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CURRENT OPINION

Pre-Exposure Prophylaxis for HIV Prevention in Women: Current Status and Future Directions

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Abstract

Pre-exposure prophylaxis (PrEP) is a promising intervention to prevent HIV acquisition, with benefits both to the individual and to population-level health. PrEP is an opportunity to complement ongoing public health efforts to eliminate HIV. For women, PrEP can also serve as a gateway to access sexual and reproductive health (SRH) services. Clinical efficacy of PrEP was initially reported in women using a 1% tenofovir vaginal gel in 2010, followed by an efficacy trial of oral PrEP using TDF/FTC in men who have sex with men (MSM). Since then, further trials have reported efficacy in oral PrEP containing tenofovir in women and heterosexual men, while the subsequent trials for women using tenofovir gel reported no efficacy, stemming from difficulties in achieving adequate adherence. In an effort to offer women additional choices to oral PrEP, alternative modalities are being tested in clinical research, including long-acting injectable formulations and intra-vaginal rings. In 2015, a meta-analysis of clinic trials and open-label extension studies led to the World Health Organization (WHO) strongly recommending the provision of oral PrEP containing tenofovir for any person at substantial risk of HIV infection, irrespective of gender or population group. Currently, PrEP services for women around the world, including those who are either pregnant or breastfeeding, remain limited. Outside sub-Saharan Africa, most PrEP programmes are focused on MSM. South Africa, Kenya, and the USA have the greatest utilization of oral PrEP by women. Yet, since 2012, of the estimated > 300,000 people globally who have initiated PrEP, a minority are women. In this narrative review, we examine the most recent literature on clinical and implementation PrEP research among women. We highlight the high burden of disease related to common sexually transmitted infections (STIs) in women, and the opportunity to integrate PrEP and other HIV prevention services, STI case management, and family planning services, as part of a more robust package of SRH services. Raising awareness on PrEP amongst women and their healthcare providers, minimizing gaps in access, and ensuring adherence and persistence of PrEP during periods of risk are critical issues if PrEP can have a meaningful impact on reducing HIV incidence in women globally.

1 Introduction: Why PrEP for Women Matters

The global HIV response has been marked by a number of notable public health successes for women. Prioritizing prevention of mother-to-child transmission of HIV (PMTCT) services has led to an impressive reduction of new vertical HIV infections, and improved antiretroviral therapy (ART) access to women more broadly, resulting in significant decreases in mortality associated with HIV infection [1]. Nonetheless, epidemiological estimates by UNAIDS reflect that women, including adolescent girls and young women (AGYW), continue to be disproportionately affected by HIV, especially in sub-Saharan Africa [2]. The primary prevention of incident HIV among women, including in AGYW, is therefore a critical priority [3].

The complexity of factors associated with women's increased risk for HIV acquisition has been long characterized in the literature, and points to the interplay of biological predictors of risk, coupled with sociobehavioral factors (e.g., mental health issues, substance use, gender-based violence),

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Table 1 PrEP clinical trials in women with reported efficacy

Clinical research study	Product investigated	Year	Number of women included in study	Efficacy reported for women
TDF2	Daily oral TDF/FTC	2012	557	49% (95% CI −22 to 81%)
Partners PrEP	Daily oral TDF mono-therapy or TDF/FTC	2012	1164 (598 randomised to TDF, 556 randomised to TDF/FTC)	TDF: 71% (95% CI 37–87%) TDF/FTC: 66% (95% CI 28–84%)
FEM-PrEP	Daily oral TDF/FTC	2012	2120	6% (95% CI −52 to 41%)
VOICE	Daily vaginal 1% tenofovir gel or daily oral TDF mono-therapy or TDF/FTC	2015	5029	TDF: −49% (95% CI −129 to 3%) TDF/FTC: −4% (95% CI −50 to 27%) Tenofovir gel: 15% (95% CI −21 to 39%)
Bangkok Tenofovir Study	Daily oral TDF mono-therapy	2013	489	79% (95% CI 17–97%)
CAPRISA-004	1% tenofovir gel (pericoital intra-vaginal)	2010	889	39% (95% CI 6–60%)
FACTS-001	1% tenofovir gel (pericoital intra-vaginal)	2015	2029	0% (95% CI −40 to 30%)
The Ring Study	Intra-vaginal ring (DPV) (monthly insertion)	2016	1959	31% (95% CI 1–51%)
ASPIRE	Intra-vaginal ring (DPV) (monthly insertion)	2016	2629	27% (95% CI 1–46%) (56% reduction in incidence among women > 21 years)

stigma and discrimination, and socioeconomic inequity [4]. Phylogenetic research has also suggested that a pattern of older men infecting younger women has played a role in the HIV transmission dynamics in high HIV burden settings such as Kwazulu-Natal, South Africa [5]. Given these patterns, introducing and scaling up evidence-based HIV prevention options for women that are effective and desirable to women is vital.

