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Pre-Exposure Prophylaxis for the Primary Prevention of HIV in At-Risk Women: Empowerment and Equity Revisited

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Abstract

Women continue to bear a disproportionate burden of the HIV epidemic's impact. The last three years have witnessed the explosive emergence of pre-exposure prophylaxis as a viable, woman-initiated, and woman-controlled candidate for the primary prevention of HIV in women. These developments have proven particularly significant for at-risk women in environments where negotiation of safe sex is difficult. In this review, we trace the recent evolution of the pre-exposure prophylaxis vision for women, delineate the clinical trials that made it all possible, and discuss ongoing efforts required for its full actualization. **(AIDS Rev. 2014;16:134-43)**

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Key words

Women. PrEP. HIV prevention. User-independent delivery.

Introduction

On June 23, 1960, the US Food and Drug Administration (FDA) approved the first combination oral contraceptive preparation (Enovid®). Thereupon, for the first time ever, women were empowered to exercise control over their reproductive destiny. In the process, the birth control pill, pre-exposure prophylaxis (PrEP) by any measure, became the first drug in history to be prescribed long term to at-risk if healthy subjects. On July 16, 2012, a semicentennial later, the FDA approved the first combination oral antiretroviral preparation (Truvada®) for the primary prevention of HIV in otherwise healthy but at-risk women (and men) who "may engage in sexual activity with HIV-infected partners"[1]. In so doing, the FDA has formally ushered in a new era in PrEP while empowering women yet again, this time against the scourge of HIV.

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Pre-exposure prophylaxis as an empowerment imperative for women was articulated by Zena A. Stein in 1990 during the first days of research into PrEP for HIV. Stein made note of the fact that "…little attention has been given to barriers to HIV transmission that depend on the woman and are under her control…including the possibility of a topical virucide that might block transmission through the vaginal route"[2]. A quarter of a century later, the promise of PrEP has been realized, at least in part. In this review, we trace the recent evolution of the PrEP vision, review the clinical trials that first demonstrated PrEP's viability, and discuss the ongoing efforts to improve its strengths and address its flaws.

Women and the HIV epidemic

The HIV epidemic has had a profound and indeed disproportionate impact on women worldwide. In 2011, 16.7 million women around the world, effectively half the global cohort, were living with HIV (Table 1)[3]. Regrettably, by 2011, the fractional coverage of women eligible for antiretroviral therapy (ART) across all low- and middle-income countries had yet to exceed 68%[4,5]. Still, this latest figure represents a marked improvement when compared with 2010, at which time the fractional coverage of women hovered around 53%[4-6]. The feminization of the pandemic has proven particularly

Table 1. Global epidemiology of HIV in women in 2011

Region	Living with HIV	New infections	Deaths	ART eligible	Young women living with HIV†
LMIC*	16,700,000	1,200,000	700,000	68%	64%
Sub-Saharan Africa	13,600,000	N/A	N/A	53%	71%

*LMIC: low- and middle-income countries; †15-24 years old, 2010 data. N/A: Not Available.
ART: antiretroviral therapy; N/A: not available.

striking in sub-Saharan Africa, where 13.6 million women (81% of the cognate global cohort) accounted for 58% of those affected (Fig. 1)[3,4]. Overall, in 2011 alone, 1.2 million women the world over were newly infected with the virus[5,7]. Concurrently, as many as 700,000 women have died of the disease[5,7]. It follows that HIV/AIDS remains the leading global cause of death among women of reproductive age (15-49 years of age)[8]. Finally, note must be made of the plight of young (15-24-year-old) women who constitute a particularly high-risk group. In 2010, 64% of young people living with HIV worldwide were women[3]. Notably, however, the corresponding representation of HIV among young women in sub-Saharan Africa proved as high as 71%[3]. As such, the latter figures account for the fact that in this highly endemic region, a woman aged 15-24 is three times more likely to contract HIV than a man of the same age[3].

