Frequently Asked Questions about the Dual Prevention Pill

April 2022

Overview

What is the Dual Prevention Pill (DPP)?

The Dual Prevention Pill (DPP) is a single, co-formulated, daily oral pill containing oral pre-exposure prophylaxis (PrEP) and combined oral contraception (COC) that prevents both HIV and pregnancy. The DPP will add to the contraceptive and HIV prevention toolbox and will be the first multi-purpose prevention technology (MPT) to go to market since male and female condoms. Because of this, the DPP will provide a critical, near-term opportunity to evaluate whether access to an MPT will increase the uptake of HIV prevention (in this case, of oral PrEP). It could also provide evidence that governments and donors need to spur investment in other MPTs, such as vaginal rings, injectables and implants.

What is the composition of the DPP and who is developing it?

Viatris (formerly Mylan), a manufacturer of generic antiretroviral drugs (ARVs) and hormonal contraceptives, is developing the DPP as a bilayer tablet containing Tenofovir Disoproxil Fumarate (300mg) and Emtricitabine (200mg) (TDF/FTC), and Levonorgestrel (.15mg) and Ethinyl Estradiol (.03mg) (LNG/EE). TDF/FTC is the only ARV indicated for the prevention of HIV in women and LNG/EE is the most popular COC in low- and middle-income countries.

The DPP will be packaged in a blister pack, similar to COC packaging (see Figure 1), rather than the pill bottles used for oral PrEP, whose rattling sound can be a barrier to discreet oral PrEP use. Packs will contain a total of 28 tablets – 21 combination ARV/COC tablets and 7 ARV-only tablets (corresponding to the placebo/ iron pill days of a COC regimen), which will need to be taken to maintain protection against HIV during the last week of the month/ cycle. Based on market research, the first 21 tablets will be pink and the last 7 will be peach-colored – not the typical blue color of ARVs (Truvada) (see Figure 2). Branding will have a women's lifestyle feel, consistent with research on oral PrEP and family planning (FP). The DPP package will have a shelf-life of 2 to 3 years.

Figure 1: Illustrative mock-up of DPP packaging by Viatris

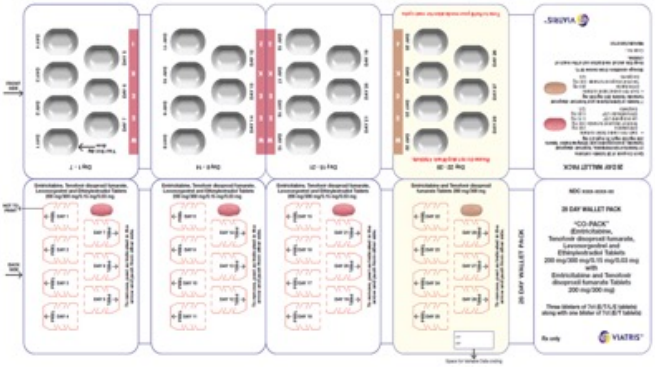


Figure 2: Proposed DPP tablet colors

The Population Council, an international research organization, is also developing an over-encapsulated DPP (a capsule containing separate TDF/FTC and LNG/EE tablets within it) for use in acceptability studies. While this product is solely for research purposes and not intended for commercial use, it will generate learnings on DPP use and user preferences that will inform introduction plans.

Why is the DPP on a 21-7 regimen as opposed to a 28-day regimen for oral PrEP?

The DPP is being formulated as a 21-7 regimen, mainly for ease of regulatory approval (as this is how COC is typically formulated and approved in its current form). Formulating the DPP with a 4-week COC may be considered in the future, as it could simplify counseling and be preferred by some women, but regulatory feasibility and client acceptability would need to be assessed. It will be important for women to understand that the last 7 days in the DPP pack are not the same as the placebo pills in a COC regimen, and that they contain oral PrEP and must be taken for each of the 7 days to maintain protection against HIV.

What opportunities does the DPP offer?