Oral pre-exposure prophylaxis (PrEP) offers women an efficacious, female-controlled HIV prevention choice. The first medicine to have an approved PrEP indication by a stringent regulatory authority (SRA) was tenofovir/emtricitabine in 2012 by the United States Food and Drug Administration (FDA) [6]. Since then, the World Health Organization (WHO) has issued a series of evidence-based recommendations that have considered how PrEP could be offered to women at substantial risk of HIV acquisition [7–9]. Countries with concentrated HIV epidemics in the Americas, Europe, Asia, and the Pacific have largely focused on oral PrEP services for MSM [10]. A number of eastern and southern African countries, with generalized HIV epidemics where ART scale-up has been the focus of HIV programs, are beginning to consider expanding access and coverage for oral PrEP to people at risk for HIV, particularly women.

2 Clinical and Implementation Guidance for Oral PrEP

The WHO's normative guidance on HIV prevention and treatment uses a process that includes the systematic review and meta-analysis of research data [11], coupled with the consideration of values and preferences of people who can benefit from health interventions (i.e., end users), the feasibility of implementation, and public health impact.

The first WHO recommendation on oral PrEP was published in 2012 when WHO specifically recommended the provision of PrEP (TDF/FTC) to MSM, transgender women, and serodiscordant couples in the context of demonstration projects [7], followed by a broader recommendation for MSM in 2014 [12]. At the time of the 2014 recommendation, the evidence for women at that point in time was less certain, given the nonsignificant findings reported from two key studies, VOICE and FEM-PrEP [13, 14]. In 2015, WHO expanded its guidance on oral PrEP by making a strong recommendation, based on the high-quality evidence from ten clinical trials [8, 9]. The latest recommendation states that any person at substantial HIV risk[1] be offered PrEP as part of combination HIV prevention [8, 9]. This recommendation is permissive for PrEP use in women, including for those pregnant and breastfeeding (Table 1).

2.1 Evidence on PrEP Effectiveness in Women

The systematic review that served as the basis for the 2015 WHO PrEP recommendation has been already described [15], and included evidence from randomized clinical trials (RCTs), open-label extensions (OLE), and demonstration projects evaluating oral PrEP containing TDF to prevent

[1] WHO defines "substantial risk" at an HIV incidence threshold above three per 100 person-years at which offering PrEP is likely to be cost-effective and potentially cost-saving.

HIV infection. For this article, we expanded the search from 2015 to include articles up until April 2018, and additionally also assessed articles on effectiveness presented at the Conference on Retroviruses and Opportunistic Infections (CROI) 2019.

The 2015 review found PrEP to be effective among men and women when data were disaggregated by sex, even when the results from FEM-PrEP and VOICE were included. In addition, the review found similar effectiveness in a meta-analysis of TDF and TDF/FTC, while noting that this was consistent with the clinical placebo-controlled trial Partners PrEP that compared the regimens directly in HIV heterosexual serodiscordant populations in Kenya and Uganda [16, 17].

When results were stratified by age, the findings were more mixed. For young women, Partners PrEP found that PrEP was effective in reducing HIV infection in women aged less than 30 years, while FEM-PrEP was not effective in preventing HIV in women less than 25 years old, most likely associated with differing levels of adherence. Results from the open-label HPTN 067 study at that time had indicated that young women could maintain high levels of PrEP use when they were made aware PrEP was effective [18]. Another OLE, that of TDF2 study in Botswana, also found that women can be highly adherent to PrEP [19].

Since March 2016, several studies were published with further information on PrEP effectiveness for women, including outcomes on HIV infection, sexual risk behaviors, and safety. The ADAPT trial (HPTN 067) in South Africa randomized women to daily, time- (twice a week plus a post-sex dose) or event- (one tablet both before and after sex) driven oral PrEP (TDF/FTC) for 24 weeks, following a 5-week directly observed weekly dosing [20]. Four of eight observed seroconversions took place post-randomization, with two in the time-driven arm and two in the event-driven arm [21]. Overall, sex acts covered by PrEP were highest among women in the daily PrEP arm as compared with the time- and event-driven arms (75% vs. 56% and 52%, respectively) [20]. Side effects were uncommon. Similarly, of the four incident seroconversions in the Partners Demonstration Project, none had TFV detected in plasma samples. A modelled analysis estimated that 80.7 HIV infections would have occurred in the absence of PrEP, making PrEP among women highly effective (effectiveness of 93%, $p < 0.0001$) [22, 23]. Sub-studies were also conducted using data from the Partners Demonstration Project related to pregnancy, fertility intentions, and adherence. One analysis found that young women were able to maintain high-levels of PrEP coverage during periods of risk [24]. Another found relatively high rates of fertility intention (80% of women desiring more children) and pregnancy rates among serodiscordant couples, with 82.9% of couples reporting PrEP or ART use during the 6 months preceding pregnancy; no seroconversions occurred.