The variables involved in the discrepant affliction of women with HIV are biological, socioeconomic, and cultural in nature. On biologic grounds alone, women are at least twice as vulnerable as their male partners as gauged by the per-act transmission probability[9]. Women may be at even greater risk during pregnancy and possibly when using hormonal contraception, an association that has recently been disputed[10]. The precise mechanism(s) underlying the differential susceptibility of the vaginal mucosa and the penile shaft to HIV infection remain unknown. In addition, the increased vulnerability of women to the acquisition of HIV is attributable to critical socioeconomic and cultural variables. In low- and middle-income countries, poor young women are especially vulnerable. Root causes include, but are not limited to, abusive and violent relationships as well as transactional survival or cross-generational sex. Anchored in gender inequity and in social class structures, the compromised position of women in male-dominated cultures is further accentuated by limited educational and employment opportunities. Stated differently, women in many regions of the globe lack the social or economic power required to negotiate safe sex with their male partners. Curtailed access to health care (e.g. female and male condoms) likely plays a significant role as well in male-to-female transmission[11].

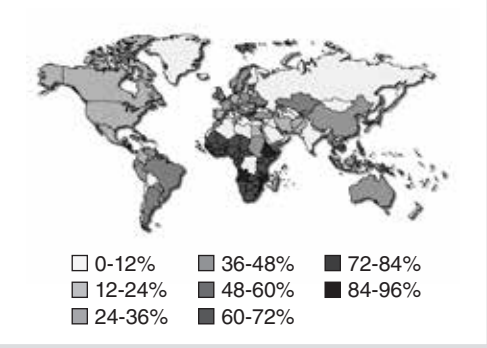

Figure 1. *Women as a percent of adults living with HIV (2011). (adapted from Kaiser Family Foundation. Women Living with HIV/AIDS (Aged 15 and Over). 2012. http://www.globalhealthfacts.org/data/topic/map.aspx?ind=4 - map [accessed Mar 31, 2013]).*

Pre-exposure prophylaxis: The concept

The development of effective strategies for the primary prevention of HIV in vulnerable women and girls remains a broadly acknowledged priority[12]. It is against this backdrop that PrEP has emerged as a novel strategy for the primary, indeed direct, prevention of HIV in at-risk women[13,14]. At its core, PrEP is about the empowerment of women to engage in preemptive neutralization of HIV at its point of entry to the female genital tract. As such, vaginal and oral PrEP harbor significant potential for curtailing the number of new cases of HIV in women and for saving lives. Successfully completed clinical trials support this contention. Indeed, a recent Cochrane Intervention Review[15] makes note of risk reduction efficacies

