol 2,50l Pharm, Ashland Polymers, Wilmington, DE, USA), and polyvinyl pyrrolidone K-90 (PVPK90; Fluka, St. Louis, MO, USA). CellTiterGlo™ assay kit was obtained from Promega, Madison, WI, USA. All the other chemicals and reagents were purchased from Fisher Scientific and Spectrum Chemicals.

2.2. Formulation development

2.2.1. Drug-polymer compatibility using microscopy

Physical stability of TFV was assessed in a series of polymers such as HPMCE5, HEC, PVPK90, and NaCMC-LV. TFV was dissolved in MilliQ water using equimolar sodium hydroxide on

a magnetic stirrer. Polymers were then added into TFV containing solution and mixed thoroughly to achieve polymer: drug ratio of 1:1, 2:1, 3:1, 4:1, 5:1 and 6:1. The resulting solution (0.5 ml) was transferred onto a 12-well cell culture plate and dried at 65°C for 3.5 h. The culture plate was then stored over saturated salt solution of 75% relative humidity (RH) at 40°C. Presence of crystals was examined under a microscope on day 7.

2.2.2. Film manufacturing

Films were manufactured using solvent cast method. A liquid blend containing all excipients was prepared by weighing required amounts of excipients and mixing in MilliQ water using an overhead mixer (Eurostar power control visc, IKA, Wilmington, NC, USA) at 50 rpm to achieve complete polymer dissolution. Glycerin was used as a plasticizer. TFV containing polymer blend was prepared by dissolving TFV in the polymer mix. The final pH was adjusted to 6–6.5 using equimolar sodium hydroxide for TFV containing formulations. To manufacture films, the polymer solution was poured on an automatic film applicator (4,340, Elcometer, MI, USA) and dried at 71°C for 16 min. The polymer sheet was peeled off the applicator and cut into $2'' \times 2''$ unit doses using a die cutter press (Tipmann Die Cutter, IN, USA). TFV was loaded in films at 1% or 2% w/w in the formulation mix, which produced 20- (low dose) or 40-mg (high dose) per unit dose of a $2'' \times 2''$ film. Films utilized in non-human primate (NHP) studies were cut into $1.1'' \times 1.1''$ to accommodate anatomical differences between humans and pigtail macaques.

2.3. Characterization of TFV films

2.3.1. Physical properties

Weight and thickness of the films were measured using a calibrated balance and calipers respectively. Water content was determined using Karl Fischer autotitrator (890 Titrando, Metrohm, FL, USA). A TX-XT Plus texture analyzer (TA instruments, DE, USA) was used for mechanical characterization. To determine puncture strength, films were placed on the film holder and a puncture probe (spherical end: 1/8 inch diameter) was passed mechanically at 1 mm/sec through the center of the film holder's aperture. The puncture strength was calculated using the following formula:

$$\text{Puncture strength}\left(\frac{\text{N}}{\text{mm}}\right) = \frac{\text{Force at break point (N)}}{\text{Thickness of the film (mm)}} \quad (1)$$

2.3.2. Drug content in films

TFV content in individual films was determined using solid phase extraction (SPE) of TFV and subsequent quantitation by ultra-performance liquid chromatography (UPLC, Acquity, Waters Corporation, MA, USA) equipped with a TUV detector and Empower data acquisition and processing software. For SPE, TFV-containing film was dissolved in 40 ml milliQ water. One ml of the film solution was further diluted with equal volume of 2% formic acid. One ml of this diluted solution was loaded on a previously activated SPE cartridge [Oasis MCX extraction cartridge, 1 cc (30 mg), Waters, USA]. The residual polymer was washed by eluting the SPE cartridge with 1 ml of 2% formic acid. TFV was extracted with 5% methanolic ammonium hydroxide solution from the eluent. Extracted TFV was estimated after an appropriate dilution with MilliQ water using UPLC. TFV was detected at 260 nm. Separation was achieved by injecting 3 µl of solution on an Acquity UPLC BEH C18 column (1.7 µm 2.1 × 50 mm, Waters) at ambient temperature. The flow rate was maintained at 0.3 ml/min. The mobile phase consisted of 90% phosphate buffer (10 mm K_2HPO_4 and 4 mm t-Butylammonium bisulfate) adjusted to pH 5.7, and 10% methanol. Drug content was estimated based on a linear regression equation generated from calibration standards.

2.3.3. *In vitro* release

In vitro release of TFV from the films was assessed using a USP 4 flow-through apparatus (CE7 smart, Sotax Corporation, MA, USA) connected to a fraction collector. TFV films were placed into 12 mm polycarbonate cells. Dissolution was carried out by circulating 100 ml of 1× PBS at a flow rate of 162 ml/min for 1 h in a closed loop configuration at 37°C. At pre-determined time points, 0.5 ml samples were collected using a programmable fraction collector. Samples were analyzed for TFV amount by UPLC as described above after appropriate dilutions with MilliQ water.

2.3.4. Compatibility with lactobacilli

Film compatibility with *Lactobacillus* species was assessed by standard microbicide safety test (32) using two American Type Culture Collection strains *L. crispatus* 33,197 and *L. jensenii* 25,258 and one clinical strain of *L. jensenii*, LBP 28Ab. TFV films were dissolved in 1.25 ml ACES [N- (2-Acetamido)-2-aminoethanesulfonic acid] buffer. This solution was mixed with 1.25 ml of lactobacilli suspension in 1× phosphate buffered saline (pH 7.4). The bacterial suspension containing dissolved film was incubated at 37°C for 30 min. Samples were taken before and after incubation was complete. Bacterial viability was determined by standard plate count. A sample was considered compatible with lactobacilli if the reduction in viability was <1 log10. ACES buffer treated or untreated bacterial suspension served as controls for the experiments.

2.3.5. Toxicity in TZM-bl cells

In vitro toxicity of TFV film towards TZM-bl cells was evaluated by standard CellTiter-Glo® assay. TFV containing and placebo films were dissolved in 4 ml of saline. Ten-fold serial dilutions were made up to $1{:}10^7$ of original solution. TZM-bl cells were plated at 1×10^4/well in a 96-well clear view plate and left to adhere overnight. Cells were treated with dilutions of film solution and incubated for 48 h at 5% CO_2 and 37°C. After 48 h, half the media was replaced with CellTiter-Glo® and luminescence was recorded. Percent viability was compared against untreated cells that received cell culture media and incubated similarly.

2.3.6. *Ex vivo* anti-HIV activity and toxicity

Human ectocervical tissues (explants) from pre-menopausal women (IRB # PRO09110431) were pre-exposed to TFV film containing solutions and experiments were conducted as previously reported (33, 34). Briefly, tissues were secured in a transwell plate with the epithelial side up. Tissues in culture were exposed to control (no treatment), placebo, or 20 or 40 mg TFV films dissolved in 2 ml media. Each transwell received 100 µl of treatment media followed by 100 µl of HIV-1_{BaL} (5×10^4 $TCID_{50}$) in media. After 24 h culture, explants were washed, fresh media was added and incubated at 37°C/5% CO_2. Media collected on various days for 21 days (and replenished) was assayed for p24 to assess infectivity. Ectocervical tissue toxicity was also conducted after 24 h exposure to treatments or control (200 µl volume) in 12 well plates. After exposure, explants were washed by dispensing DPBS. The explants were transferred and incubated with MTT solution at 37°C/5% CO_2 for 3 h and optical density (OD) of the solution was recorded at 595 nm. The explants were collected, dried overnight, and weight was recorded to correct OD by dividing with tissue weight.

2.3.7. Stability testing

Films manufactured at two doses were subjected to a 24-month long-term stability at 25°C/60% RH and a 6-month accelerated stability at 40°C/75% RH according to International Conference on Harmonisation (ICH) guidelines. Stability samples collected at different time points were assessed for weight, thickness, TFV content, water content, puncture strength, and dissolution. Additionally, compatibility of films with lactobacilli was evaluated at specific time points.

