HIV pre-exposure prophylaxis for women
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Abstract
Women and girls comprise nearly half of HIV-infected individuals globally and 20% of new infections in the United States, indicating an urgent need to optimise HIV prevention options in this population. HIV pre-exposure prophylaxis (PrEP) – where antiretrovirals are administered to HIV-non-infected individuals at risk of HIV acquisition – is a promising, female-controlled HIV prevention strategy but has so far been underutilised in women. Clinical trial data demonstrate efficacy of daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for reduction of HIV acquisition among women when used consistently. Limited HIV risk perception and suboptimal PrEP awareness among women and healthcare personnel are among the challenges with PrEP delivery for women. Future research into the development of new drugs and delivery systems, and integrating PrEP delivery with reproductive healthcare services, provide opportunities to optimise this prevention strategy for women.

Keywords: Pre-exposure prophylaxis, women’s health, HIV prevention

Introduction
Women and girls currently make up 47% of the nearly 37 million people living with HIV/AIDS globally [1]. Despite advances in HIV and opportunistic infection treatment, HIV infection remains one of the leading causes of death among women of childbearing age worldwide [2]. In sub-Saharan Africa, where women make up nearly 60% of people living with HIV/AIDS, young women are up to eight times more likely to acquire HIV than similarly aged men [3,4], highlighting women and girls’ vulnerability to infection. In the United States, women account for 19% of new HIV infections and 25% of persons both diagnosed with AIDS and who die with HIV/AIDS [5]. Racial and ethnic disparities in the burden of HIV in the United States are magnified in women; black and Hispanic women are disproportionately affected, with 80% of new cases occurring in these groups. Additionally, geographic inequalities exist in the United States, with an increasing burden of both new HIV infections and later-stage diagnoses occurring among women in the south and southeast.

Women are particularly vulnerable to HIV infection due to a complex array of social, behavioural and biological factors. Although 80% of new HIV infections in women in the United States occur from sexual transmission [5], women may lack control over many strategies known to reduce sexual risk, such as mutual monogamy, consistent condom use and male circumcision. Women may additionally face intimate partner violence, discrimination, stigma, substance use, mental health disorders, poverty and lack of access to education and/or healthcare, all of which contribute to increased HIV acquisition risk via multiple overlapping mechanisms. Finally, women are biologically twice as susceptible to HIV during unprotected vaginal sex compared to men, and this risk further increases with unprotected anal sex, if the partner has a high HIV viral load, in the setting of mucosal inflammation, or if either partner has a sexually transmitted infection [6]. Female-controlled methods of HIV prevention (Table 1) are therefore needed along with strategies to maximise their effectiveness.

Pre-exposure prophylaxis (PrEP) is a female-controlled HIV prevention strategy that urgently needs to be optimised and implemented in high-risk populations, including women. Clinical practice guidelines issued by the US Centers for Disease Prevention (CDC) in 2014 [7] and the World Health Organization in 2015 [8] recommend PrEP with daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; Truvada) for individuals at substantial risk of HIV, including women, as part of combination HIV prevention. The CDC estimates that 468,000 heterosexual women in the US currently have indications for PrEP [9]. Despite this, PrEP has been underutilised as a prevention strategy in women. Here we review factors pertinent to PrEP delivery for women, including results from PrEP efficacy trials, toxicity concerns, and challenges and opportunities for PrEP implementation, focusing on women in the United States.