- **Accelerated Research Timeline:** The DPP combines two previously approved products, bypassing the need for a separate, large clinical trial to demonstrate safety and efficacy.
- **Accelerated Product Introduction:** DPP introduction builds on the foundations and lessons learned from contraceptives, oral PrEP and ongoing planning for next-generation products. In turn, future MPTs are likely to build on the regulatory, delivery and financing lessons generated from DPP introduction and scale-up. Strengthening HIV and FP linkages and platforms for the DPP could ready health systems for other MPTs.
- **Potential Catalyst for HIV/Sexual and Reproductive Health (SRH) Integration**: The DPP may foster integration of HIV prevention and SRH services and systems, needed to deliver a dual-indication product. Emerging evidence indicates FP and oral PrEP have higher uptake when they are delivered together.
- **Potentially Broader Donor Base:** As donor resources for HIV prevention and FP are increasingly limited, the DPP may attract wider range of funders interested in creative HIV and SRH interventions to support introduction and scale.
- **Potential to Address Challenges with other Prevention Products:** One pill instead of two makes DPP more convenient – possibly motivating women to sustain adherence and effective use – and it expands choice for women who want to reduce their risk of both unintended pregnancy and HIV. There is a higher acceptance of contraceptives among women while oral PrEP continues to face stigma and acceptability issues. Combining products offers the chance to reach users with a product they feel meets their overall HIV prevention and SRH needs. End user perspectives on the DPP can also influence the development of future MPTs.

What are the potential risks to successful DPP introduction?

The DPP may face risks related to uptake and effective use, as both oral contraceptive pills and oral PrEP have high rates of early discontinuation, and awareness of oral PrEP is low in many settings. Providers may be reluctant to offer the DPP because it feels like an added burden, particularly in FP settings where additional training for the delivery of oral PrEP will be required, counseling approaches will need to be adapted, or due to stigmatizing beliefs such as the perception it could encourage younger women to have sex. Governments and funders may face trade-offs as they plan to invest in rolling out new prevention products, like the dapivirine vaginal ring and long-acting injectable cabotegravir (CAB-LA), which could impact resources available for the DPP.

Potential Users of the DPP

Women use different contraceptive pills. Will the DPP cater to a diverse range of needs?

Developing multiple contraceptive components for the DPP is challenging. Currently, LNG/EE is the most popular COC in high HIV-burden countries and will be used for the DPP. Other options are being considered for future development.

How will DPP packaging be designed to support use?

The DPP will be packaged in a blister pack to more closely resemble COC packs, with sheets that can be torn off weekly to make it user-friendly. Packaging will contain comprehensive instructions for use to support users (in line with regulatory requirements), and packs will include color-coding and numbered weeks to indicate sequencing of pill-taking. Through ongoing market research and consultations, additional ways to make the product and packaging user-friendly will be explored.

Will the size of the DPP serve as a barrier to uptake and use?

The DPP in development by Viatris has been compressed as much as possible. F/TAF, another formulation for oral PrEP which is smaller than TDF/FTC, is being explored for future DPP tablets, though it has not yet been approved for use among those at risk for HIV through vaginal sex. A DPP with TAF could be 50 percent smaller than the current DPP with TDF/FTC, and could follow the initial DPP by a few years.

What are the potential side effects of the DPP?

The World Health Organization has affirmed that there are no drug-drug interactions between oral PrEP and COC and that oral PrEP and COC can be "safely taken together." A bioequivalence study is currently underway to better understand the side effects of the DPP and whether they are different from those experienced when taking oral PrEP and COC together. Oral PrEP and COC share similar common side effects, such as headache and nausea, while rarer side effects for each differ. In initial DPP end-user research, women were concerned about potentially more intense side effects with a combined COC/oral PrEP pill. Planned research, including acceptability studies enrolling OC users, will also evaluate side effects and other clinical outcomes of DPP use.

Who is likely to use the DPP?