2.4. Tenofivir film assessment in macaques

2.4.1. Test products

For testing film product PK and safety in macaques, the size of the films used was 1.1″ × 1.1″, which is approximately one-third of the human size 2″ × 2″. Films containing 11.2 mg and 5.1 mg TFV (equivalent to 40 and 20 mg/film human dose respectively) and a drug-free placebo film (matched formulation with no active drug) were evaluated in the multiple dosing safety study. Of note, pharmacokinetic evaluation was performed using the high dose 11.2 mg film (equivalent to 40 mg human size film) and compared against a gel product (15 mg dose).

2.4.2. Animals

Sexually mature female *Macaca nemestrina* were obtained from a colony of animals at the Washington National Primate Research Center. Prior approval for use of the monkeys in the protocols was obtained from the Institutional Animal Care and Use Committee at the University of Washington. Animals were handled humanely, and experiments were performed within the National Institutes of Health's laboratory animal use guidelines. Animals were not hormonally synchronized or otherwise altered to control for menstrual or hormone status.

2.4.3. Tenofovir film safety and PK evaluation in pigtail macaques

Films were evaluated in the NHP model for PK and safety after vaginal administration. Six macaques were enrolled in the multiple dosing safety study. Three test articles including two TFV films (5.1 mg/film and 11.2 mg/film) and a placebo film were evaluated. A three-arm crossover study design was utilized, where each animal controlled for herself by completing each of three arms of the study. A minimum of three-week recovery period was incorporated between experiments. TFV or placebo film products were administered daily to the vaginal fornix on days 1–5 and 8–11 (Table 1). After a 30-minute resting period, biological samples were collected. Samples were also collected on follow-up days 12 and 15. Cervicovaginal colposcopy, pH and cytology smears, and vaginal swabs for microflora were collected prior to film insertion and at 30 min after product application. Complete sampling schedule is shown in Table 1.

Standardized colposcopic assessments were conducted by a team of three cross-trained technologists following WHO Guidelines (35) and standardized colposcopy guide designed specifically for pigtail macaque studies (36). Vaginal and ectocervical mucosal surfaces were evaluated for erythema, edema and epithelial integrity as well as any unusual findings. Observations were noted on daily examination record forms and documented by digital photography. Vaginal secretion samples were collected with polyester tipped swabs. Vaginal swabs were utilized for microbiota, vaginal pH and cytology assessments.

Comparative PK was evaluated in a separate experiment, after a single vaginal administration of a 1.1″ × 1.1″ 11.2 mg TFV film or 15 mg TFV gel (1.5 ml of 1% TFV gel), in eight animals per arm. Blood samples collected at baseline, 1, 2, 4, 6, 24, 48, and 168 h were processed for plasma and stored frozen until analysis. Vaginal biopsies were collected at 24 h and 168 h after dosing. Plasma and tissue concentrations of TFV and tissue levels of TFV-diphosphate (TFV-DP) were quantified using validated

TABLE 1 Sampling schedule for safety assessment. Sample collection was made before (0) and 30 min after (30) film placement.

Assessment	Time (min)																			
	Day 1		Day 2		Day 3		Day 4		Day 5		Day 8		Day 9		Day 10		Day 11		Follow-up	
	0	30	0	30	0	30	0	30	0	30	0	30	0	30	0	30	0	30	Day 12	Day 15
Film administration	x		x		x		x		x		x		x		x		x			
Vaginal swabs	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Colposcopy	x		x				x		x		x				x				x	x

analytical methods. Non-compartmental PK parameters were estimated (Phoenix WinNonlin v.8.3; Certara, Cary, NC).

2.4.4. Identification of key microbiota by cultivation

Vaginal swabs were inoculated onto agar plates for semi-quantitative culture analysis. Inoculum on each plate was streaked into four quadrants to isolate colonies. Columbia agar with 5% sheep blood (PML Microbiologicals, Wilsonville, OR) and BBL™ Human bi-layer Tween agar (HBT; Becton Dickinson and Company, Sparks, MD) plates were incubated aerobically in 5%–6% CO_2, 36–37°C, for at least 48 h and used to isolate and identify the following microorganisms: *Lactobacillus* species, viridans *Streptococcus*, beta-hemolytic (Group A–D, F, or G) *Streptococcus*, *Enterococcus* species, *Escherichia coli*, aerobic indole-negative Gram-negative rods, *Staphylococcus aureus*, coagulase-negative staphylococci, diphtheroids, yeast, and other aerobic Gram-positive rods and cocci. Laked Blood Kanamycin agar (PML Microbiologicals), HBT, and DifcoTM Rogosa Selective Lactobacillus agar (prepared on-site; Becton Dickinson and Company) plates were incubated anaerobically, 36–37°C, for 4–7 days and used to identify Lactobacillus, non-pigmented and pigmented anaerobic gram-negative rods. Identification of microorganisms was done using colony and bacterial morphologies and phenotypic tests described in Manual of Clinical Microbiology (37). This semi-quantitative analysis was previously described and correlated to quantitative log growth in colony forming units per milliliter vaginal fluid (cfu/ml) (38). Growth within the initial zone of inoculum, 1+, was equivalent to 10^2 cfu/ml; the second quadrant, 2+, was 10^5 cfu/ml; the third quadrant, 3+, was 10^6 cfu/ml; and the fourth quadrant, 4+, was 10^7 cfu/ml. Lactobacillus and viridans Streptococcus were additionally tested for the production of hydrogen peroxide using tetramethylbenzidine agar plates, prepared in-house (38, 39).

2.5. Statistics

Data was evaluated for statistical significance using one-way and two-way analysis of variance (ANOVA) with Tukey's post-hoc tests where applicable. PK parameters were tested for paired differences among formulations (Friedman test) and, if statistically significant, between each pair of formulations (Wilcoxon signed ranks test; IBM SPSS, v.25.0. Armonk, NY). A difference of $p < 0.05$ was considered statistically significant. To analyze film stability data for drug content, linear regression and 95% confidence interval bands were used.

3. Results

3.1. Formulation development and characterization of TFV films

Thin film dosage forms intended for vaginal use possess small size and mass (<0.5 g). Therefore, incorporating large doses of drug in polymeric thin films can be challenging. Drug solubility in the film matrix plays an important role in the film quality as it affects the film's visual aspects as well as drug release and storage stability. For TFV film development, our efforts were centered around formulating a stable film platform, wherein TFV exists in a solubilized form and remains molecularly dispersed under storage and use.

3.1.1. Excipient selection and formulation development

TFV has pH-dependent solubility with optimum solubility observed at pH 6.5. It was identified that with the use of sodium hydroxide and by increasing the polymer ratio, TFV can be solubilized, and crystallization inhibited. In preformulation studies, short-term storage (7 days) under an accelerated condition (40°C/75% RH) served as a screening method to identify excipients that efficiently incorporated TFV without crystallization. Several film-forming polymers (HPMCE5, HEC, PVPK90 and NaCMC-LV) were evaluated for their ability to achieve high drug loading level of TFV. **Supplementary Figure S1** shows microscopy images of TFV mixed with various polymers at 1:1, 2:1, 3:1, 4:1, 5:1 or 6:1 polymer to TFV ratio (P:T). At a P:T ratio that was equal to or greater than 3, no crystal could be detected after 7 days in samples containing HEC, PVPK90 or NaCMC-LV. The samples retained their transparency as well, indicating at least micron-scale miscibility between TFV and polymer. For HEC containing samples, banded spherulites were observed at P:T 1:1, while crystals grew into much looser fibers at P:T 2:1. For PVPK90 containing samples, banded spherulites were observed at P:T 1:1 and P:T 2:1. For NaCMC-LV containing samples, crystals appeared to be much more irregular. Notably HPMCE5 was found to be highly non-uniform and clear phase separation was observed. At low P:T ratios namely 1:1, 2:1 or 3:1, separation occurred throughout the samples while at high P:T ratios namely 4:1, 5:1 or 6:1, separation occurred on the edges. Based on these results, both HEC and PVPK90 were found to be suitable polymers to incorporate TFV.