Women in clinical trials of oral PrEP
Randomised clinical trials of PrEP have demonstrated the efficacy of daily oral TDF-containing regimens for reduction of HIV

<table>
<thead>
<tr>
<th>Table 1. Overview of female-controlled HIV prevention methods</th>
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<tbody>
<tr>
<td><strong>Female condom</strong></td>
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<tr>
<td><strong>Diaphragms</strong></td>
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<td><strong>Microbicides</strong></td>
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<td><strong>Oral pre-exposure prophylaxis</strong></td>
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<td><strong>Injectable pre-exposure prophylaxis</strong></td>
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<td><strong>Partner antiretroviral treatment</strong></td>
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Email: ansheth@emory.edu
acquisition. However, efficacy of daily oral TDF-based PrEP has been highly variable across these randomised clinical trials (Table 2), with a relative reduction in HIV acquisition of 44% in men who have sex with men (MSM) and transgender women (iPrEx) [10], 67–75% in heterosexual HIV serodiscordant couples (Partners PrEP) [11], 62% in heterosexual men and women (TDF2) [12] and 49% in people who inject drugs (Bangkok Tenofovir Study, BTS) [13]. An additional placebo-controlled study among MSM and transgender women (IPERGAY) [14] demonstrated an 86% reduction in HIV acquisition using an intermittent, pericoital PrEP dosing strategy. On the other hand, two additional placebo-controlled studies of daily oral TDF-based PrEP conducted specifically among African women at risk for HIV infection (FEM-PrEP and VOICE) failed to demonstrate efficacy of daily oral TDF or TDF/FTC in reducing HIV acquisition [15,16].

In contrast to these disappointing results from FEM-PrEP and VOICE, which together enrolled over 5000 women, subgroup analyses of women in Partners PrEP, TDF2 and BTS demonstrated that daily oral TDF-based PrEP does reduce the risk of HIV acquisition in women. In Partners PrEP, which included 1785 Kenyan and Ugandan women with an HIV-infected partner (52% of the overall study population), efficacy among women was 66% with TDF/FTC and 71% with TDF, and efficacy remained between 64% and 84% even among subgroups of women at the highest risk of HIV acquisition [11,17]. In the TDF2 study, conducted among heterosexual men and women in Botswana, efficacy of daily oral TDF/FTC among the 557 women in the trial (45.7% of the overall study population) was 49%, although the limited endpoints in each subgroup reduced statistical power [12]. In BTS, which included 489 women who use injection drugs in Thailand (20% of the overall study population), efficacy of daily oral TDF in women was 79% [13].

Overall, high adherence was noted in trials that reported high PrEP efficacy, and HIV acquisition across studies, including those that enrolled women, was associated with lower PrEP adherence as adjudicated by objective measures, such as drug levels in various biomatrices. In both FEM-PrEP and VOICE, poor adherence to study drug was thought to explain the negative findings. Adherence rates to the active drug were below 40% among women in FEM-PrEP and approximately 30% among women in VOICE, based on plasma tenofovir levels [15,16]. Furthermore, over half of the women in VOICE had no tenofovir detected in plasma during any study visit, suggesting that most women in this trial were not taking the provided PrEP drug at all [15]. In Partners PrEP, by contrast, 82% of participants who did not acquire HIV had detectable plasma tenofovir levels; detectable tenofovir levels were associated with 86–90% risk reduction in HIV acquisition [11]. Similarly, in TDF2, 80% of participants who did not acquire HIV had detectable plasma tenofovir levels, and participants who did not acquire HIV were more likely than those who did to have detectable study drug [12]. In BTS, 66% of participants overall had detectable plasma tenofovir levels; detectable levels were associated with 70% risk reduction in HIV acquisition [13].

Women in clinical trials of topical PrEP

Five clinical trials have investigated the topical delivery of antiretroviral agents for the prevention of HIV acquisition in women (Table 3). The CAPRISA 004 study showed a 39% reduction in HIV acquisition among 889 women in South Africa with use of vaginal microbicide containing 1% tenofovir gel before and after sex [18]. However, two subsequent studies (VOICE and FACTS 001) failed to demonstrate any prevention efficacy with the use of either daily [15] or coitally driven [19] intravaginal tenofovir gel, respectively, among over 4000 women combined. In CAPRISA 004, tenofovir gel worked best among women who used it the most; cervicovaginal fluid tenofovir concentrations of ≥1000 ng/mL were associated with 65% and 76% protection against HIV, respectively [20]. However, in VOICE, women randomised to use daily vaginal tenofovir gel did not demonstrate reduced rates of HIV acquisition, although only 25% of women in the tenofovir gel group had detectable plasma tenofovir levels [15]. Those using 1% tenofovir gel with detectable plasma levels had a significantly lower likelihood of HIV acquisition than did those with no tenofovir detected (HIV incidence: 1.9 vs 6.1 per 100 person-years, adjusted hazard ratio [15]: 0.34, 95% confidence interval [CI] 0.13–0.87; P=0.02).