Additional pharmacokinetic studies were identified in our updated search. One study examined intracellular tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate in dried blood spots using specimens from men and women [25], showing that TFV-DP exhibited a median half-life of 17 days, and achieving steady state in 8 weeks. Another study examined dose frequency ranging to establish adherence benchmarks for TDF/FTC using male and female subjects [26], demonstrating consistent findings for steady-state daily-dosing serum TFV and PBMC TFV-DP with what was reported in highly effective PrEP clinical trials.

Adherence to oral PrEP is a critical predictor of protection against HIV infection, and has been consistent across clinical trials and in meta-analysis. A range of factors can impact a woman's ability to take PrEP as directed during a period of elevated risk for HIV. For example, Roberts et al. found that HIV-negative women who reported intimate partner violence (IPV) in the previous 3 months were more likely to have low PrEP adherence [adjusted risk ratio 1.49, 95% confidence interval (CI) 1.17–1.89], but this effect diminished over time and did not remain significant 3 months after the reported exposure [27]. Additionally, a post hoc analysis from the Partners PrEP trial examined the relationship between PrEP efficacy and abnormal vaginal microbiota, finding no difference in efficacy for women with and without bacterial vaginosis [28].

2.2 What About Safety?

Regarding safety, oral PrEP has been shown to have no evidence of an increased proportion of adverse events, and this observation has held for women as well as men when disaggregated by sex [15]. However, small decreases in renal function among women taking PrEP in Thailand have been reported [29]. The Bangkok Tenofovir Study reported that in participants receiving tenofovir, creatinine clearance was lower in men than in women ($p < 0.001$), while the difference did not change significantly over time ($p = 0.67$). A sub-study from the Partners PrEP RCT examined differences between 3- and 6-month creatinine clearance monitoring, and found no significant difference, suggesting 6-month monitoring is sufficient [30].

A number of clinical trials have also reported on a small decrease in bone mineral density (BMD) during the first 24 weeks of PrEP use that did not progress thereafter, including one study published after the WHO search that reported small yet reversible decreases in BMD among African women [31–33]. The data on the effect of TDF/FTC on BMD in adolescent boys and girls are limited, and its measurement is challenging. An analysis from the VOICE

Box 1. Key messages on PrEP for pregnant and breastfeeding women

- You can use PrEP throughout pregnancy and breastfeeding.
- HIV infection can occur at high rates during pregnancy and breastfeeding.
- The risk of passing HIV infection onto a baby is higher if the mother becomes infected while she is pregnant.
- The existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection.

trial found small but significant declines in BMD among a sub-set of female participants with tenofovir detected in plasma samples [31]. This reversed after PrEP was stopped. No studies (including those among adolescent boys) have found an association between PrEP and fractures. Data from the treatment of adolescents with HIV with TDF/FTC suggest that growth was not impaired [34].

An important implementation consideration for PrEP provision is advice on the time to protection when initiating PrEP. Pharmacological evidence points to adequate protection in women with TDF-containing PrEP being reached after seven daily doses [9, 56].

2.3 PrEP During Pregnancy and Breastfeeding

Based on the clinical and implementation guidance of WHO, PrEP containing tenofovir can be used by HIV-negative women who are either pregnant or breastfeeding [35, 36]. PrEP can be provided to complement established HIV prevention strategies for pregnant and breastfeeding women especially in very high HIV incidence settings (Box 1). Tenofovir-based regimens are the most widely used antiretroviral treatment (ART) regimens in people living with HIV worldwide [37], and the safety profile of tenofovir has been well characterized for HIV treatment among pregnant and breastfeeding women and their infants [38, 39].

Based on a systematic review by Mofenson et al., maternal/child adverse outcome data in HIV-infected and HIV-uninfected pregnant/breastfeeding women receiving TDF alone or in combination with other drugs compared with non-TDF regimens were examined [36]. A total of 26 articles in HIV-infected and seven in HIV-uninfected women were identified and included in the analysis. The studies from HIV-uninfected women include five hepatitis B virus (HBV) mono-infection studies, and two PrEP studies, Partners PrEP study [40], and the VOICE trial [41]. No statistically significant differences were observed between TDF and comparison non-TDF regimens in pregnancy incidence, stillbirth/pregnancy loss, preterm delivery less than 37 weeks, low birth weight < 2500/< 1500 g, small for gestational age, birth defects, or infant (> 14 days) or maternal mortality. Furthermore, a prospective, short-term, open-label oral TDF/FTC PrEP study conducted among 50 HIV-uninfected breastfeeding Kenyan and Ugandan mother-infant pairs found very low levels of study drug in infant blood (tenofovir was undetectable in 94% of samples), further suggesting oral TDF/FTC PrEP is safe to use for breastfeeding women and their infants [42].