To increase viscosity which supports manufacturability during the film coating phase, NaCMC-LV was incorporated. The formulations were divided into groups containing either HEC or PVPK90. Increasing NaCMC-LV increased viscosity in both groups (**Supplementary Table S1**). A 2% w/w NaCMC-LV was found to be optimal for manufacturability. To improve film quality such as flexibility, well-known film forming polymer, HPMCE5, was included in the matrix (HEC or PVPK90 based). Even though HPMCE5 and NaCMC-LV when tested individually at 2% w/w were unable to impart any advantage to TFV solubilization, the final film formulation remained crystal-free as evidenced from x-ray diffraction pattern of the mixture (**Supplementary Figure S2**). Microscopy was not conclusive on these samples due to their translucent nature. Glycerin was incorporated as a humectant and plasticizer to improve the tactile properties. The final formulation selected was HEC-based because the films formed were superior and easy to detach from the substrate. The final optimum formulation contained HEC, NaCMC-LV, HPMC E5, and glycerin in the ratio shown in

TABLE 2 TFV formulations showing percent (% w/w) of each ingredient.

Ingredient	Dose	
	20 mg/film	40 mg/film
HEC	6	6
HPMC E5	6	6
NaCMC-LV	2	2
Glycerin	2	2
Sodium Hydroxide	0.14	0.28
Tenofovir	1	2
MilliQ Water	82.86	81.72

Table 2. Formulations containing TFV at 1% w/w (20 mg/2″ × 2″ film) and 2% w/w (40 mg/2″ × 2″ film) utilized the same composition of excipients.

3.1.2. Film characterization and stability testing

The characterization of low and high dose TFV films is shown in Table 3. TFV films were smooth, soft, flexible and translucent in nature. Drug loading in films was determined to be within 85%–115% of the target dose levels. As shown in Figure 1, an immediate drug release was observed with greater than 50% of TFV released within 15 min, which reached plateau in 60 min. Visually, TFV films showed complete solubilization in aqueous media. Water content (<10% w/w) remained within the acceptance criteria. *In vitro* toxicity assessment ensured that TFV films do not affect the viability of TZM-bl cells and lactobacilli strains (Figure 2). TFV and placebo films exhibited minimal impact on ectocervical tissue viability (Figure 3A) compared to the positive control N-9 ($p < 0.001$). In the explant HIV-1_{BaL} challenge study, placebo films showed increase in infectivity with time and remained comparable to control group (Figure 3B). Both 20 mg and 40 mg TFV films showed reduced HIV-1 p24 at all days tested, confirming that TFV from films can protect tissues from HIV. A statistically significant ($p < 0.05$) difference was observed between TFV-containing groups compared to placebo and control at all the time points tested. Both low and high dose films showed similar *ex vivo* anti-HIV activity. Overall, the TFV films had acceptable characteristics including dissolution, safety, and anti-HIV activity.

To determine that films remain stable during storage, stability of low and high dose TFV films was monitored at room temperature (25°C/60% RH) and accelerated (40°C/75% RH) storage conditions as per ICH guidelines. Weight and thickness of the films remained unchanged throughout the stability testing period. As shown in Figure 4 and Supplementary Figure S3, drug content remained within the acceptable limits (85%–115%) for low and high dose films for 24 months at long-term storage and 6 months at accelerated storage conditions. At all the time points evaluated, the percent drug release in the *in vitro* dissolution method was greater than 50% at the 15 min

TABLE 3 Day zero characterization of TFV films (2″ × 2″).

Property	20 mg/film	40 mg/film
Appearance	Soft, flexible, translucent	Soft, flexible, translucent
Weight (mg)	362.90 ± 15.96	390.65 ± 20.83
Thickness (μm)	103.64 ± 20.63	110.91 ± 5.39
Water content (%)	3.49 ± 0.51	8.15 ± 0.71
Puncture strength (N/mm)	67.78 ± 10.57	51.49 ± 3.32
Drug content (mg/film)	19.74 ± 0.46	42.42 ± 1.99
Drug release (% at 15 min)	77.72 ± 9.07	60.04 ± 5.18
Lacto toxicity	Not toxic	Not toxic

The data is presented as mean ± SD (n = 3–11).

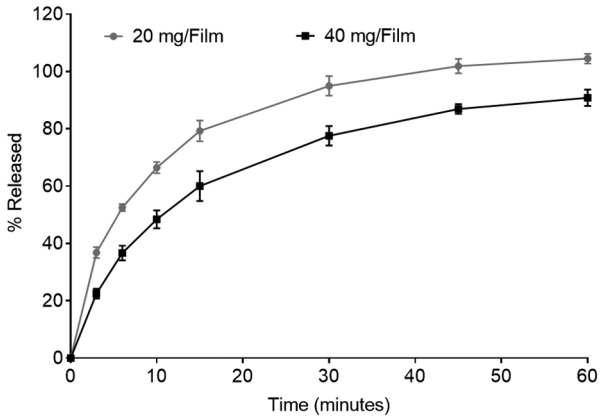
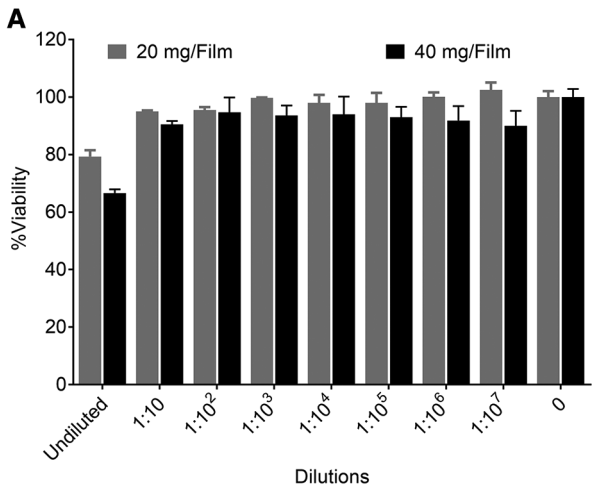


FIGURE 1
In vitro dissolution profile showing drug release from 20 mg and 40 mg tenofovir films for 60 min (n = 3–4).



B

Strain	Log difference after 30 min incubation	
	20 mg film	40 mg film
L. crispatus ATCC 33197	-0.047	-0.144
L. jensenii ATCC 25258	-0.005	0.004
L. jensenii LBP 28Ab	0.054	0.115

FIGURE 2
In vitro safety of tenofovir containing films. (A) Percent viability (mean ± standard deviation) of TZM-bl cells exposed to different dilutions of film solution (n = 3) ranging from 0.5 pg/ml to 5 mg/ml TFV (low dose film) and 1 pg/ml to 10 mg/ml (high dose film) compared to unexposed cells (n = 6). (B) Toxicity of films to lactobacilli at single concentration (8 and 16 mg/ml for low and high dose films respectively).