In FACTS 001, tenofovir gel used in the same manner as in CAPRISA 004 (before and after sex) was not effective in preventing HIV in young South African women (aged 18–30 years) [19]. Despite extensive adherence support and counselling, only 13% of women consistently used the product (≥80% of sex acts per month) and 22% had tenofovir detected in cervicovaginal lavage samples at all quarterly study visits. However, detectable tenofovir levels in cervicovaginal lavage samples from women who reported recent sex was associated with a significant 52% reduction in HIV acquisition.

Due to these challenges with adherence among women, longer-acting methods of drug delivery have also been investigated as an alternative to daily or coitally driven oral or topical PrEP. Most recently, two studies that jointly enrolled over 4500 women in 22 African sites reported reduction in HIV acquisition with monthly insertion of a vaginal ring containing the antiretroviral drug, dapivirine. MTN 020-ASPIRE demonstrated a 27% reduction in HIV incidence with the dapivirine ring, which increased to 37% when excluding two sites with low retention and adherence [21]. Protection against HIV was higher among women over 21 years of age (56%) but not observed among women 21 years of age or younger, who also demonstrated reduced adherence rates based on the measurement of dapivirine levels in plasma and returned rings. The second study, known as the Ring Study, demonstrated a 31% reduction in HIV incidence with the dapivirine ring, and 37% reduction among women over 21 years of age [22]. In this second study, higher levels of product adherence based on residual dapivirine levels in returned rings were associated with increased protection (up to 65% reduction in HIV acquisition).