The currently available safety data indicate that there does not appear to be a safety-related rationale for contraindicating PrEP during pregnancy/breastfeeding or for discontinuing PrEP in HIV-uninfected women receiving PrEP, such as sex workers in South Africa's high-burden districts, who become pregnant and whose HIV risk persists [43]. However, pharmacovigilance that includes robust approaches such as cohort studies and registries should be a priority that is adequately supported by national authorities and accounted for in strategic planning efforts around PrEP roll-out (Table 2).

2.4 Adolescent Girls and Young Women

Adolescent girls and young women (AGYW) are disproportionately affected by HIV in sub-Saharan Africa, accounting for a quarter of new infections [2]. For adolescents and young adults, the evidence for tenofovir-containing PrEP (TDF/FTC) stems from three studies. ATN 110 and ATN113 were conducted in the USA among young MSM, while Champs PillPlus (*NCT02213328*) included 99 girls and 49 boys in South Africa [44–46]. In all studies, continuation on PrEP was a challenge as young people struggled to take a daily pill, with a noted age-specific decline in adherence over time. Based on these studies, it appears that adolescents and young adults (24 years old or less) may benefit from additional monitoring and adherence support that incorporates their needs in order to prevent HIV acquisition [47]. Unitaid is funding implementation projects in South Africa and Brazil that are exploring PrEP service delivery to adolescents [48].

As a result of the findings from ATN 113, which demonstrated that TDF/FTC is safe and well tolerated in HIV uninfected at-risk adolescent males aged 15–17 years, both the FDA and the European Medicines Agency (EMA) extended the PrEP indication on TDF/FTC to adolescents

Table 2 Summary of different antiretroviral (ARV)-based prevention products (tested or currently in the pipeline) for women

Product type	Status of research	Regulatory status
Vaginal gel		
1% tenofovir gel (CAPRISA 004, VOICE) *Abdool Karim et al., 2010* [55] *Marrazzo et al., 2015* [14]	Efficacy trials completed, no additional studies being planned	Unlikely to move to product registration
Oral tablets		
TDF-containing (e.g., TDF alone, TDF-FTC) *WHO EML, 2017* [142]	Efficacy trials completed, ongoing implementation/demonstration projects	TDF/FTC approved with a PrEP indication (both originator and generic)
TAF/FTC (DISCOVER, large RCT currently underway is only recruiting MSM and transgender women in high income countries *DISCOVER study protocol:* NCT02904369	Phase 1 pharmacokinetic study completed in 72 women Efficacy trial underway in MSM	Indication for treatment, but not for PrEP (pending completion of DISCOVER and submission to regulatory authorities by product developer)
Maraviroc *Gulick R et al., 2017* [143]	Phase 2 study completed	Unlikely to move to product registration
Long-acting injectables		
Rilpivirine (NNRTI): HPTN 076 *HPTN 076 protocol:* NCT02165202	Phase 2 study completed	No, study development has been discontinued and unlikely to move to product registration
Cabotegravir (integrase inhibitor): HPTN 084 is an RCT of 32,000 women in Botswana, Kenya, South Africa, Uganda, and Zimbabwe [68]	Ongoing Phase 3 study, with estimated study completion May 2022	Filing for regulatory approval pending on Phase 3 study
Vaginal rings		
Dapivirine (DPV)	Two independent randomized clinical trials completed, ASPIRE and the Ring Study *ASPIRE protocol:* NCT01617096 *IPM 027 protocol:* NCT01539226 Two open label extension studies currently underway, anticipated completion by end of 2018 or early 2019 [61, 62]	Currently being considered by EMA/WHO under Article 58 procedure, and potentially by other regulatory authorities, including US FDA
Other sustained delivery approaches		
Vaginal films [144]		
Patches [145]		
Implants (e.g., slow release formulations to be inserted under the skin similar to contraceptive implants) [146]		
Vaginal insert [147]		
Multipurpose products (e.g., matrix vaginal rings containing 200 mg DPV and 320 mg levonorgestrel) [148]		

who weigh at least 35 kg [49, 50]. Given most safety and efficacy data stems from adult clinical trials, the additional evidence being generated from implementation research and programs will support future normative guidance development and inform service delivery models, including how to optimize adherence.