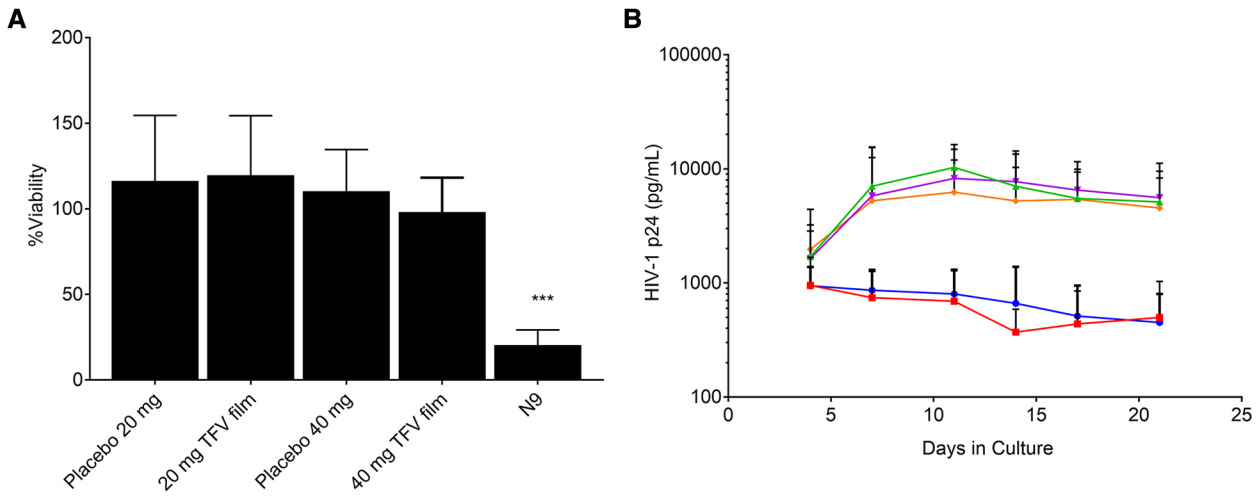


FIGURE 3
Ex vivo evaluation of films in ectocervical tissues (**A**) tissue viability (n = 5–6) and (**B**) Protection from infectivity in an *ex vivo* HIV-1 challenge model (n = 5–6). Orange = control, magenta = placebo film (20 mg), green = placebo film (40 mg), red = 20 mg tenofovir film, blue = 40 mg tenofovir film.

dissolution time point (Figure 4B and Supplementary Figure S3). Puncture strength remained within the acceptance criteria at different time points and conditions tested (data not shown). Water content remained below 10% w/w at all time points tested. TFV films showed compatibility with various strains of lactobacilli throughout the stability testing period (Supplementary Tables S2–S5).

3.2. Film evaluation in pigtail macaques

3.2.1. Safety assessment

The safety of the TFV film products (5.1 and 11.2 mg/1.1″ × 1.1″ film) was evaluated in a multiple exposure setting over a two-week period. Table 1 shows the schedule for product administration and biological sample collection. The goal of the safety study was to determine if daily use of either placebo or TFV-containing films show any safety-related changes within the female genital tract and whether these effects are attributable to film formulation and/or dependent on TFV dose.

Safety was assessed using a suite of qualitative (visual) and quantitative assessments. Colposcopy was used to visualize film placement and monitor adverse events based on anatomical and physiological changes (Figure 5). Colposcopic observations commonly noted in the genital mucosal tissues included erythema, edema, petechiae, and grossly white findings (vaginal). Examples of adverse tissue findings included severe erythema, breach in the integrity of the mucosal epithelium and/or tissue friability. Two individual instances of friable areas on a vaginal wall were noted in this study (a single incident in each of the two test product arms, in the same animal). The low incidence and transitory nature of these findings do not indicate a product-related safety concern. Throughout the study, there was no evidence of TFV film related tissue abnormalities.

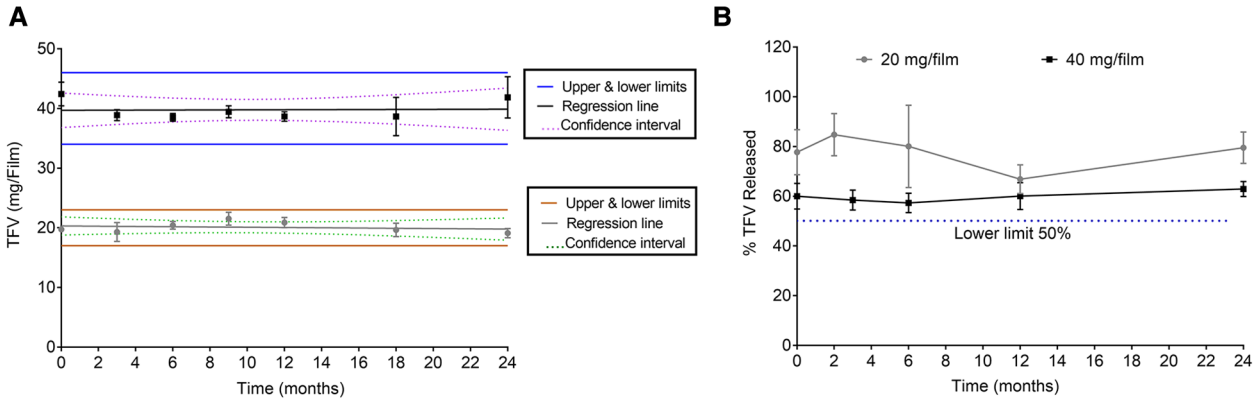


FIGURE 4
Stability assessment of 20 and 40 mg films at 25°C/60% RH storage conditions. (**A**) Drug content (n = 5). (**B**) Percent dissolution at 15 min (n = 3). Drug content from day zero was used for percent dissolution calculations.

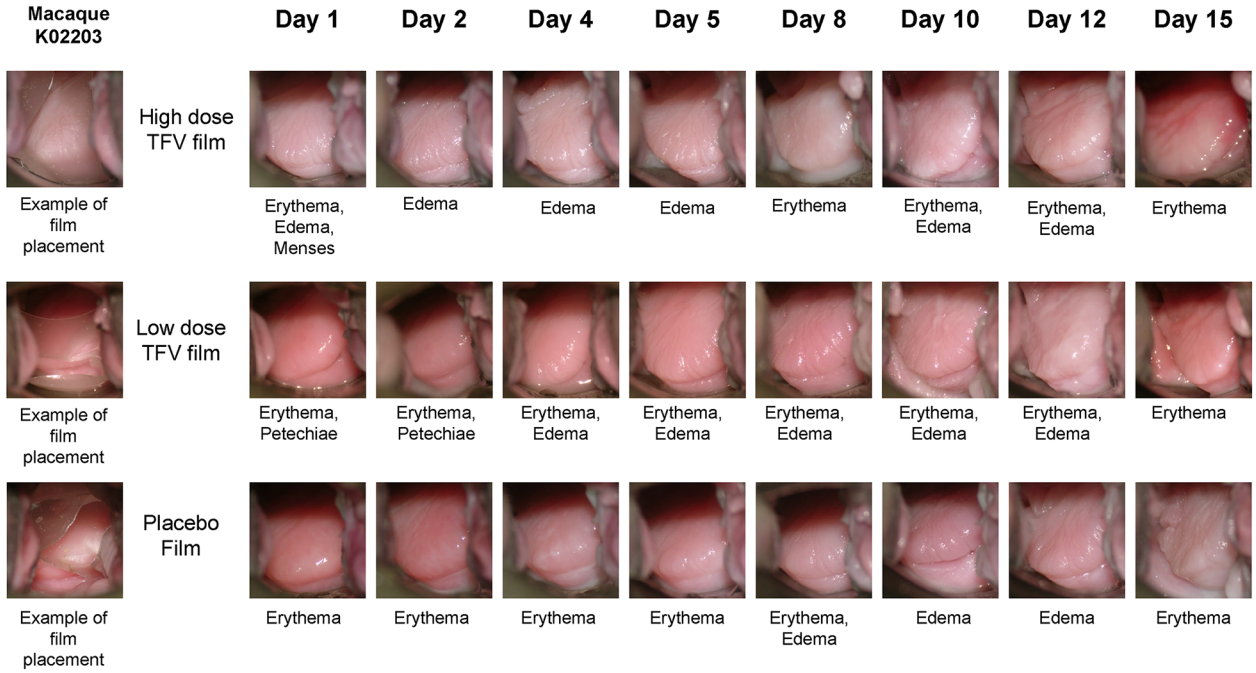


FIGURE 5
Representative colposcopic images of macaque genital tract showing film placement (left) and observations of adverse events. Adverse events are scored based on visual observation of anatomical changes using our previously published guide (35). Note that the events seen may not be fully captured in the field of view of colposcopic photo.