Pending regulatory approval, the DPP will likely be indicated for all women of reproductive age. However, early DPP introduction will likely be geared toward women ages 20+ because they exhibit higher rates of oral contraception (OC) and oral PrEP use than younger women and girls. Early feedback from country stakeholders indicated that prioritizing younger women and girls during early introduction could stigmatize the DPP, despite their acute need for HIV and pregnancy prevention. Country governments will decide on priority populations for introduction, which could include those <20 years old. The product label and instructions for use will not limit use to women 20-40 years old. Acceptability studies will include women ages 16-40 to understand preferences across age groups. These studies and end-user research will develop approaches and messages for different user segments.

Will women on longer-acting contraception, including injectable contraception, be offered the DPP?

The DPP will be offered to women as one option among other FP and HIV prevention products. Users of longer-acting contraception satisfied with their current method would not be encouraged to switch to the DPP and would be offered another HIV prevention product such as oral PrEP, male and female condoms, the dapivirine vaginal ring (DVR) or injectable cabotegravir (CAB) for PrEP, depending on availability. If a woman is no longer satisfied with her current method or is interested in switching to the DPP (e.g., for the addition of HIV prevention or desire for a shorter-acting product), she will have the option to switch to the DPP.

Is the DPP recommended for breastfeeding women?

While COC (and thus the DPP) is not advised until six months postpartum, postpartum visits are an entry point for FP counseling. The DPP may be appealing given high HIV incidence in this period, and some postpartum women may prefer a contraceptive method with a shorter return to fertility.

Market Preparation and Introduction

Regulatory Process and Evidence Generation

What studies will be conducted to generate evidence for DPP regulatory review?

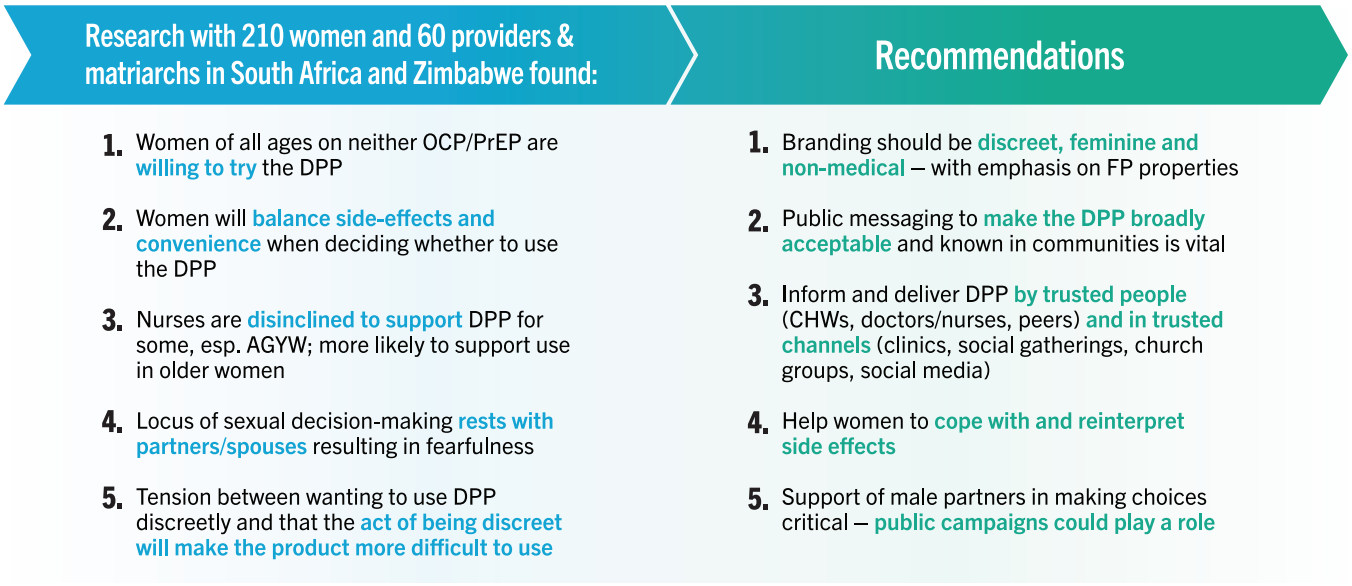
Since both oral PrEP and COC are already approved for regular use and are safe and efficacious on their own, these drugs will be further tested in combination in an approach formally known as a ***bioequivalence study***. Bioequivalence would be achieved if the DPP is absorbed in the body at a statistically similar rate to oral PrEP and COC pills when taken separately. If the DPP shows equal or similar bioequivalence to oral PrEP and COC separately, the product developers will submit the DPP for regulatory review to the US FDA, tentatively in 2023.