2.5 Is TDF/FTC the Only Drug for PrEP that Women Can Use?

TDF/FTC is the medicine most widely used for PrEP across all settings, and remains the only product approved by SRAs and the National Medicines Regulatory Authorities (NMRAs). However, TDF/3TC for PrEP is included in the WHO Essential Medicines List (2017), where WHO states that FTC is interchangeable with 3TC (consistent with what is recommended for treatment of HIV infection) based on a technical consultation by WHO in 2016 [51].

For TDF monotherapy (300 mg as a daily tablet), the evidence largely stems from the Partners PrEP trial. The WHO meta-analysis and the Partners PrEP trial [15–17] found that TDF alone and TDF/FTC are comparably safe and effective for heterosexual men and women. TDF alone as PrEP was also effective in the Bangkok Tenofovir Study [52], of which 20% ($n = 489$) of study participants were women. There is limited evidence on the use of TDF alone for PrEP [53] among MSM although there is an ongoing phase II study in Brazil evaluating the use of TDF/3TC for PrEP [54]. WHO's implementation guidance states that if available, single-agent TDF is an allowable option for use as PrEP for the prevention of heterosexual HIV transmission, although in practice, no national program or implementation project has used or is planning to use TDF alone. A policy review identified national PrEP guidelines that recommend TDF monotherapy in addition to the fixed-dose combinations of TDF/FTC or TDF/3TC [10]. Six countries recommend TDF/3TC for PrEP in addition to TDF/FTC (Pakistan, South Sudan, Namibia, Kenya, Zambia, and Zimbabwe), while Lesotho's guidelines currently recommend exclusively TDF/3TC.

3 Choice Matters: What Other Biomedical HIV Prevention Products May Be in the Horizon for Women?

Female-controlled, user-friendly strategies to prevent HIV among women remain limited. For PrEP, the principle of offering additional options for preventing HIV acquisition in women remains central to the research pipeline for other antiretroviral (ARV)-based prevention methods. Since taking an oral daily tablet can be a challenge, other formulations such as gels and vaginal rings have been explored (Table 2), while long-acting injectables are currently being studied.

Tenofovir's pharmacological properties resulted in making it an attractive candidate for a topical gel that women could use. To date, of three completed trials of vaginal tenofovir gel (used daily and coitally), only one demonstrated efficacy in women: CAPRISA 004 [55]. The reported efficacy of tenofovir gel in CAPRISA 004, however, never translated into consideration by regulatory authorities, as the level of efficacy was not deemed sufficient for moving forward with this particular product. Since the initial publication for the CAPRISA tenofovir gel, a follow-up study reported lower efficacy of PrEP among women who have vaginal dysbiosis [56].

Over the past 2 years, focus has shifted to the dapivirine (DPV) intra-vaginal ring and its potential role to reduce HIV incidence in women. The silicon-based ring provides sustained-release of drug and is designed to be effective with monthly use. Two large studies showed moderate efficacy of vaginal rings among women from Malawi, South Africa, Uganda, and Zimbabwe, with a 27% reduction in incidence in the ASPIRE study (MTN-020) and 31% reduction in The Ring Study (IPM 027) [57, 58]. Post hoc analyses indicated the DPV-ring may reduce the risk of HIV acquisition up to 65% in women who were adherent to the product [59]. As with oral PrEP, concerns remain around the use of the ring in younger women (e.g., 18–21 years of age) who did not adhere to the extent of older women, and were therefore not protected from HIV acquisition. An interim analysis from the open-label extension study of ASPIRE (HOPE MTN-025) indicates that in an open-label setting, where women know they are taking active drug, adherence may be enhanced in study participants [60]. Information from the final analyses of the open label extension studies, HOPE (MTN 025) and DREAM (IPM 032), will be made available in 2019 [61, 62].

In addition to the rings, multi-purpose technologies (MPTs) that incorporate contraception, HIV, and STI prevention agents in a single product [63] and products using nanotechnology, including the role of polymer-based nanoparticles to counteract the pathogens associated with the anatomical region of the vagina are being investigated [64–66]. In order to counter recurrent concerns about adherence from oral PrEP and DPV studies, a long-acting injectable formulation of cabotegravir (CAB-LA) is currently being assessed in two independent efficacy trials. HPTN 083 (in MSM and transgender women) [67] and HPTN 084 (African women) are currently recruiting participants [68].

4 The Other STIs: Ignored but Not Forgotten

Complications resulting from both bacterial and viral STIs can have a severe impact on sexual and reproductive health (SRH) in both men and women, including the

increased risk associated with HIV acquisition [69]. However, complications disproportionately affect women in a number of ways, including risk for cervical cancer and infertility [70, 71]. Gonorrhea in women, for example, can lead to complications such pelvic inflammatory disease, ectopic pregnancy, and infertility, as well as increased transmission and acquisition of HIV [72, 73].

