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Anti-Retroviral–Based HIV Pre-Exposure Prophylaxis for Women: Recent Advances and Next Steps

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Abstract

There is a daunting challenge to prevent human immunodeficiency virus (HIV) acquisition in women at high risk of acquiring HIV. Of the 37 million people globally living with HIV, more than half are women. Women account for nearly 60% of adults with HIV in sub-Saharan Africa, where unprotected heterosexual sex is the primary driver of the epidemic. While male condoms are effective, they are not always used, and this is not something women can control. Women urgently need prevention tools they can decide to use, independent of a husband or partner. Pre-exposure prophylaxis (PrEP), in which HIV-uninfected persons with ongoing HIV risk use antiretroviral (ARV) medications as chemoprophylaxis against sexual HIV acquisition, is a promising new HIV prevention strategy. We review recent advances in the development of new biomedical HIV prevention interventions with a highlight of findings from pivotal clinical trials, as well as a discussion on future generation strategies for women.

Keywords: HIV, women, tenofovir, dapivirine, pre-exposure prophylaxis

1. Introduction

In 2015, 2.1 million people became newly infected with Human Immuno Deficiency Virus (HIV) and 1.1 million died from Acquired Immuno Deficiency Syndrome (AIDS) related illnesses [1]. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Report, 70 percent of the 37 million people estimated to be living with HIV reside in sub-Saharan Africa [1]. In this setting, where unprotected heterosexual sex is the primary driver of the epidemic, women account for nearly 60 percent of adults with HIV.

While existing HIV-1 prevention interventions including behavior change, use of male and female condoms, treatment of sexually transmitted infections (STIs), male circumcision, and uptake of antiretroviral (ARV) treatment to reduce the infectiousness of persons with HIV-1 have gone a long way in controlling the spread of HIV-1 infection [2–6], HIV-1 rates in young women in resource limited settings remain unacceptably high [1]. This is in part, because many HIV-1 prevention methods require the participation or consent of a male partner. Women urgently need prevention tools they can decide to use, independent of a husband or partner [7]. Developing HIV prevention options that women can use therefore remains a global concern, given the soaring rates of HIV infection among women. Pre-exposure prophylaxis (PrEP), in which HIV uninfected persons with ongoing HIV risk use antiretroviral medications as chemoprophylaxis against sexual HIV acquisition, is a promising new HIV prevention strategy [8–11].

2. HIV prevention biomedical interventions

2.1. Microbicides

2.1.1. CAPRISA 004

Tenofovir gel was the first ARV-based microbicide to be tested in an effectiveness trial. CAPRISA 004 was a phase 2B microbicide study that tested peri-coitally applied 1% TDF vaginal gel among 889 South African women conducted from May 2007 to March 2010. The trial found a 39% (95% CI, 6–60%; $p = 0.017$) lower HIV infection rate in women using 1% tenofovir gel as compared to the women using placebo gel when used in a coitally dependent regimen [12]. Tenofovir gel was shown to be safe when used up to 12 h before sex and again within 12 h after sex (BAT), for a maximum of two doses in 24 h. The drug was found to be 54% effective among women who were the highest adherers (gel adherence > 80%). Participants who adhered to the dosing regimen in more than 80% of sex acts were the least likely to acquire HIV (54% lower risk of infection).

2.1.2. FACTS 001

FACTS 001 was a phase III safety and effectiveness double-blind, randomised, placebo-controlled trial of pericoital tenofovir 1% gel for HIV prevention in 18–30 year Women at nine sites in South Africa [17]. The study evaluated the safety and effectiveness of pericoital TFV 1% gel when using the BAT-24 regimen (before and after sex; no more than 2 doses in 24 h) among women at nine sites in South Africa. A total of 2059 women were randomized to tenofovir 1% gel or to placebo and instructed women to apply the gel 12 h before and within 12 h after sex, the same schedule used in CAPRISA 004. The study was conducted between Oct 2011 and Aug 2014. In 3036 person-years of observation accrued, 123 HIV infections occurred (HIV incidence: 4.0/100 women years); 61 in the TFV arm and 62 in the placebo group (incidence rate ratio [IRR], 1.0; 95% CI: 0.7–1.4). In a nested case-cohort sub-study ($n = 214$) that

examined TFV drug levels in quarterly cervicovaginal lavage (CVL) samples in HIV seroconverters vs controls, high TFV in CVL was significantly associated with a reduction in HIV acquisition (HR, 0.52; 95% CI, 0.27–0.99; $p = 0.04$).