Clinical cross-over acceptability studies are planned in South Africa and Zimbabwe to compare women's experiences using a DPP to separate Truvada and COC pills.

Human-centered design (HCD) research will be conducted with end users, providers, male partners and matriarchs on the DPP in order to better understand women's motivators, barriers and behaviors, how people who are significant in their lives may influence their beliefs or decisions, and to shape product development, demand generation and branding strategies. Initial HCD reseach has been completed in South Africa and Zimbabwe (see Figure 3).

Implementation research will be designed in collaboration with governments and initially conducted in Kenya, South Africa and Zimbabwe, across urban and rural settings and among different segments of women to to evaluate acceptability, impact, cost-effectiveness and feasibility. Pragmatic research will be valuable for understanding end-user preferences as well as how to streamline delivery and determine counseling messages that resonate with potential DPP users.

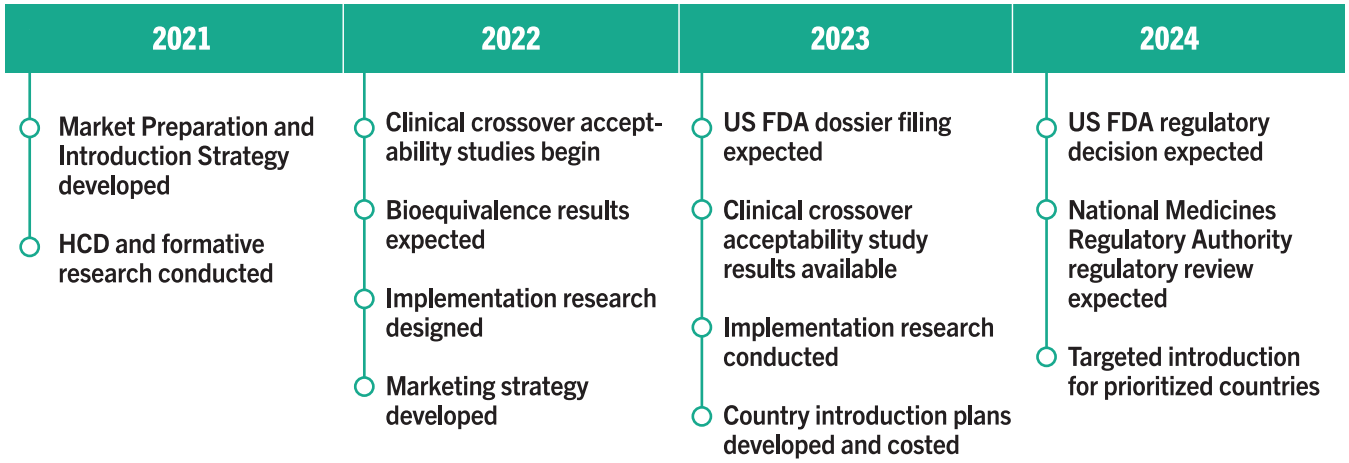
Figure 3: Key findings and recommendations from HCD research in South Africa and Zimbabwe



What is the planned regulatory pathway and when might the DPP be available?

Viatris will file a 505(b)(2) with the US FDA (for drugs that do not have an approved equivalent but already have data on safety and efficacy), with approval estimated in 2024. Following or in parallel with US FDA approval, depending on country requirements, Viatris will file with national and regional regulators in countries with high HIV burden/incidence and medium-to-high rates of OC use.