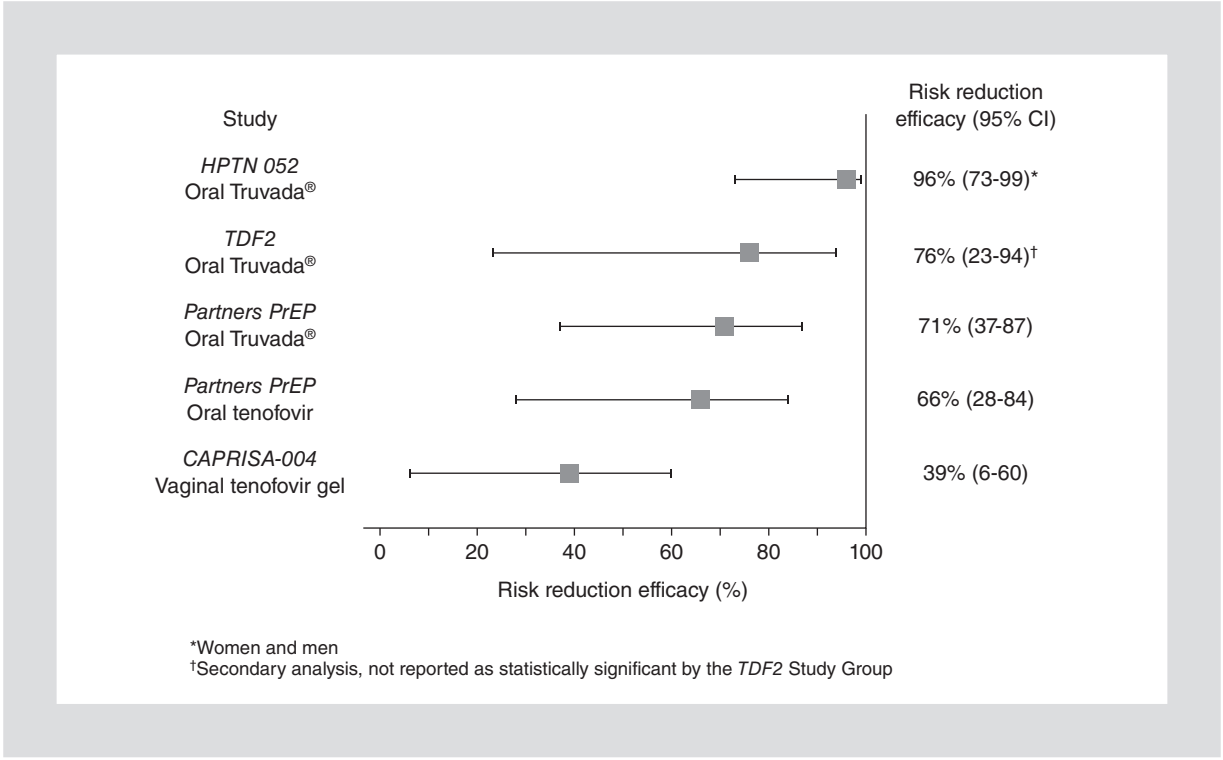

Figure 2. *Risk reduction efficacies for HIV by at-risk women.*

(RRE) ranging from 39 to 71% (Fig. 2)[16-18]. Moreover, corrected for adherence, RREs ranging from 54 to 90% may be achievable[16-18]. Similar conclusions have been reached by several modeling efforts[19]. Still, much remains to be done to document the anticipated real-world utility of PrEP in at-risk women and the population impact thereof[20,21].

Pre-exposure prophylaxis versus treatment as prevention

In parallel with efforts to develop and validate the PrEP concept, the notion of treatment as prevention (TasP) was being explored. An indirect prevention paradigm targeted at HIV-positive subjects, TasP was the subject of a phase III, two-arm, multi-site, randomized trial (HPTN 052)[22]. Powered by 1,763 stable, heterosexual, HIV-discordant couples, HPTN 052 was designed to compare the effectiveness of early (CD4 counts 350-550/mm^3) and delayed (CD4 counts ≤ 250/mm^3) initiation of daily oral ART in preventing the seroconversion of the HIV-negative partner[22]. Discontinued on April 28, 2011 by the Data and Safety Monitoring Board (DSMB) for efficacy, HPTN 052 revealed the early initiation of ART to be associated with a striking RRE of 96%[22]. As such, PrEP and TasP may be viewed as complementary in impact, divergent in approach, but united in promise. However, the precise relative role of PrEP and TasP in combating HIV is the subject of ongoing discussions, without any clear consensus at present.

Concluded pre-exposure prophylaxis trials: Early successes

The very first indication of the effectiveness of a vaginal PrEP regimen in the prevention of HIV in at-risk women was reported by the Center for the AIDS Program of Research in South Africa (CAPRISA) on July 19, 2010 at the 5th International AIDS Conference. The study in question, CAPRISA-004, a phase IIb, two-arm, double-blind, randomized, placebo-controlled trial, was designed to evaluate the efficacy and safety of peri-coital prophylaxis against HIV with a vaginal 1% (40 mg) gel formulation of tenofovir disoproxil fumarate (TDF) (Table 2)[16]. This competitive reverse transcriptase inhibitor (RTI), an acyclic nucleotide (AMP) analogue RTI (NtARTI), though investigational as a microbicide, constitutes a widely used component of oral HIV therapy. The study population consisted of 889 sexually active, HIV-negative, 18 to 40-year-old women from hyperendemic urban and rural regions of the KwaZulu-Natal province of