Considering all adherence data, the FACTS 001 team calculated that women used gel for an average of 50–60% of sex acts. Majority of participants were not able to achieve sufficiently high levels of gel coverage required for protection which underscores the need for a range of HIV prevention options for young women which may be easier to integrate into their lives.

2.2. Oral PrEP

2.2.1. Partner's PrEP

The Partners PrEP Study was a three-arm phase III, randomized, double-blind, placebo-controlled, 3-arm trial of daily oral TDF & FTC/TDF PrEP for the prevention of HIV acquisition by HIV seronegative partner in heterosexual HIV serodiscordant partnerships. It was one of the two landmark studies that provided evidence to support US Food and Drug Administration approval for FTC-TDF PrEP. The study demonstrated PrEP HIV protective effectiveness against HIV infection of 67% (95% CI 44–81%, $p < 0.0001$) for TDF and 75% (95% CI 55–87%, $p < 0.0001$) for FTC/TDF [13] compared to person receiving placebo. The HIV protection effects of TDF and FTC/TDF were in women and men. For TDF, efficacy among women was 71% and was 63% among men; for FTC/TDF, efficacy was 66% in women and 84% in men—all were statistically significant. In a follow-on open-label demonstration project of integrated delivery of ART and PrEP for prevention in HIV sero-discordant couples, the investigators observed virtual elimination of incident HIV [13].

2.2.2. FEM-PrEP Study

The FEM-PrEP Study was a phase 3, randomized, placebo-controlled, trial that assessed of the effectiveness of daily oral FTC/TDF for HIV prevention among HIV-uninfected women 18–35 years in Kenya, South Africa and Tanzania [14]. The trial was stopped early by Independent Data Monitoring Committee due to futility at the time of study stop. No significant safety concerns were noted. Adherence by self-report and pill counts was high, but plasma drug levels revealed that only 15–26% of samples from seroconverters had TDF detected and only 26–38% of non-seroconverting controls. Thus, the investigators concluded that PrEP adherence was too low to assess PrEP's HIV protection. Less than 40% of the HIV-uninfected women in the TDF–FTC group had evidence of recent pill use at visits that were matched to the HIV-infection window for women with seroconversion.

2.2.3. TDF2 study

The TDF2 study was a phase 2B study that assessed the safety, adherence and efficacy of daily oral FTC/TDF in 1200 (45.7% women) HIV-uninfected heterosexual male and female participants aged 18–39 years conducted in Botswana [15]. After a 1563 person-years of observation

(median, 1.1 years; maximum, 3.7 years), FTC/TDF PrEP resulted in a 62.6% reduction in HIV acquisition for participants assigned to FTC/TDF compared to placebo (HR, 0.37; CI, 21.5–83.4, $p = 0.013$). As treated analysis provided protective efficacy of 77.9% (95% CI, 41.2–93.6; $p = 0.01$) for FTC/TDF versus placebo, overall, and 75.4% (23.7, 94.4; $p = 0.02$) for women. No significant safety concerns were noted, though participants randomized to the FTC/TDF arm did experience more nausea, vomiting and dizziness than those randomized to placebo.

2.2.4. MTN-003/Vaginal and Oral Interventions to Control the Epidemic (VOICE)

Was a phase 2B safety and effectiveness study of tenofovir 1% gel, tenofovir disoproxil fumarate tablet and emtricitabine/tenofovir disoproxil fumarate tablet for the prevention of HIV infection in women [16]. The primary aim of the VOICE trial was to estimate the safety and effectiveness of daily treatment with vaginal TFV gel, as compared with placebo gel, and of oral TDF and oral TDF-FTC, as compared with oral placebo, in preventing sexually acquired HIV-1 infection in women.