Vaginal pH did not differ by the type of product or length of use. As shown in Figure 6A, pH remained within 5.5 and 7.6 during the two-week study period and no statistical differences were observed between the three arms. Following TFV film exposure, mean polymorphonuclear (PMN) counts increased notably in the higher dose TFV film arm, and remained within the normal range in the lower dose TFV and placebo arms (Figure 6B). The increase observed in the high dose film was sporadic. However, by the end of the study and in the follow-up period (Days 12 and 15), the mean PMN counts subsided to the

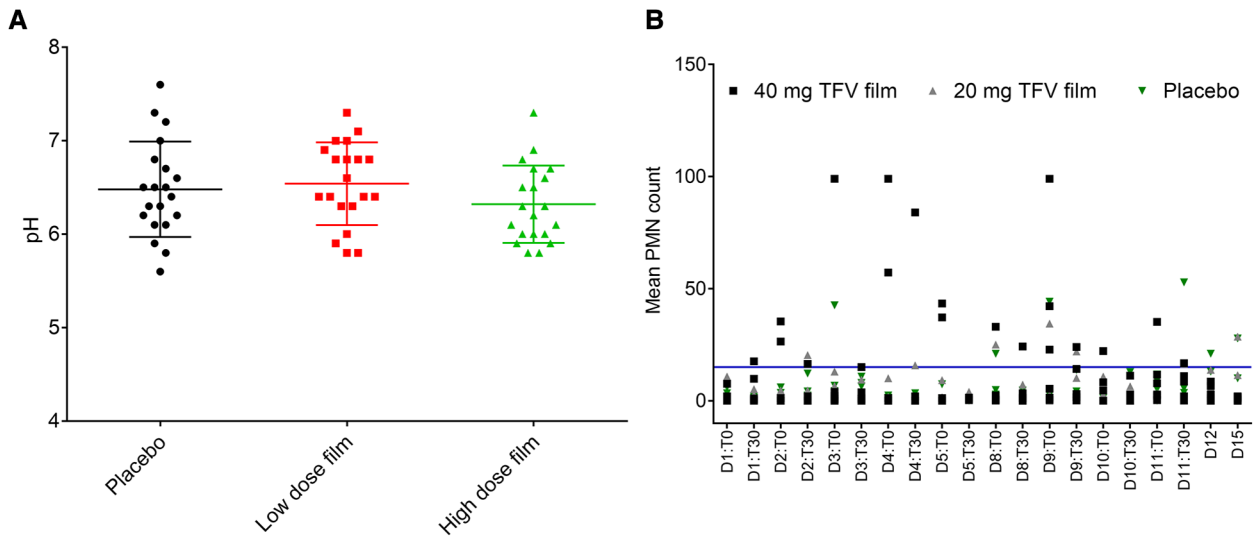


FIGURE 6
Effect of placebo and TFV (20 mg and 40 mg) films on pH and polymorphonuclear (PMN) cell influx in the female genital tract of macaques. (A) Dot plot data shows pH measured for 15 days in macaque cervicovaginal swabs before and after product application. (B) Influx of PMNs quantified in vaginal swabs before (T0) and 30 min after (T30) film application and days 12 (D12) and 15 (D15) follow up time period. A transient increase, especially in TFV 40 mg film, was observed, which later receded to around baseline levels in the follow up period. Blue line shows the upper limit of normal range (0–15) of PMN presence in pigtail macaques (unpublished data).

normal range. Product impact on vaginal microbiota was determined by increase or decrease in growth of selected microorganisms over time. Product use did not impact colonization by lactobacilli and viridians streptococci which produce H_2O_2. Apart from small transient changes at few time points, in general, no adverse changes were noted for either of these microorganisms. Overgrowth of deleterious populations of microorganisms such as *E. coli* and *S. aureus* was monitored. Small changes were noted in *E. coli* and *S. aureus*, but they did not coincide specifically with product insertion days. *G. vaginalis* was not detected in any of the macaque study arms. Fluctuations in the presence of some other microorganisms were noted across all three study arms, notably the non-H_2O_2 producing lactobacilli and viridans, and aerobic gram-positive rods and cocci. The significance of these shifts is unknown and not deemed significant to the safety profile.

3.2.2. Pharmacokinetic evaluation of TFV film vs. gel

Plasma TFV levels reached peak concentrations between 1 h (gel) and 4 h (Film) before decaying gradually over time to concentrations below the lower limit of TFV quantitation between 7 and 24 h post-dosing (**Figure 7** and **Table 4**). The point estimates for all reported PK parameters were numerically higher for the 11.2 mg film when compared to the gel, however, testing for paired differences, no statistical significance was noted.

TFV concentrations in vaginal tissue 24 h after dosing were measurable in all animals in both arms. The concentrations following the 11.2 mg film were greater than those of the 15 mg gel ($p = 0.016$); by 168 h, only the 11.2 mg film formulation had quantifiable TFV concentrations in most animals (**Table 4**). At 24 h, TFV-DP was quantifiable in all animals receiving the 11.2 mg film and approached statistical significance ($p = 0.055$) compared to gel arm, which had quantifiable concentrations in one-half or fewer of the animals; by 168 h, all, except one, TFV-DP samples were below the LLOQ.

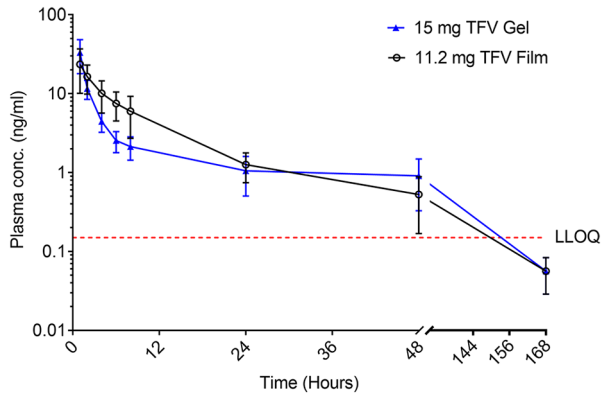


FIGURE 7
Plasma concentration (mean ± SEM) of TFV vs. time of TFV film and gel products administered vaginally in pigtail macaques. LLOQ–lower limit of quantitation.

4. Discussion

Given the favorable acceptability and ease of administration, thin films are an advantageous dosage form for vaginal delivery of PrEP against HIV and HSV-2. We postulated that the film dosage form can be utilized for delivery of TFV at a dose similar to that previously utilized in the clinically evaluated TFV gel formulation, which amounted to 40 mg of TFV per film. We describe here the development of a thin polymeric film carrying low (20 mg) and high (40 mg) dose of TFV, and evaluation for PK and safety in pigtail macaques. The goal of this work was to provide an alternate TFV vaginal product to a gel that eliminates some of the barriers for acceptable user qualities while maintaining adequate characteristics, performance, and safety. Further, vaginally applied films may have enhanced user acceptability due to advantages including portability, avoidance of applicator for administration that impact cost, ease of use, discretion and lack of leakage.

Film formulation development efforts were met with several challenges related to TFV solubility in film excipients and physical stability. The choice of major excipients was limited due to their impact on film quality and inability to form a continuous matrix required for film formation. The use of solubilizers such as surfactants and cosolvents to achieve target TFV dose was intentionally avoided in this work due to published reports suggesting potential for an increase in viral infectivity in vaginal tissue with commonly used solubilizing excipients (40). Initial studies attempted to identify a polymer matrix that achieved high TFV solubility and remained amenable for convenient manufacturing. Extensive excipient screening by microscopy and visual determination for color change guided selection of polymers that were compatible with TFV. Excipients including HPMCE5, HEC, PVPK90 and NaCMC-LV were selected as film forming polymers due to their acceptable regulatory status, well documented safety profile, and history of use in thin film formulations for vaginal and oral delivery (41–43). An accelerated study at 40°C/75% RH for 7 days (**Supplementary Figure S1**) suggested that the individual polymer-TFV ratio must be adjusted to 3 or higher to achieve physical stability in any of these individual polymers except HPMCE5. At all polymer concentrations tested, TFV was found to be immiscible with HPMCE5, resulting in phase separation. Given the favorable results from HEC, NaCMC-LV, and PVPK90, a series of prototype placebo formulations were developed using a combination of one film forming polymer (i.e., HEC or PVPK90) and the viscosity enhancer NaCMC-LV. It was identified that greater than 2% w/v NaCMC-LV concentration increased viscosity of the liquid blend drastically leading to bubble entrapment and difficulty in casting films. Therefore, the concentration of NaCMC-LV was maintained at 2% w/v.