Adherence and PrEP efficacy in women

Self-reported adherence can be inaccurate. In several PrEP efficacy trials, as summarised above, pharmacological measures of adherence were critical to study interpretation. However, the discrepant efficacy results from trials including women only (e.g. FEM-PrEP and VOICE) versus a trial conducted in men and transgender women (iPrEx), despite similar proportions of participants with detectable study drug, raises concerns that poor adherence may have greater consequences for women than men in the context of PrEP. Concentrations of tenofovir diphosphate are up to 100-fold higher in rectal tissue than vaginal tissue after TDF administration [23–25], suggesting that higher levels of adherence to daily TDF/FTC-based PrEP may be necessary for protection from vaginal exposure [26]. Concentration thresholds for tenofovir or its metabolites in various biomatrices that correlate with protection from HIV infection have been estimated for MSM based on pharmacokinetic modelling in conjunction with incidence data from PrEP studies [27]. For instance, four doses a week of TDF/FTC seems to provide 96% protection against HIV for MSM. Similar data to allow for analogous modelling studies in women have not been available to date, but are urgently needed.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Proportion of women</th>
<th>Intervention</th>
<th>Overall efficacy</th>
<th>Efficacy among women</th>
<th>Adherence</th>
<th>Efficacy based on adherence</th>
</tr>
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<tbody>
<tr>
<td>iPrEx</td>
<td>2499 men and transgender women who have sex with men</td>
<td>339 (14%)</td>
<td>Daily oral TDF/ FTC vs placebo</td>
<td>44% (95% Cl: 15–63%)</td>
<td>36 HIV infections in TDF/ FTC group vs 64 in placebo group</td>
<td></td>
<td>51% of seronegative subjects vs 9% of HIV-infected subjects</td>
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<td></td>
<td>Followed for median 1.2 years</td>
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<td>No detectable drug among transgender women who acquired HIV</td>
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<td></td>
<td>339 (14%) classified as transgender women</td>
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<td></td>
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<td>95% risk reduction with detectable study drug, 90% reduction with 16 fmol tenofovir-diphosphate/million PBMCs, 96% reduction estimated by taking 4 doses/week</td>
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<tr>
<td>Partners PrEP</td>
<td>4758 HIV-mutually disclosed serodiscordant couples in Uganda and Kenya where seropositive partner was not eligible for ART enrolment</td>
<td>1785 (52%) women</td>
<td>Daily oral TDF vs TDF/ FTC vs placebo</td>
<td>67% (95% Cl: 44–81%)</td>
<td>No difference in efficacy between men and women</td>
<td></td>
<td>No detectable plasma tenofovir levels in 83% who did not acquire HIV vs 31% who acquired HIV</td>
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<tr>
<td></td>
<td>Followed for median 23 months</td>
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<td>86% risk reduction for TDF and 90% for TDF/FTC with detectable tenofovir level</td>
</tr>
<tr>
<td>TDF2</td>
<td>1219 heterosexual men and women in Botswana</td>
<td>557 (45.7%) women</td>
<td>Daily oral TDF/ FTC vs placebo</td>
<td>62.2% (95% Cl: 51–83.4%)</td>
<td>9 HIV infections in TDF/ FTC group (0.65/100 person-years) vs 13 in TDF/ FTC group (0.50/100 person-years) vs 52 in placebo group (1.99/100 person-years)</td>
<td>49%</td>
<td>Detectable plasma tenofovir levels in 80% who did not acquire HIV vs 50% who acquired HIV</td>
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<td></td>
<td>Followed for median 1.1 years</td>
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<td>HIV acquisition associated with lower plasma concentrations of tenofovir and emtricitabine</td>
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<td>BTS</td>
<td>2413 men and women who use injection drugs in Thailand</td>
<td>489 (20%) women</td>
<td>Daily oral TDF vs placebo</td>
<td>48.9% (95% Cl: 9–72.2%)</td>
<td>17 HIV infections in TDF group (0.35/100 person-years) vs 33 in placebo group (0.68/100 person-years)</td>
<td>78.6%</td>
<td>Detectable plasma tenofovir levels in 66% overall</td>
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<td></td>
<td>Followed for average 4 years</td>
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<td>70% risk reduction with detectable tenofovir level</td>
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<tr>
<td>FEM–PrEP</td>
<td>2120 heterosexual women in South Africa, Kenya, Tanzania</td>
<td>100% women</td>
<td>Daily oral TDF/ FTC vs placebo</td>
<td>No reduction in HIV acquisition risk (HR: 0.94, 95% CI: 0.59–1.52)</td>
<td>33 HIV infections in TDF/ FTC group (4.7/100 person-years) vs 35 in placebo group (5.0/100 person-years)</td>
<td>N/A</td>
<td>Adherence 95% by self-report, 88% by pill count, but &lt;40% by plasma tenofovir levels (≥10 ng/mL)</td>
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<td></td>
<td>Followed for 1407 person-years</td>
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<td>No statistically significant association between HIV seroconversion and plasma tendofovir levels</td>
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<td></td>
<td>Study terminated early due to lack of efficacy</td>
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<tr>
<td>VOICE</td>
<td>5029 heterosexual women in South Africa, Uganda and Zimbabwe</td>
<td>100% women</td>
<td>Daily oral TDF vs TDF/ FTC vs oral placebo vs daily vaginal 1% tenofovir gel vs vaginal placebo gel</td>
<td>No difference in HIV acquisition risk by study group; 312 HIV infections (5.7/100 person-years) TDF: HR:1.49 (95% Cl: 0.97–2.29) TDF/FTC: HR: 1.04 (95% Cl: 0.73–1.49)</td>
<td>N/A</td>
<td>Adherence 90% by self-report, 86% by returned pills; plasma tenofovir detected in 30% of group on TDF and 29% of those on TDF/FTC</td>
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<td></td>
<td>5509 person-years follow-up</td>
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<td></td>
<td></td>
<td>No statistically significant association between plasma tenofovir detection and HIV incidence in oral TDF or TDF/ FTC groups</td>
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</tbody>
</table>