A total of 5029 were enrolled in the study were followed up monthly and assessed for HIV seroconversion. A total of 312 HIV-1 infections occurred; the incidence of HIV-1 infection was 5.7 per 100 person-years. In the modified intention-to-treat analysis, the effectiveness was –49.0% with TDF (hazard ratio for infection, 1.49; 95% confidence interval [CI], 0.97–2.29), –4.4% with TDF-FTC (hazard ratio, 1.04; 95% CI, 0.73–1.49), and 14.5% with TFV gel (hazard ratio, 0.85; 95% CI, 0.61–1.21). Adherence to study product among those in the active arms was generally very low. TFV was detectable in 30%, 29%, and 25% of random plasma samples from participants in the TDF, TDF-FTC, and TFV gel arms of the study, and an inverse correlation was demonstrable between detection of TFV in plasma and characteristics predictive of HIV-1 acquisition.

2.2.5. Partner's demonstration project

OLE projects have been called for as part of the pathway to scale-up of PrEP. Previous studies like the Partner's PrEP that assessed effectiveness of oral truvada and tenofovir for HIV prevention among sero-discordant couples in Kenya and Uganda have shown that when participants are given the active product through open-label access projects, even those with previous poor adherence during the clinical trial are now more likely to use product when they know they are now using the active product [13]. From a protection level of about 73% in the partner's PrEP, researchers have reported substantially reduced HIV risk of up to 95% when used with high adherence [17], **Figure 1**.

2.3. Vaginal rings

2.3.1. MTN-020— A Study to Prevent HIV Infection with a Ring with Extended ring (ASPIRE)

Intravaginal rings offer a strategy to deliver antiretroviral PrEP medications with lesser opportunities for adherence challenges than for daily oral pills or vaginal gels [18]. ASPIRE was a phase III study conducted among 2629 sexually active HIV-negative women ages 18–45 at 15 clinical research sites in Malawi, Uganda, South Africa and Zimbabwe to determine

whether a vaginal ring containing the ARV drug dapivirine is a safe and effective method for protecting against the sexual transmission of HIV when used by women for a month at a time. The study found HIV risk was reduced by 27% overall—for women group assigned to use the dapivirine ring compared placebo ring group—and 37% in a planned second analysis that excluded data from two sites with less than ideal retention and adherence. Notably high protection (56%) was observed in women >21 years, who also appeared to use the ring most consistently, **Figure 2** [10].

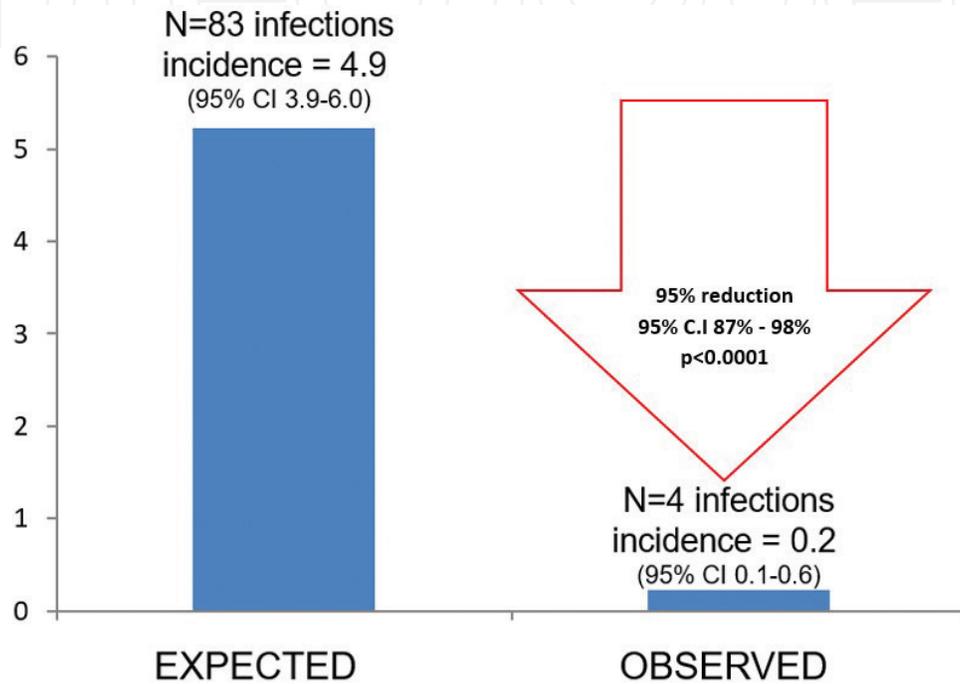


Figure 1. HIV incidence in Partner's PrEP demonstration project [17].