Figure 4: Key Milestones for DPP Development



How will communities be engaged in the development and rollout of the DPP?

An advisory group comprised of country and regional civil society advocates as well as end users, including adolescent girls and young women, will engage with product developers and input into product development and introduction plans on a periodic basis. More details about specific engagement opportunities will be available in the near future.

Early Introduction

Will the DPP be marketed in sub-Saharan Africa only?

Viatris plans to submit the DPP for regulatory review by the US FDA and there is a potential market for the DPP in the US, where OCP use is high and access to HIV prevention among cisgender women and women of color in particular has been limited. Current introduction planning efforts are focused on Kenya, South Africa and Zimbabwe, where there is higher HIV burden, moderate-to-high OC use and unmet need for FP and enabling environments. Other countries with higher OC use and HIV prevalence may also be countries where the DPP could have impact.

With high LARC use among women in sub-Saharan Africa, why are product developers introducing the DPP as an oral contraceptive pill?

OC use in the region has been generally stable over the years,[1] indicating there is a population of women who may prefer the flexibility of short-acting contraceptives that are immediately reversible and user-controlled. The DPP will not be offered to women who are on LARCs.

Why might it make sense to introduce the DPP in South Africa, even though the use of oral contraceptive pills is not common?

Although the use of OC is not common in South Africa compared to other modern contraceptive methods (e.g., injections and implants), a study by the Population Council estimates that South Africa has the highest number of potential DPP users within the region among the countries evaluated.[2] It found that given South Africa's large population size, the number of HIV-negative OC users who could potentially convert to the DPP is high. South Africa also has a large number of estimated HIV-negative condom users and women with an unmet need for FP. Moreover, South Africa is rapidly scaling up oral PrEP,[3] which could tap into a new population of oral PrEP users who are also interested in pregnancy prevention.

How will country-level leadership be engaged to lead introduction planning?

In 2019, DPP Consortium partners conducted a series of consultations in Kenya, South Africa and Zimbabwe with Ministries of Health (MOH), implementing partners, regulatory authorities and other key stakeholders to understand perceived benefits and challenges of rolling out the DPP. Stakeholder inputs informed the development of the Market Preparation and Introduction Strategy for the DPP. Follow-on consultations with MOH in Kenya, South Africa and Zimbabwe are planned, with future plans to co-design country introduction roadmaps and implementation research.

What are considerations for DPP introduction alongside the dapivirine vaginal ring and CAB-LA?

While the DPP is likely to be introduced in parallel with the dapivirine vaginal ring and CAB-LA, these new products do not provide contraceptive benefits – a concern that is top-of-mind for many women. The DPP, therefore, may offer an additional benefit to these other PrEP products and may appeal to certain women at certain times in their lives. While the DPP contains a shorter-acting oral PrEP pill – which might be a barrier for some users compared to the dapivirine vaginal ring or CAB-LA – this combination offers the earliest opportunity to assess if uptake and effective use of biomedical HIV prevention increases with an MPT formulation.

[1] Data from USAID, STATcompiler, https://www.statcompiler.com/en/; Performance Monitoring for Action (PMA), https://www.pmadata.org/.

[2] Begg L, et al., Estimating the market size for a dual prevention pill: adding contraception to pre-exposure prophylaxis (PrEP) to increase uptake. *BMJ Sex Reprod Health* 2020;0:1–7. doi:10.1136/bmjsrh-2020-200662.

[3] AVAC, Global PrEP Tracker, https://data.prepwatch.org/.

Service Delivery

What service delivery channels are most appropriate for the DPP?

While a variety of service delivery channels and health worker cadres are trained to deliver OC, because the DPP contains oral PrEP, it will need to be delivered in settings where trained providers are authorized to prescribe and monitor oral PrEP. An initial analysis of service delivery channels includes public-sector FP and HIV clinics as potential channels for DPP introduction. Recent expansion of differentiated delivery models, including mobile, pharmacy and community-based models as well as multi-month dispensing for oral PrEP, indicate potential for diversified channels and cadres that could deliver the DPP in the future.