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; HR, hazard ratio; CI, confidence interval; PBMC, peripheral blood mononuclear cells; ART, antiretroviral therapy.
Other biological factors that increase the susceptibility of young women to HIV infection, such as genital mucosa immaturity or inflammation, other sexually transmitted infections, hormonal effects, or high partner HIV viral loads, may require higher levels of adherence to PrEP for adequate efficacy [27]. Additionally, a number of behavioural factors have been identified that reduced adherence to PrEP in the clinical trials conducted among women. First of all, women may not have perceived themselves to be at risk for HIV in FEM-PrEP and VOICE. By contrast, in Partners PrEP, women were in known serodiscordant relationships, motivating them to be more adherent to PrEP. Stigma may also impact PrEP uptake and adherence, as was reported by women in VOICE [28]. Finally, younger age has been associated with decreased PrEP adherence across multiple studies.

Data from open-label PrEP studies suggest that TDF/FTC-based PrEP may confer even higher rates of protection in the real-world setting, likely related to improvements in adherence with known effectiveness. The PROUD study [30], the iPrEx open-label extension (OLE) study [31] and the US Demo Project [32] all demonstrated high rates of protection from HIV acquisition with open-label PrEP in mainly MSM populations. Data from women in open-label studies to guide optimal dosing strategies in this population has been more limited. Preliminary data from the Partners demonstration project estimated 96% reduction in HIV transmission among over 1000 heterosexual serodiscordant couples in Kenya and Uganda using PrEP as a ‘bridge’ until the HIV-infected partner received ART for 6 months [33]. In the open-label ADAPT study (HPTN 067) conducted among heterosexual women in South Africa, women had better adherence (defined by plasma tenofovir concentrations) with daily dosing of oral PrEP than with two alternative intermittent dosing strategies [34].

In summary, oral and topical PrEP studies show that PrEP generally works when used consistently, even in women. However, these studies highlight the challenge of developing prevention methods that are acceptable and easy to use, particularly for young women at risk, and reinforce the urgent need to expand prevention options and optimise PrEP delivery for this population.

**Toxicity concerns in women**

Although PrEP was generally well tolerated over the relatively short durations of follow-up in the clinical trials, kidney and bone toxicities have been observed with long-term use of TDF in HIV-infected populations [35]. In Partners PrEP, use of TDF-containing PrEP for a median of 36 months was associated with a small (2–3 mL/min/1.73 m²) decline in estimated glomerular filtration rate (eGFR) which rebounded to baseline levels by 8 weeks after drug discontinuation [36]. Additionally, daily oral PrEP with TDF/FTC was not significantly associated with proximal tubule dysfunction [37].