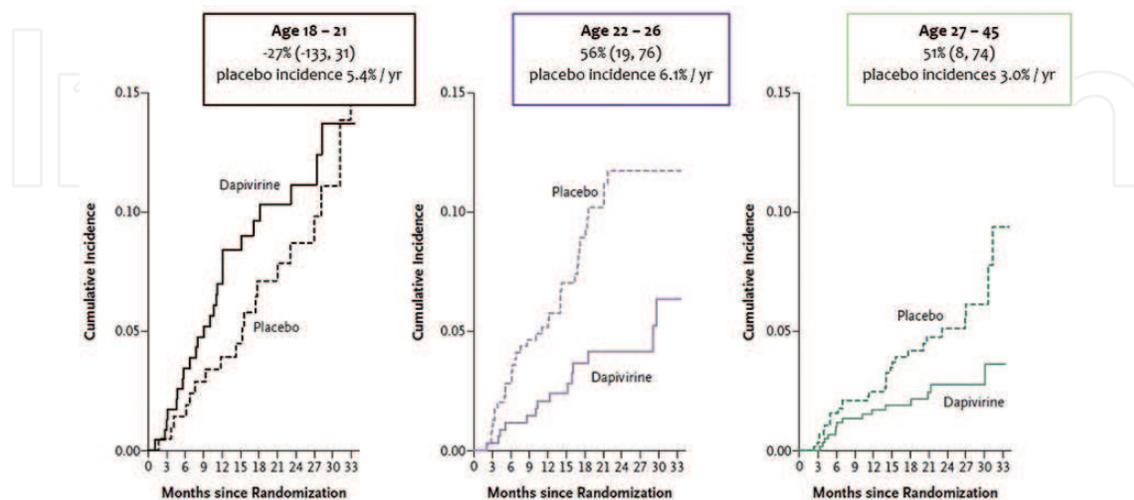


Figure 2. Age and HIV-1 protection in ASPIRE [10].

A summary of the outcomes of recent HIV prevention trials among women is provided in **Table 1**.

| Study | Study population | Sample size | Results |
|-----------------------------------------------------------------------------------------|------------------------------------------|-------------|------------------------------------------------------------------------------------------------|
| CAPRISA 004 <i>South Africa</i> (Tenofovir Gel) | Women | 889 | 39% [CI = 6–60] effectiveness of coitally- dependent vaginal TFV gel |
| iPrEx <i>Brazil, Ecuador, Peru, South Africa, Thailand, US</i> (Oral Truvada) | Gay men, other MSM, transgender women | 2499 | 44% [CI = 15–63] effectiveness of daily oral FTC/TDF |
| TDF2 Study <i>Botswana</i> (Oral Tenofovir) | Men and women | 1200 | 62% [CI = 22–83] effectiveness of daily oral FTC/TDF |
| Partners PrEP Study <i>Kenya, Uganda</i> (Oral Truvada/Tenofovir) | Serodiscordant couples | 4758 | 67% [CI = 44–81] efficacy daily oral TDF 75% [CI = 55–87] efficacy daily oral FTC/TDF |
| FEM-PrEP <i>Kenya, S Africa, Tanzania</i> (Oral Truvada) | Women | 1950 | Futility of daily oral FTC/ TDF 6% [CI = –52 to 41] |
| ASPIRE <i>Uganda, Malawi, South Africa, Zimbabwe</i> | Women | 2629 | 27% [CI= 1–46] effectiveness of dapivirine vaginal ring |

Table 1. Outcomes of recent HIV prevention trials involving women.

2.3.2. MTN-025—HIV open-label prevention extension (HOPE)

HOPE is an open-label study of vaginal ring for preventing HIV among former ASPIRE participants. Women who took part in ASPIRE, a trial that found a vaginal ring containing an antiretroviral (ARV) drug called dapivirine was safe and helped protect against HIV, are now being offered the opportunity to use the ring as part of a new study called HOPE. HOPE builds on the results of ASPIRE by gathering additional information on the ring's safety, how women use the ring knowing that it can help reduce their risk of HIV and the relationship between adherence and HIV protection. Women who participated in a similar study called the RING study by the international partnership for microbicides (IPM) are being followed up under the dapivirine ring extended access and monitoring (DREAM OLE) protocol.