Despite the fact that HPMCE5 was immiscible with TFV, it improved the visual and tactile (e.g., flexibility) quality of the films. HPMCE5 addition to the formulation was supported by the hypothesis that the contribution of potential physical instability by HPMCE5 could be mitigated with the addition of

TABLE 4 Non-compartmental pharmacokinetic parameter estimates for plasma and observed sample times for tissue. Values are median (lower quartile, upper quartile).

Matrix-Analyte	Parameter	Units	Film 11.2 mg	Gel 15 mg
Plasma TFV	T_{max}	hrs	4 (1, 8)	1 (1, 2)
	C_{max}	ng/ml	20.4 (5.6, 60.1)	17.9 (8.0, 66.5)
	C_{max}/D	ng/ml/mg	1.8 (0.5, 5.4)	1.2 (0.5, 4.4)
	T_{last}	hrs	24 (8, 72)	7 (2, 17)
	AUC_{last}	ng-hr/ml	189 (132, 333)	94 (44, 243)
	AUC_{last}/D	ng-hr/ml/mg	16.9 (11.8, 29.8)	6.3 (2.9, 16.2)
Vaginal Tissue TFV	24-hr	ng/mg	11.5 (2.8, 197.6)*	0.4 (0.2, 3.2)
	168-hr	ng/mg	0.10 (0.07, 0.12)	BLQ (BLQ, 0.08)
Vaginal Tissue TFV-DP	24-hr	fmol/mg	274 (76, 1,860)#	4 (BLQ, 58)
	168-hr	fmol/mg	BLQ (BLQ, BLQ)	BLQ (BLQ, BLQ)

T_{max}, time to peak concentration; C_{max}, peak concentration; C_{max}/D, C_{max} divided by dose in mg; T_{last}, time to last concentration above the LLOQ; AUC_{last}, area under the concentration time curve to the last concentration; AUC_{last}/D, AUC divided by dose in mg.
BLQ, below the lower limit of assay quantitation (LLOQ); LLOQ plasma TFV 0.31 ng/ml, tissue (median of LLOQ for each sample times biopsy weight) TFV 0.003 ng/mg, TFV-DP 3.5 fmol/mg.
*p = 0.016 Film 11.2 mg vs. Gel 15 mg.
#p = 0.055 Film 11.2 mg vs. Gel 15 mg.

other polymers to solubilize TFV. Translucent, yet uniform, films with different amounts of HPMCE5 were manufactured. XRD was used to examine the crystallinity of those samples after subjecting them to 40°C/75% RH for 7 days. As shown in Supplementary Figure S2, no peaks supporting the crystallinity of TFV could be detected in all samples. Although PVPK90 films also inhibited TFV crystallization, the processability of these films was inadequate (hard to peel off the substrate). Therefore, HEC-based formulation was selected for future studies, which produced acceptable films. Furthermore, previous microbicide trials have utilized HEC-based gels with acceptable safety. To increase flexibility of the films, glycerin was incorporated at 2% w/v in the solution. Glycerin also acts as a humectant to preserve water in the films and imparts a smooth and soft feel to the films.

TFV films prepared at low (20 mg) and high (40 mg) doses using the optimized formulation showed acceptable physicochemical attributes. Films had appropriate dissolution, toxicity, and activity results (Figure 2). It is anticipated that the product would be administered close to the time of coitus making rapid drug release optimal to achieve pharmacologically relevant concentrations in the female genital tract. The *in vitro* toxicity assessment in TZM-bl cells and different strains of lactobacilli as well as *ex vivo* tissue viability showed favorable safety results for advancement to preclinical studies (Figures 2, 3). Moreover, TFV films retained antiviral activity in *ex vivo* ectocervical tissues suggesting that TFV exposure from films retained the biological activity and will provide *in vivo* activity.

Both low and high dose TFV films showed excellent stability for 24 months at long-term storage, and 6 months at accelerated storage conditions. All the attributes remained within the specifications and films retained their physicochemical and safety properties supporting further development of TFV films as a marketable product. TFV films produced in this work remained soft, smooth and flexible throughout the stability testing period (Figure 4 and Supplementary Figure S3). Overall, the developed film platform was shown to be safe and stable.

Based on favorable physical properties and *in vitro*/*ex vivo* toxicity profile, both the low and high dose TFV films were advanced to preclinical animal testing in a well-established pigtail macaque model. The safety profile of the developed TFV film was evaluated after repeated film exposure (Table 1) by monitoring for changes in pH, PMN infiltration, microbiota, and colposcopy-assisted adverse events. The effect of repeated exposure was investigated for two reasons, firstly to stress the cervicovaginal environment, and secondly to simulate real-use conditions where women tend to use the film repeatedly in a short period of time. In a span of 15 days study period, the genital tract of pigtail macaques was exposed to nine films. Although minor adverse events were noted, these were not related to film use. The vaginal pH was monitored since alteration can impact susceptibility to infections (44). The vaginal pH remained between 5.5 and 7.6 throughout the study, and the effect of TFV product use on pH alteration was not observed (Figure 6). A small rise in PMN infiltration was observed with high dose film during the film exposure period, but subsided to baseline levels at the end of the study. The clinical ramifications of this transient increase in PMNs in the high dose group is not readily discernible. However, this transient increase did not coincide with any tissue-related events from colposcopy and thus does not suggest inflammatory response with product use. Finally, the vaginal microflora, especially the H_2O_2-producing lactobacilli remained largely unaltered with product use suggesting the inertness of this platform on innate factors.

While the median for all PK parameters was higher for the higher dose 11.2 mg film than the gel, these were not statistically significant due to inconsistent trends across formulations within individual animals. The more sparsely sampled tissue indicated higher tissue TFV and TFV-DP concentrations with the film compared to the gel, though most samples were below the LLOQ one week after dosing. These results are expected given the leaky nature of the gel compared to films. Films deliver precise doses to the vagina and their low weight contributes to insignificant leakage and dilution of the innate factors. In two separate clinical

studies published previously evaluating TFV films, it was shown that the 40 mg TFV films developed here have shown TFV and TFV-DP levels similar to or higher than gels in vaginal fluids, plasma, and tissues and also suggested increased acceptability among women participants (30, 31). Overall, the TFV high dose film was found to be stable, efficacious, and safe based on *in vitro*, *ex vivo*, and *in vivo* studies. Importantly, high dose film showed TFV and the active metabolite levels similar or better than the gel formulation indicating potential effectiveness against HIV and HSV-2 acquisition in women. Two doses of TFV films (10 mg and 40 mg) were subsequently scaled-up and investigated in healthy women for safety, acceptability, and pharmacokinetics (30, 31).

5. Conclusions

A stable vaginal thin film platform that incorporated clinically relevant dose of TFV (40 mg) and non-toxic excipients was successfully developed. TFV was shown to retain antiviral activity *in vitro* and *ex vivo* when formulated into the film dosage form. Safety of the developed film formulation was supported through *ex vivo* exposure studies and *in vivo* studies in the macaque model. TFV films did not show any toxic effects on the vaginal epithelium. The TFV film formulations were shown to retain similar physicochemical characteristics and performance attributes for at least 24 months. In the *in vivo* macaque studies, the high dose TFV film showed higher tissue TFV exposure compared to a gel product. Combined, these findings support advancement of this rationally designed quick-release TFV film product as an on-demand product choice for women at increased risk of HIV and HSV-2 infections.

Data availability statement

The datasets presented in this article are not readily available because the data sets may not be released given the IP restrictions around Film development. Requests to access the datasets should be directed to rohanlc@upmc.edu.

Ethics statement

The animal study was reviewed and approved by IACUC, University of Washington.