### Table 3. Summary of randomised clinical trials of topical PrEP in women at risk of HIV acquisition

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Intervention</th>
<th>Overall Efficacy</th>
<th>Adherence</th>
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<tbody>
<tr>
<td>CAPRISA 004</td>
<td>889 heterosexual women in South Africa</td>
<td>Pre- and postcoital vaginal 1% tenofovir gel vs placebo gel</td>
<td>39% overall efficacy</td>
<td>54% risk reduction when gel adherence ≥80% vs 38% when adherence 50–80% vs 28% when adherence &lt;50%</td>
</tr>
<tr>
<td>VOICE [15]</td>
<td>5029 heterosexual women in South Africa, Uganda and Zimbabwe</td>
<td>Daily oral TDF vs TDF/FTC vs oral placebo vs daily vaginal 1% tenofovir gel vs vaginal placebo gel</td>
<td>No difference in HIV acquisition risk by study group; 312 HIV infections (5.7/100 person-years)</td>
<td>Plasma tenofovir detected in 25% of tenofovir gel group</td>
</tr>
<tr>
<td>FACTS 001</td>
<td>2029 heterosexual women aged 18–30 in South Africa</td>
<td>Pericoital vaginal 1% tenofovir gel vs placebo gel</td>
<td>No difference in HIV incidence by study group; 61 HIV infections in tenofovir gel group (4/100 person-years) vs 62 in placebo group (4/100 person-years)</td>
<td>13% with consistent use (≥200% of sex acts per month), 22% with tenofovir detected in cervicovaginal lavage samples at all quarterly visits</td>
</tr>
<tr>
<td>ASPIRE [21]</td>
<td>2629 heterosexual women in Malawi, South Africa, Uganda and Zimbabwe</td>
<td>Dapivirine impregnated vaginal ring every 4 weeks vs placebo vaginal ring</td>
<td>27% (95% CI: 1–46%) overall</td>
<td>82% of plasma samples and 84% of returned rings demonstrated adherence based on dapivirine levels</td>
</tr>
<tr>
<td>Ring Study [22]</td>
<td>1959 heterosexual women in South Africa and Uganda</td>
<td>Dapivirine impregnated vaginal ring every 4 weeks vs placebo vaginal ring in 2:1 randomisation</td>
<td>30.7% (95% CI: 0.9–51.5%)</td>
<td>83% of plasma samples and used rings indicated adherence based on dapivirine levels</td>
</tr>
</tbody>
</table>

Abbreviations: TDF, tenofovir disoproxil fumarate; FTC, emtricitabine; HR, hazard ratio; CI, confidence interval.
there were no differences in BMD loss by gender [38]. The clinical significance of these declines is not known, but women face a higher risk of osteoporosis at baseline than men, so the reduction in BMD observed with long-term use of TDF may be of particular concern.

**PrEP, conception, pregnancy and contraception**

PrEP is one of several strategies that can protect women who are trying to conceive from HIV acquisition. The CDC recommends the daily use of oral TDF/FTC as PrEP for 1 month before and 1 month after attempted conception in HIV-negative women planning pregnancy with an HIV-positive male partner [7]. TDF/FTC is widely used among pregnant and breastfeeding women worldwide for the treatment of HIV, and neither agent has been associated with significant short-term health risks for the fetus or infant. In an analysis from Partners PrEP, pregnancy incidence, birth outcomes and infant growth did not differ between women receiving TDF or TDF/FTC compared with placebo at the time of conception [39]. Longer-term studies of the impact on TDF/FTC use during pregnancy are in progress, as are larger studies to examine the use of PrEP during conception.

For women not desiring pregnancy, TDF/FTC-based PrEP is not expected to interact with hormonal contraceptives. In an analysis from Partners PrEP, women reporting oral contraceptive use had high pregnancy incidence (10–18% per year), comparable to women who were not using contraception (15–17% per year), but this lack of contraceptive effectiveness was similar among women assigned PrEP and placebo. Pregnancy incidence was low among women reporting injectable contraceptives (5% per year) and implants (<1% per year) and did not differ by study arm, confirming that these methods in combination with PrEP provide effective protection against pregnancy and HIV infection [40]. In FEM-PrEP, more incident pregnancies occurred in the group of women receiving TDF/FTC compared to placebo, but this difference was not statistically significant after adjustment for baseline variables [41]. However, as in Partners PrEP, women on combined oral contraceptives were more likely to become pregnant than those on injectable agents, regardless of study arm. Women on combined oral contraceptives were also less likely to adhere compared to injectable users, suggesting that even though pharmacokinetic interactions are not expected between TDF/FTC and hormonal contraceptives, pharmacodynamic and/or behavioural interactions should be explored in future studies.