2.4. Discussion

High HIV incidence among young women in Africa [1] highlights the need for female-controlled HIV prevention. Social, structural and economic disparities perpetuate vulnerabilities of women. The lower social and economic power of women makes it difficult for them to negotiate safe sex [18]. In stable partnerships, condom use is low, and women are often unaware of their partner's HIV status [19]. Therefore, a need exists for HIV prevention methods that

women can initiate themselves. Scaling up of proven biomedical technologies for women at high risk is therefore a high priority. Daily oral tenofovir-based PrEP, dapivirine vaginal ring and antiretroviral treatment as prevention are some of the promising biomedical technologies for prevention options for women.

Multiple studies of PrEP have shown that oral ARVs, when used consistently, reduce the risk of HIV infection in people who are at high risk by up to 92% including among women [5]. Currently, FTC-TDF is the medication with a label indication as PrEP against HIV acquisition recommended by the World Health Organization (WHO) and the United States Centers of Diseases Control and Prevention [20, 21]. Consequently, recent landmark approvals in sub-Saharan Africa, including South Africa [22] and Kenya [23], and commitment from large-scale funding partners (including PEPFAR) are leading to accelerated roll-out of TDF-based PrEP for high-risk populations. TDF alone or TDF with lamivudine are other as an alternative to suggested by WHO [24]. Importantly, other new oral PrEP drugs (e.g. maraviroc) are currently being evaluated [25]. Although some PrEP trials in African women did not show effectiveness against HIV [14, 16, 26], follow-on analyses from those two studies have consistently provided strong evidence of very low adherence to PrEP in those studies [16, 27].

Prevention technologies such as vaginal ring containing ARV provide tremendous promise for the HIV prevention field as they provide HIV prevention options that fit in women's lives. The recent demonstration of moderate HIV protection conferred by monthly vaginal ring containing medication dapivirine is a step in right direction. An important feature of the dapivirine ring is its high level of safety [28]. This excellent safety profile also suggests that minimal medical monitoring would be needed, potentially making it both a practical and cost-effective option in under-resourced settings. The next step is to ensure that the vaginal ring is safe for all women at risk of HIV acquisition including pregnant and breastfeeding women.

For HIV uninfected women in known serodiscordant partnership, initiation and sustained use of ART by their infected male partners are another highly effective prevention options for couples [5]. Women who want to conceive or with HIV positive partners who have not yet initiated ART, PrEP as bridge to ART prevention strategy is an attractive and highly effective HIV option. In PrEP as a bridge to ART strategy, PrEP is offered to HIV-uninfected person as a 'bridge' to ART in the discordant partnership—that is, until ART initiation by the HIV-infected partner and for the first 6 months after ART is started or viral suppression. This strategy demonstrated nearly elimination of HIV transmission within serodiscordant couples in Uganda and Kenya [29].

A robust pipeline of new PrEP drugs and formulations is not only important for advancing demonstrated success of products but also for addressing limitations of current biomedical technologies with the ultimate goal of prevention options that fit women's needs to ensure they will be used at scale. The current pipeline of ARV-based prevention products includes oral pills (maraviroc), vaginal rings (tenofovir), vaginal and rectal gels, vaginal films, long-acting injectable ARVs (rilpivirine, cabotegravir) and multipurpose technologies that could combine ARV to reduce women's risk of HIV and STIs while providing effective contraception.

3. Summary

Oral PrEP trials have demonstrated a decrease in HIV infection rates of between 44 and 77%. But it is now proven that with good adherence, Truvada, a once-a-day pill can reduce HIV infection rates by at least 92%. Because of high level of effectiveness, oral PrEP has been licensed for high-risk populations in the US, Canada, Kenya and South Africa. Efforts to have the dapivirine vaginal ring licensed for HIV prevention among women are currently underway. The process is an important one that takes time. It's anticipated that regulatory approvals could be received by 2018 in some countries in Africa. Results of the ASPIRE and RING studies are a boost to efforts focused on developing and evaluating next generation products, such a 3-month ring (just four rings would provide a woman a full year of protection), and combination rings that can provide protection against HIV, other STIs and unintended pregnancy. A vaginal ring could offer an important option as part of combination strategies or as a stand-alone method for women unable or not willing to use other strategies like medical male circumcision, condoms and oral PrEP.

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