Management of bacterial STIs in many countries, especially in resource-constrained settings, is limited by the fact many countries resort to syndromic management. As a result, STIs are undiagnosed in women, resulting in significant health implications, including the risk for emergence of antimicrobial resistance [74, 75]. Nucleic acid testing (NAT) is the more optimal approach to diagnose an STI, but remains costly and operationally challenging for most services where women seek care, including in those settings offering PrEP in Africa. HPTN-082, a study evaluating oral PrEP in young women in Zimbabwe and South Africa, reported on high levels of curable STIs (39%), including 29% prevalence at baseline for chlamydia [76]. Many of these STIs were asymptomatic and would have been missed on syndromic management approaches, supporting the argument for the need to shift away from syndromic to diagnostic approaches. Therefore, it is important to consider that women presenting for PrEP at a clinical facility should be offered the benefit of enhanced sexual health services, including male and female condoms, appropriate diagnoses and treatment of syphilis, chlamydia and gonorrhea, and opportunities for cervical cancer screening and treatment. The budget impact of including asymptomatic STI testing remains a challenge for PrEP programs in resource-limited settings [77].

5 Unmet Need for Contraception, Contraceptive Choice, and Safer Conception

The most recent global data indicates that of women of reproductive age (15–49 years) who are married or in a union, 63% used some form of contraception [78, 79]. The greatest unmet need for family planning is in Africa, where one in five women have an unmet need for family planning. Providing contraceptive choice and the prevention of unintended pregnancies for women within HIV programs is seen as a programmatic priority in African countries. Family planning providers have the opportunity to ensure women are aware of and offered HIV testing to enable them to make informed contraceptive and HIV prevention choices, including PrEP. For women who wish to conceive safely in serodiscordant partnerships or when their partner's HIV status is unknown, offering PrEP can be considered [80, 81].

6 Real-Life PrEP Uptake in Women

The current state of PrEP implementation outside of research highlights how services are being offered largely to cisgender MSM in high-income settings. Outside of Africa, oral PrEP is starting to be provided under national public sector health systems (e.g., partial or full reimbursement by the state), including in France, Norway, Belgium, Portugal, Scotland, Wales, Canada, Brazil, the USA, Australia, and Vietnam [10]. Currently, the USA represents the largest share of global PrEP use, with roll-out starting soon after FDA approval in 2012. Nine studies identified in our updated systematic review reported on the uptake of PrEP among women in clinical, non-research settings within the USA [82–90]. An additional study revealed that women accounted for 42% of PrEP initiations earlier in implementation (2012–2014), but that proportion reduced to 12% (2014–2015), and 9.8% by 2016 [91]. Although US coverage has been associated with MSM, African-American women have been under-represented in both PrEP research and services, despite having a disproportionately higher risk for HIV infection [92, 93].

South Africa was the first country in sub-Saharan Africa not only to have national guidelines on PrEP, but to offer PrEP under a national, phased-in, roll-out [94]. Currently, PrEP is available at 34 sites across the country, with a focus on PrEP provision to female sex workers, MSM, university students, and AGYW [95]. In addition, other initiatives are underway, including DREAMS, which is focusing on PrEP provision to AGYW in a select number of countries, including Kenya, Malawi, Mozambique, South Africa, Uganda, Swaziland, and Zimbabwe [96]. Female sex workers in eastern and southern Africa are prioritized for PrEP provision given their ongoing risk for HIV, particularly in Kenya, South Africa, and Zimbabwe [97–101]. Kenya and Eswatini's national implementation has focused on a broader heterosexual approach when roll-out began in 2017 [97, 101]. Since the inception of the Kenya program, over 20,000 men and women have initiated PrEP in over 40 facilities, although continuation on PrEP among those who initiate PrEP has been a challenge [97]. Recent reports from Kenya from a subset of PrEP users indicated that an appreciable 11% of women had used PrEP while pregnant [98].

West Africa has had very limited implementation of oral PrEP, with some formative research and demonstration projects having been conducted (e.g., Benin, Senegal, Cote d'Ivoire) [102]. In Nigeria, a pilot project has been exploring different models of service delivery for serodiscordant

Box 2. High uptake and retention of PrEP among female sex workers in India

India is the world's second most populous country (104) with a concentrated HIV epidemic in key populations (104). Although there is no PrEP policy in place, nor has PrEP been included in India's Targeted Interventions, a PrEP demonstration project was conducted among female sex workers in Mysore and Kolkata. The implementing partners were two established community based organizations, Ashodaya and Durbar Mahila Samanwaya Committee (DMSC), in partnership with the University of Manitoba in Canada (105).

The project has been assessing acceptability and the reasons why sex workers choose to accept or decline PrEP initiation, evaluating accessibility by looking at different PrEP delivery strategies (e.g. clinic based pick-up or home delivery by peer educators), and monitoring adherence and trying to better understand, as is done in most demonstration projects, the reasons for people's discontinuation.