**PrEP in transgender women**

Despite the high rates of HIV infection among transgender women, studies of PrEP efficacy in this group are extremely limited. In a subgroup analysis of the iPrEx trial, which included 339 transgender women (14% of study participants), there were 11 HIV infections in the PrEP group and 10 in the placebo group (HR: 1.1, 95% CI: 0.5–2.7) [42]. However, none of the transgender women who acquired HIV infection had detectable study drug, compared with 18% of seronegative transgender women and 52% of seronegative MSM. A recent qualitative study evaluated PrEP acceptability among 30 transgender women in San Francisco and reported low PrEP knowledge but high interest, citing the ability to obtain PrEP from a trans-competent provider as essential to PrEP uptake and adherence [43]. Further research is urgently needed to investigate correlates of PrEP efficacy, uptake and adherence in this population.

**Challenges surrounding PrEP implementation for women**

**Perception of HIV risk**

One challenge for implementation of HIV prevention tools in women is that women at risk for HIV infection may have limited awareness of their partner’s HIV risk, thereby underestimating their own risk [44,45] and decreasing their motivation to initiate and/or adequately adhere to PrEP. Healthcare providers may also not adequately assess for HIV risk among women, influencing their recommendation and prescription patterns for PrEP. Risk factors for HIV acquisition in women can be both direct (i.e. high-risk sexual behaviour, personal substance use, presence of genital infections) and indirect (partner’s risk behaviour, HIV density of sexual networks) [46,47], but are frequently challenging to identify. Women may not recognise their own HIV risk, may feel shame or stigmatised for admitting their true HIV risk, may not accurately know their partners’ risk behaviours, or may feel that they are unable to discuss these risks (i.e. in the setting of intimate partner violence).

Formal HIV risk assessment tools have been developed to predict annual HIV incidence in women and serodiscordant couples in Africa [48,49] and MSM in the US [50], but no such tools exist for US women. These tools account for factors such as marital status, substance use, unprotected sex, age and partner HIV viral load; risk stratification is cost-effective in identifying those with the greatest need of PrEP. However, these tools need adaptation to the US context, with incorporation of population-specific data, such as local HIV prevalence, to effectively predict HIV risk among US women. The US-based tool should also account for local contextual and structural factors that may affect risk, such as residing in a community with poor access to healthcare or poor HIV prevention education [47,51]. This may be especially important for black women in the United States since the high prevalence of HIV in their sexual networks increases risk of HIV acquisition even when the number of sexual partners is low [47].

Successful use of PrEP in women may also rely on accurate risk perception. In the FEM–PrEP trial, 52% of women who acquired HIV felt they had no chance of becoming HIV infected; a post hoc analysis revealed an association between some risk perception and PrEP adherence [52]. In a study of 359 high-risk heterosexual clients in a US STD clinic (35% female), 84% perceived themselves at no or low risk for HIV despite low condom use (<20%) and good HIV transmission knowledge. Lack of interest in PrEP was associated with ‘low perceived risk’ in this study [53]. Research is needed to fully characterise the relationship between risk perception and PrEP willingness, uptake and adherence in US women. Providers should be educated on performing an accurate risk assessment and appropriately identifying women who may most benefit from PrEP.

**Awareness and acceptance of PrEP among women**

In order to optimise the usage of PrEP in women, it is critical to understand awareness of and willingness to use and/or recommend PrEP among women and healthcare personnel. In the United States, previous studies examining PrEP awareness revealed that only 10–20% of US women at risk for HIV infection had heard of PrEP or post-exposure prophylaxis (PEP) [54,55]. Furthermore, a qualitative focus group study of 144 women at risk for HIV infection conducted in 2013 found that participants expressed anger about not having heard of PrEP prior to the study, as PrEP was considered by these women to be a valuable HIV prevention option [55].
PrEP awareness among US healthcare providers serving women is also suboptimal. Data from a national survey of 342 US family planning providers revealed that only 38% were able to correctly define PrEP and only 37% correctly stated rates of PrEP efficacy [56]. Only 22% of providers believed that PrEP education was important, and 66% were uncomfortable providing education about PrEP. Providers identified lack of PrEP training and cost of PrEP as barriers to implementation. In another survey of 189 HIV healthcare providers, only 19% had ever prescribed PrEP and of these, only 28% had prescribed PrEP to heterosexual women [57].