Author contributions

LR and SH: contributed to the conception of the film platform, obtained funding, supervised studies, assisted with data analysis, and revised the manuscript. HA: performed and supervised experiments, conducted data analysis, and wrote sections of the manuscript. SP: performed and supervised experiments, conducted data analysis and generated figures, wrote the first draft of the manuscript and handled subsequent revisions. MB and SH: contributed to microbiological testing, YS and DP: designed and executed animal studies and analysed safety data, CWH and SP performed pharmacokinetic data analysis. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1217835/full#supplementary-material

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Turning the promise of multipurpose prevention technologies into a market reality: a commentary

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The promise of multipurpose prevention technologies (MPTs) for the prevention of HIV and unintended pregnancy are on the horizon. While many are still in clinical development, others are closer to becoming a realistic, accessible option for users, like the dual prevention pill (DPP). Researchers, governments, donors, and implementers will have to collaboratively address systemic challenges to successfully introduce and scale-up MPTs. To ensure the rollout of MPTs is successful, the global community should address user and country-specific needs, coordinate with advocates and policymakers, and set a realistic plan for product introduction and scale-up that considers the needs of both family planning (FP) and HIV programs, while laying the groundwork for future new product introduction. To achieve these aims, global and regional stakeholder coordination should emphasize country-led, person-centered decision-making while addressing: (1) procurement and supply chain barriers; (2) the potential burden on health systems; and (3) the impact on current programs.

KEYWORDS

HIV prevention, contraception, multipurpose prevention technologies, MPTs, PrEP (pre-exposure prophylaxis), family planning (FP) PrEP-FP integration, dual prevention pill, informed choice

1. Introduction

As of 2021, women and girls represent 54% of the 38.4 million people worldwide currently living with the human immunodeficiency virus (HIV), and in sub-Saharan Africa (SSA), women and girls account for 63% of all new HIV infections (1). More than 160 million women and girls who want to avoid pregnancy were not using contraceptives in 2019, with nearly a third of women with unmet need for contraception living in SSA (2, 3). Use of contraceptive methods can substantially improve maternal and adolescent health by averting unintended pregnancy and maternal mortality, supporting women's and girls' empowerment, and contributing to economic and social development (4, 5). Previous analysis mapping has shown that multipurpose prevention technologies (MPTs), which are products that prevent unintended pregnancy and sexually transmitted infections (STIs), including HIV, will have the greatest impact in SSA (6). The demand for combination contraceptive and HIV prevention products by women in these regions is further supported by end-user acceptability studies in multiple SSA countries (7).

The promise of MPTs for the prevention of HIV and unintended pregnancy is on the horizon. Interventions to address this significant overlap of HIV incidence and unmet need for voluntary family planning (FP) are crucial, especially to reach the United Nations Sustainable Development Goal of good health and well-being and the Joint United Nations Programme on HIV/AIDS goal of ending the AIDS pandemic by 2030 (8). Currently, the only available MPTs are male and female condoms, but these are associated with an array of challenges like acceptability, consistent use, partner negotiation, cost, and access (9–11). While many novel MPTs are in pre-clinical and early clinical development, such as intravaginal rings and microarray patches, others like the dual prevention pill (DPP) are closer to becoming a realistic, available option for users (12). The DPP is a daily oral pill combining a hormonal contraceptive and an antiretroviral pre-exposure prophylaxis (PrEP) for HIV, products each of which individually have stringent regulatory approval and are registered in many countries in SSA (13).

Whereas previous commentaries have focused on challenges and opportunities to align MPT research and development, we seek to outline the complex endeavor of "rolling out" an MPT product within a health system and the key issues that must be addressed to make it as smooth as possible (11, 14, 15). Researchers, governments, donors, and implementers will have to collaboratively address the systemic challenges outlined below to successfully introduce and scale-up MPTs. Alignment of investments, regulatory processes, and programmatic vision across HIV and FP–services that have traditionally been siloed–will be essential to prepare existing programming infrastructure for the roll out of the first novel MPT (16).

While many programs are funded to implement single indication products, like oral PrEP and a wide range of short and long-acting contraception, and numerous lessons have been drawn from this work, the first introduction of a novel MPT will undoubtedly serve as a test case, and impact future advocacy, interest, research, and introduction of this new class of products (17–19).

2. Key considerations for moving forward with novel MPT Introduction

To ensure the rollout of MPTs is successful, the global community should address user and country-specific needs, coordinate with advocates and policymakers, and set a realistic plan for product introduction and scale-up that considers the needs of both FP and HIV programs, while laying the groundwork for future new product introduction. To achieve these aims, global and regional stakeholder coordination should emphasize country-led, person-centered decision-making while addressing: (1) procurement and supply chain barriers; (2) the potential burden on health systems; and (3) the impact on current programs (20).

2.1. Procurement and supply chain barriers

Procurement and structural supply chain barriers to overcome before introducing novel MPTs include policy change and its subsequent operationalization, integration of supply infrastructure, and consistent commodity funding support. For example, the United States President's Emergency Plan for AIDS Relief (PEPFAR) currently does not procure contraceptives, and donor funding for HIV and FP commodities does not always overlap, which can be due to differences in HIV burden and modern contraceptive prevalence rates (21). Moreover, donors have limited funding for commodities, often prioritize a singular health mandate, and/or support existing vertical HIV or FP programs which each tend to have their own separate financing, supply chains, and service delivery systems. For example, the PEPFAR program, while supportive of integrated supply chain systems, is required to achieve HIV specific outcomes and efficiencies that may not be possible through use of national integrated supply chain systems, so parallel quantification, procurement, storage, transportation, and logistics management systems have been established for HIV commodities in many countries.

The addition of a new product to a supply chain system has far reaching funding and technical assistance implications to program areas such as advocacy, planning and forecasting, guidelines development and training, packing, distribution, and data collection and monitoring, among others. To justify pivoting commodity procurement strategies and systems to include new products and taking on the additional costs and work required to introduce and sustain a new product, there must be significant evidence of the value and utility of the product to help achieve health system objectives and meet desires of clients (22). For an MPT, the justification will need to be twofold, illustrating that MPTS benefit both health intervention areas of HIV prevention and FP programs, in terms of cost-effectiveness and increasing access and acceptability relative to the standard of care. Additionally, programmatic considerations such as determining which department of the Ministry of Health will manage and have responsibility for MPTs will affect decisions regarding the funding, inclusion, and distribution of MPTs through an integrated or vertical supply chain.

Since new products are not immediately available in affordable, generic formulations or locally manufactured, the ability of countries to purchase such (brand name) products may be sharply restricted by national and/or donor procurement budgets. This is a particular challenge to MPT introduction, because generic and/or low cost versions of the individual drugs that comprise the MPTs (e.g., oral contraceptive pills and PrEP) are most likely already being procured, have existing rationale and program placement, and have funds and technical assistance allocated to them in countries that are targeted for MPT introduction, which may reduce interest and urgency to introduce a new product. While there is a push for localization of manufacturing, obtaining locally or regionally produced products may be difficult and/or require significant investment. Donors can work with initiatives like the United Nations-backed

Medicines Patent Pool (MPP) to facilitate a pathway to generic manufacturing for low- and middle-income countries through patent pooling and non-exclusive voluntary licensing; however, this can take years from initial product availability to generic availability (23).

Often new product development and introduction does not result in increased funds for commodity procurement, meaning countries and donors must make difficult decisions when integrating new products within already constrained budgets. For example, it may be possible for the DPP to be more cost effective than oral PrEP over time, but it is expected to be more expensive than the oral daily contraceptive pill currently used in SSA countries. Financing for this extra cost will likely need to be carried by HIV prevention commodity budgets (20). These decisions can have a major impact on commodity security and availability across the reproductive health space, from the manufacturer to the client (24, 25).

2.2. Burden to health systems

As mentioned above, "single issue" funding streams have created or reinforced separate service delivery channels within health systems for what could more appropriately be holistic sexual and reproductive health care. Integrating these separate streams of care provides a comprehensive approach to the user's evolving prevention needs and ultimately results in greater public health impact. However, integrating an established health system, while potentially cost effective in the long term, first requires political will, followed by coordination of national and sub-national management teams, targeted demand generation for clients, supply chain planning, task shifting among facility- and community-based health workers, and capacity strengthening of managers and staff. In particular for the latter, counseling clients on options for FP and HIV prevention while still maintaining voluntarism and informed choice and limiting provider bias will be critical (13, 22).