In Kolkata, the sex worker community is associated with a brothel area known as Sonagacchi, where there is over a decade of strong community mobilization and peer support. The Kolkata site started recruiting in January 2016, and screened a total of 843 women, 678 of which qualified under the project criteria to initiate PrEP. A total of 78 participants withdrew from the study, reflecting a high retention rate which reflects the project's support system in place. Project investigators cite the critical role of the nature of the PrEP service, which is community-based, with adequate time spent in counselling women prior to recruitment and peer-base monitoring of PrEP users during follow-up. Based on monitoring data, adherence has been reported until January 2018 to be 81% in these women.

PrEP was not provided as a standalone biomedical intervention, but it was framed as a package of services under the targeted interventions services which is mandate by India's national HIV programme.

couples across three states [103]. The outcomes from that project have already supported the inclusion of PrEP in the country's ARV guidelines in 2016, and should be informing the roll-out of PrEP.

India, home to large generic drug manufacturers, including tenofovir-based regimens, has seen the initial provision of PrEP to female sex workers (Box 2), and current plans are underway to offer PrEP to MSM.

7 Why Awareness of PrEP in Women Matters

The literature suggests that women, when provided with information on the effectiveness of PrEP, are generally supportive of the intervention [106]. In a systematic review of the values and preferences across all populations, Koechlin et al. described how a majority of study participants welcomed PrEP as a suitable HIV prevention option for themselves and for others. However, one challenge of PrEP provision is the pervasive lack of knowledge on PrEP among women. Even in the USA, where PrEP was adopted 7 years ago, knowledge of PrEP remains limited, as was reported, for example, in Chicago where only 29% of women had heard of PrEP [107].

A number of initiatives aim to raise awareness of PrEP in women and tackle the stigma associated with PrEP use. In the USA, for instance, the COMPASS initiative is aiming at advancing HIV prevention efforts in Southern states, particularly in African-American women, as part of a 10-year, US$100 million partnership between Gilead Sciences and community-based organizations [108]. In the UK, the Sophia Forum is a platform that has developed an online portal for information on PrEP in women (http://womenandprep.org.uk) [109]. In eastern and southern Africa, demand generation is a focus on the part of both governments and other actors, such as the OPTIONS Consortium [110] and the US-funded DREAMS initiative [111]. South Africa, given the disproportionately high rates of HIV infection in AGYW, is positioning oral PrEP as one element of a package of services under the She-Conquers program, which also aims at addressing issues around employment, adolescent pregnancy, and gender-based violence [112].

8 Discussion and Conclusion

Addressing ARV-based prevention for HIV in women is opening up a broader conversation around women's SRH needs, their existing choices, and prevention options into the future. PrEP roll-out across countries is raising questions on how to increase women's PrEP awareness, expand access to quality PrEP/SRH services, and ensure

medication adherence is optimized in those who initiate PrEP. UNAIDS global targets ambitiously aim to reduce new HIV infections to < 500,000 annually and provide oral PrEP to 3 million people by next year in 2020 [113, 114]. In the field of contraception, the FP2020 partnership aims to achieve 120 million additional girls and women having modern contraceptives by 2020 [115]. Of note, calls for action on violence (both sexual and physical assault) against women can be synergistic with efforts to strengthen HIV combination prevention and SRH services [116]. Current efforts to expand and accelerate evidence-based interventions for SRH services for women, including PrEP, remain insufficient, and these targets are likely to be missed.

As described in our review, reported efficacy estimates of oral TDF-based PrEP across trials have varied. These differences have largely been understood in the context of adherence. Women randomized to take PrEP who did not achieve steady adherence were at increased risk of HIV acquisition. Other factors have been proposed as having an effect on oral PrEP's effectiveness, even in the context of adherence. Such factors include the predominant subtype, and the intensity of exposure to HIV [117]. As we move forward with clinical trial and implementation research of other products, including the DPV vaginal ring, these factors will have to be accounted for in both study design and subsequent analyses. The interpretation of efficacy estimates stemming from studies, even when "moderate," will raise questions as to "what is good enough" to advance products into submission for regulatory approval at the country level. We do not need to look too much further than the two efficacy trials for the DPV intra-vaginal ring, for instance [57, 58]. The public health imperative of responding to ongoing HIV transmission in women, particularly in high HIV incidence settings such as South Africa, has been an argument for why the DPV vaginal ring should be approved for use by regulators, as it will confer an additional option for women.