However, once aware, many US women seem interested in using PrEP as an HIV prevention tool. In a focus group study of 26 black women, many participants expressed interest in PrEP and indicated a preference for daily pill use compared to a vaginal gel due to greater privacy, convenience and ease of administration [47]. Barriers to PrEP willingness included cost and concern about side effects. A telephone survey of 1509 US women (1068 black, 441 white) indicated that 69% of black women and 54% of white women would be willing to use PrEP [58]. Factors predicting PrEP willingness included lower socioeconomic status, risky sexual behaviours, greater social support and healthcare provider recommendation. Barriers to PrEP willingness included embarrassment about asking providers for PrEP and cost. Black women were more likely than white women to want PrEP, especially if their significant others were using PrEP and if their doctor recommended it. Another qualitative study in 144 women (92% black) indicated that many would be willing to use PrEP if the cost was covered, if there were minimal side effects, if the efficacy of the drug was reasonable and if PrEP was delivered by trusted providers such as their own physicians [55].

These studies highlight the important role healthcare personnel may play in PrEP implementation for US women. Data from HIV clinicians has demonstrated that HIV serodiscordance is the single most important factor predicting willingness to prescribe PrEP to women, whereas barriers to prescribing include concerns about drug resistance, increases in high-risk behaviour and drug costs [57]. Results from a survey of sexually transmitted diseases and family planning clinic providers in the southeastern United States demonstrated that willingness to prescribe PrEP was associated with higher PrEP knowledge, older provider age and the belief that PrEP empowered women [59].

Overall, these data emphasise the need for better PrEP education aimed at women and healthcare providers serving women, including those in reproductive health or family planning clinics. Targeted approaches to PrEP messaging are needed to optimise uptake in different subpopulations. Studies have also underscored the requirement for PrEP education and training for general practitioners and women’s health providers to ensure that accurate information about PrEP efficacy, side effects and cost assistance is disseminated so that women at risk for HIV can make informed choices about the use of this new prevention tool.

Conclusions and future directions

The only currently approved method of PrEP requires adherence to a daily oral medication. Studies of new PrEP agents and formulations are in progress, but must incorporate examination of different dosing strategies and delivery systems in women. For example, if an extended dosing interval of an oral medication, a long-acting injectable agent or implant, or a microbicide provided in a vaginal ring could reduce HIV acquisition in women, barriers to use might be reduced and adherence could be improved. Combining the HIV prevention method of PrEP with another benefit, such as contraception (e.g. via multipurpose prevention technologies, such as vaginal rings, or long-acting agents that combine PrEP with hormonal contraceptives), may offer an additional motivation for adherence. Preclinical or early clinical studies are already under way for such strategies in women.

Prevention of HIV in women should stem from an increased awareness of HIV risk factors, through routine HIV screening and provision of effective and safe female-controlled HIV prevention methods. Maintaining consistent and sustainable adherence to PrEP has been a significant challenge to PrEP in clinical trials that include women and may be especially important in women during periods of high HIV risk due to the tissue disposition of the drugs. PrEP is generally safe during conception, pregnancy, breastfeeding, and for use with contraceptives, but additional studies in these areas are needed as are studies evaluating long-term safety of PrEP in women. Finally, much like the experience with contraception, women need a variety of options for PrEP to facilitate its use. Thus, research into development of new drugs and delivery systems are needed, as is research on attitudes and acceptability of various products in diverse populations of women.

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References