When integrating an MPT into existing FP, HIV, or integrated service delivery packages, operational considerations at the facility and community levels will need to be updated such as those related to policies and procedures, training, supervision and management structures, health information systems, records keeping, short- and long-term client follow-up, health education, product promotion, and community engagement. Furthermore, complexities within the supply chain management structure like funding, procurement, delivery systems, storage and supply tracking, information management, and training on quantification and forecasting for the new product, will also have to be addressed. Separate from service delivery and supply chain, there is a need for adequate governance and policy coordination to ensure products with multiple indications, often overseen by different departments, are rolled out with both programs in mind (26).

Implementation planning and operations research can tackle many of the outstanding questions for roll out of a new MPT in health systems. Specifically, it could help to identify how to appropriately manage and monitor the introduction and routine provision of a new product, support its eventual scale-up, and guide sustainability efforts. Such research can also provide data for decision-making around the opportunity costs of choosing an MPT over other products in countries with limited donor support and to inform the added value of a new product for potential users.

2.3. Programmatic impact

As MPTs come to market, the initial and long-term programmatic impact needs to be considered; hard trade-offs may need to occur when making decisions between MPTs and existing FP and HIV prevention products. Clients may feel influenced to use one product that has multiple indications due to convenience, even if they would not choose the same indications, durations, and/or product type for separate, singular products. Voluntarism and informed choice are cornerstones of FP programming; thus, counseling for both unintended pregnancy and HIV prevention must continue emphasizing choice even with the availability of products with multiple indications vs. singular indications (27). Clients who choose an MPT will have to be supported and monitored through decisions of continued use, switching, or discontinuation, all adding to the time, cost, and capacity of the service delivery structure.

Moreover, FP and HIV prevention programs, often siloed, should consider critical issues surrounding co-delivery of available FP and HIV prevention products in anticipation of an MPT product becoming available soon. Expanding existing programming and integration efforts in the immediate future can be a cost-effective way to make co-delivery a reality and create successful pathways for MPT introduction and scale up (21). Additionally, understanding of sociocultural issues, values, and preferences and prioritization of client perspectives must continue to be considered when integrating FP and HIV services and introducing the added option or choice of an MPT. Among these considerations are gender norms, social norms, intimate partner violence, partner negotiation, and stigma or discrimination that impede access to and use of FP and/or HIV services, including health provider biases (28).

3. Discussion

We have outlined three major challenges that need to be addressed to introduce and scale up the first novel MPT efficiently and effectively. In terms of timeline, the novel MPT closest to becoming a market reality is the DPP, and the next step in the successful introduction of this product will be to bring together the global community such as manufacturers, governments, donors, providers, clients, implementers, advocates, and more to create an equitable, ethical, and sustainable plan for roll out and eventual scale up. The global community should also critically evaluate the tradeoffs of rolling out the DPP vs. continuing to have separate, single indication products depending on country priorities and whether the country-context is a good fit.

3.1. Bridging research with implementation

As a new generation of prevention technologies like MPTs comes closer to market reality, steps must be taken to bridge research with implementation to meet the needs of clients and achieve the greatest impact. It will be particularly important to bring together the local and global scientific communities to provide data and support to Ministries of Health and other key decision makers to help inform plans for country level procurement, introduction, and scale up of MPT products. Among key decision makers should be representatives from the populations who can most benefit from integrated products and services. Meaningfully engaging women, girls, and civil society advocates ensures a user-centered approach is responsive to the sexual and reproductive health needs and wants of the intended populations for MPTs (29). For example, the PEPFAR/USAID funded MOSAIC project which focuses on the introduction and access of new HIV prevention technologies in SSA, has a team of paid youth advocates under the age of 30 called the MOSAIC NextGen Squad. With members from the 10 countries MOSAIC works in, the group is meaningfully engaged to hold MOSAIC researchers and programmers accountable for ensuring the project's plans, activities, monitoring and evaluation, and learning efforts respond to young people's diverse needs, preferences, and lived experiences, including those of adolescent girls and young women (30).

Lessons from contraceptive research and programming have shown that availability of a greater method mix increases adoption and continuation rates, lessening the unmet need for FP (31). However, it is not easy to simply introduce a new prevention technology into national health systems, as learned from oral PrEP programming (32). Increasingly, implementation science has been identified as an integral approach for new product introduction because it offers frameworks, tools, and methodologies that support the systematic, holistic roll out of a new product using a socio-ecological model (33, 34). Ultimately, insight gained from implementation science studies and related work leads to better informed choice counseling and adherence strategies to respond to clients' evolving needs across their lifetime (35). It further provides national stakeholders and communities with a sustainable pathway to scale up prevention interventions through a continuous, research-to-practice learning process.

3.2. Next steps

Current research to inform rollout of the DPP includes formative studies and randomized crossover trials addressing user and provider preferences, acceptability, and adherence in South Africa and Zimbabwe (36). While targeted research-to-roll out efforts are underway to make the DPP the first MPT market reality, there is a need to expand on product-neutral MPT programming that includes coordinated global procurement and integrated approaches to introduction across health disciplines; the following outlined activities should start sooner than later to mitigate any delays in terms of transition from product R&D to introduction. A joint implementation science agenda will be imperative to allow for research results to be shared across countries and regions and to facilitate expedited application of learnings; this agenda should be set and coordinated by a global, normative body like the World Health Organization which has strong relationships with national governments. Governments, donors, implementers, users, and civil society organizations should work hand-in-hand to address procurement and financing barriers now in the early stages of planning, understanding the potential demand and market size for an MPT and changes to the contraceptive prevalence rate and HIV incidence. Investments in MPTs should be integrated and person-centered so the value of a multipurpose product can be realized for users and health systems; thus far, funding opportunities for MPTs has been limited and there is a need for innovative funding and financing strategies to leverage current funding opportunities. Through global coordinated action, successful implementation science, and realistic planning, integrated programs with a wide-range of products, including MPTs, will respond to the needs of women and girls and empower decision-making over their sexual and reproductive health.

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

All authors contributed to the conceptualization, writing, and review of the manuscript. All authors contributed to the article and approved the submitted version.

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The reviewer BYH declared a shared affiliation with the author JM to the handling editor at time of review.

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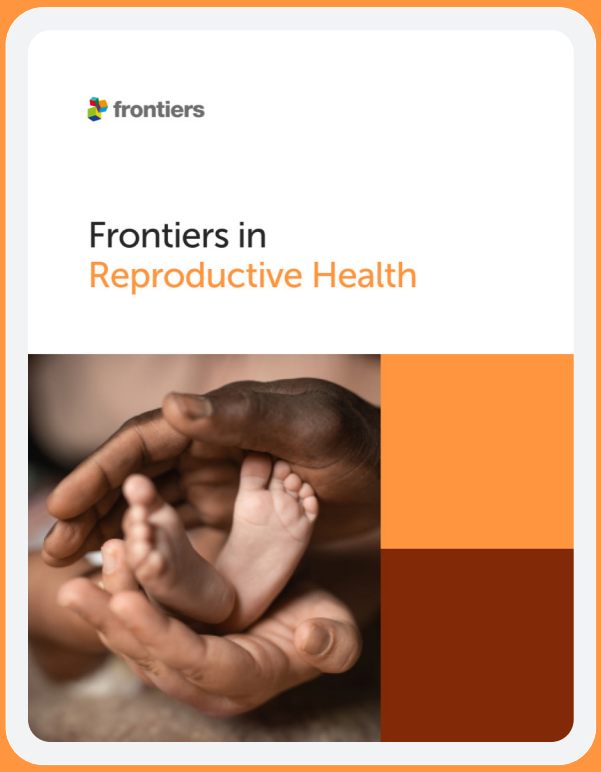

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