How will delivery of the DPP balance HIV testing and prescribing requirements with the more decentralized approach to OC delivery?

In many countries, OC is available over-the-counter and is delivered by diverse cadres in a variety of delivery settings, including through pharmacy and community-based channels. By contrast, current oral PrEP policies typically require a prescription, initiation by a trained provider and HIV testing every three months. Since the DPP contains oral PrEP, DPP users will likely need to follow oral PrEP testing and prescribing requirements.

However, recent expansion of differentiated and self-care approaches to oral PrEP delivery, including multi-month dispensing and HIV self-testing, as well as delivery of oral PrEP in FP clinics and private sector channels, show an encouraging move towards aligning oral PrEP and OC delivery. Preparing health systems for the DPP could help open up additional channels for oral PrEP, in line with where women prefer to access services, and accelerate PrEP/FP integration. In addition to generating insights through acceptability studies and HCD research, the DPP Consortium will develop recommendations for provider counseling messages and a private sector delivery and financing strategy to identify how to align the DPP with OC delivery practice to the extent possible.

What are some of the messaging/counseling considerations for the DPP?

HCD research is ongoing to develop messaging around the DPP. While this work will help craft specific messages for the DPP, given that side effects and adherence to daily pills are barriers to continuing both OC and oral PrEP use, messaging and counseling will need to address side effects of both products and promote successful adherence and effective use strategies. Counseling around missed pills and switching methods as fertility intention or HIV risks change will require more support than typically provided in FP programs.

Cost and Funding

Will the DPP be affordable?

Product developers will aim to ensure that the DPP costs as close as possible to oral PrEP and COC separately, recognizing that these products tend to be highly subsidized. Donors and governments can look to subsidize DPP costs in order to make it available for free or very low cost to users. As the DPP scales up, the price is likely to reduce.

What are considerations for manufacturing the DPP?

TDF/FTC is available at scale volumes, but the DPP is different than TDF/FTC on the market today because it will contain hormonal products for contraception. Furthermore, the DPP will be packaged in blister packs (not bottles). For these reasons, the DPP must be manufactured at hormonal contraceptive facilities, and the additional packaging may impact price.

Viatris will be the initial manufacturer of the DPP with sufficient manufacturing capacity to supply 250,000+ women per year with the DPP. Viatris may be able to increase capacity further with additional packaging equipment.

Who is funding the development of the DPP?

DPP development and market introduction planning efforts to date have been supported by the Children's Investment Fund Foundation (CIFF), the Bill & Melinda Gates Foundation (BMGF), the US Agency for International Development (USAID) and WCG Cares.

Why should funders consider investing in the DPP?

The DPP requires fewer resources to bring to market than any other MPT in the pipeline because there is no need for a long clinical trial. Bioequivalence studies are small and can be done quickly. Planned acceptability studies and implementation research will lend further insights on how to market the DPP to optimize potential uptake. Further, the DPP will be rolled out sooner than any other MPT, presenting a learning opportunity for all MPTs in the pipeline that will be introduced in the future. As a combined product, it could help break down persistent HIV and FP siloes, tapping into commitments made around SRH integration inspired by the ECHO trial. Even as other products are approved (e.g., the dapivirine vaginal ring and CAB-LA), there is likely a market for the DPP as a short-acting product. And while funding for HIV prevention and FP is under pressure, as countries scale up oral PrEP, delivery costs are likely to decrease, leading to a more favorable environment for the DPP.

For inquiries, updates and resources on the development of the DPP, please visit prepwatch.org/dpp.

Acknowledgments

This document was developed in partnership with HIV prevention and SRH stakeholders.

About the DPP Consortium

The DPP Consortium is coalition of organizations, including AVAC, CHAI, Mann Global Health, Viatris and the Population Council, that are implementing market preparation and introduction activities for the DPP. These efforts are supported by CIFF, the Bill & Melinda Gates Foundation (BMGF), the U.S. Agency for International Development (USAID) and WCG Cares.