Seven years after the FDA approved TDF/FTC for PrEP, uptake of PrEP in women remains woefully low, both in the USA and in other countries [118]. What is urgently needed is a strategic, rapid transition from having policies and target setting on paper to meaningful support of demand generation efforts and equitable access to SRH services. Provision of PrEP and models of care have to be tailored to local epidemiology, and social and cultural context, amongst other elements, to ensure they are attractive and accessible to women. As women, particularly younger women in sub-Saharan Africa, remain at ongoing and substantial risk for acquiring not just HIV but other bacterial/viral STIs, we propose a much more holistic approach to PrEP provision. Strategic and collaborative efforts are needed to integrate where possible existing and future PrEP into primary health [119], SRH services, and other entry points of care. Therefore, moving beyond HIV prevention and thinking about integration of PrEP within sexual health service platforms can provide the opportunity to reduce both HIV and STI incidence in women. Strengthening of promotion and implementation of established HIV and STI interventions, including the use of male and female condoms, and screening for and treatment of STIs, will be a key component of such a platform.

There is a paradigm shift on the syndemic of HIV and other STIs over the past year, and PrEP could indeed serve as a gateway for women into SRH services, which would include effective HIV prevention interventions [120]. Coordinated national-level HIV and SRH/STI strategies and responses are needed, as highlighted in Kenya's PrEP implementation through its national framework [121], which recognizes the vital piece of generating demand for PrEP through advocacy, community engagement, and media.

Barriers to uptake and persistence (staying on PrEP) for oral PrEP in women will need to be better understood and effectively addressed at all levels, from the individual to structural factors. Awareness, lack of risk perception of HIV, concerns about drug side effects, stigma associated with taking PrEP, uncertainty about the drug's efficacy, and lack of partner support are often cited as barriers in both initiation of and persistence on PrEP [122, 123]. Gender-based and intimate partner violence, particularly in young women and sex workers who can benefit from HIV and SRH services, are inherently tied to HIV risk and PrEP services have to account for their role in access and adherence to PrEP. Social science in imperative. Qualitative SRH research in women, with a particular focus in AGYW, and their social environment can also help us better understand the local and cultural context, and insights can be gained around how women can feel empowered by using PrEP [124]. For example, a qualitative study from Cape Town highlighted the complexities of risk perception and awareness in HIV-uninfected pregnant and postpartum women, such as barriers to condom use in pregnancy, low perceived risk after alcohol consumption, and lack of control over decisions in sex [125].

The question remaining is on how understanding MSM-focused PrEP programs can provide useful insight to shape PrEP services for women at scale. Implementing PrEP services to scale for MSM in high-income countries with concentrated HIV epidemics has taken time, but the contribution of PrEP in reducing new HIV infections is starting to be observed [126–131]. Clearly, the successes of these MSM-focused PrEP programs has in part been due to community awareness, demand from MSM themselves, and community mobilization to access PrEP, even online where formal public health systems have not been offering PrEP [132].

PrEP programs focused on women are in their infancy, and in most settings uptake remains modest, while continuation on PrEP is often low, particularly among young women

[133]. PrEP programs for sex workers in India, Kenya, Senegal, South Africa, and Zimbabwe are beginning to provide evidence that PrEP may have an important place for women who have on-going substantial HIV risk [99, 134–138]. As we have emphasized, adherence is a critical predictor of oral PrEP's effectiveness by users themselves. The mechanisms in real-life implementation by which we can enhance PrEP adherence (and persistence when a woman's risk is sustained over a longer period of time) will be critical as we look towards the future when additional options become available to women, whether that is a long-acting injectable product or a vaginal ring.

Countries are also asked to consider the role of PrEP delivery to pregnant and breastfeeding women, especially where high rates of HIV incidence are being reported, while ensuring that active pharmacovigilance of PrEP use in these women and their infants is undertaken [139]. Modeling, for instance, suggests that in South Africa, between 2020 and 2030, offering PrEP to pregnant and breastfeeding women would reduce new HIV infections in the country by 2.5% (conservative scenario) and 7.2% in an optimistic scenario [140]. PrEP provision, if scaled-up, would also have a benefit to reducing MTCT transmission, from in utero/intrapartum transmission to breastfeeding transmission.

In closing, collaborative platforms such as the WHO's Global PrEP Coalition can support harmonizing and leveraging HIV and STI programs to foster unified approaches in terms of clinical guidance, financial synergies, and public health efficiencies [141]. Oral PrEP, as it becomes integrated into SRH services, can serve as the platform for future integration of other products, including MPTs, when they become available. If we are to deliver on the UNAIDS and FP2020 targets, a holistic SRH model where oral PrEP can be positioned will have to promote choice, and SRH rights of young women and girls in all our collective efforts.

Compliance with Ethical Standards

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Conflict of interest Ioannis Hodges-Mameletzis, Virginia Fonner, Shona Dalal, Nelly Mugo, Busi Msimnga-Radebe, and Rachel Baggaley declare that they have no conflicts of interest relevant to the content of this article.

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