Table 2. Pre-exposure prophylaxis: Completed clinical trials

Trial	Completed	Location	Intervention	Participants (age range)	1.º Outcome	RRE
CAPRISA-004	2010	SA	Peri-coital vaginal tenofovir gel (1%)	889 HIV(–) women (18-40)	Seroconversion	39%
TDF2	2011	Botswana	Daily oral Truvada® tablets	1,219 HIV(–) men and women (18-39)	Seroconversion	62%*
Partners PrEP	2011	Kenya, Uganda	1. Daily oral tenofovir tablets 2. Daily oral Truvada® tablets	HIV(–) partners of 4,758 HIV– serodiscordant couples (18-65)	Seroconversion	71% (tenofovir) 67% (Truvada®)
FEM PrEP	2011	SA, Kenya, Tanzania	Daily oral Truvada® tablets	2,120 HIV(–) women (18-35)	Seroconversion	Halted for futility
VOICE	2013	Uganda, SA, Zimbabwe	1. Daily oral tenofovir tablets 2. Daily oral Truvada® tablets 3. Daily vaginal tenofovir gel	5,029 HIV(–) women (18-45)	Seroconversion	1. Oral tenofovir and vaginal tenofovir arms halted in 2011 for futility 2. Oral tenofovir proved ineffective

*Men and women.
SA: South Africa.

South Africa[16]. Overall, independent of the degree of adherence, peri-coital prophylaxis with the tenofovir gel reduced HIV acquisition by a modest but significant 39%[16]. As such, CAPRISA-004 furnished the first proof-of-concept for the utility of vaginal PrEP in the prevention of HIV in women. However, CAPRISA-004 also drove home the indispensability of adherence, especially for pregnant subjects[23]. Indeed, further analysis of the data revealed that the RRE of the intervention was directly correlated with the drug adherence level (imperfectly assessed by self-reporting and gel applicator count). Specifically, drug adherence levels of < 50, 50-80, and > 80% were associated with RREs of 28, 38, and 54%, respectively.

Before too long, a phase III, three-arm, double-blind, randomized, placebo-controlled trial, Partners PrEP, was designed to assess the efficacy and safety of daily prophylaxis with oral tenofovir or Truvada® in HIV-negative partners of HIV-serodiscordant couples[17]. Truvada®, a co-formulation of tenofovir (TDF) with emtricitabine, a nucleoside analog RTI (NARTI) also known as FTC (fluorinated 3'-thiacytidine), is frequently applied to oral HIV therapy. The study population consisted of 4,758 stable, heterosexual, HIV-serodiscordant couples from rural and urban Kenya and Uganda[17]. In 38% of couples receiving tenofovir and 36% of couples receiving Truvada®, the seronegative partner was a woman. Monthly bottle and pill counts suggested an exceptionally high adherence rate of 97%[17]. Discontinued on July 10, 2011 by the DSMB for efficacy of both treatment arms, Partners PrEP revealed daily prophylaxis with oral tenofovir or Truvada® to afford female partners with RREs of 71 and 66%, respectively[17]. However, rigorously adherent subjects (documented by measuring the circulating levels of tenofovir) displayed RREs of 86 and 90%, respectively[17].

Concurrently, a phase IIb, two-arm, double-blind, randomized, placebo-controlled trial, TDF2, was designed to evaluate the efficacy and safety of daily prophylaxis against HIV with oral Truvada® in heterosexual men and women[18]. The study population consisted of 1,219 sexually active, HIV-negative, 18 to 39-year-old men (54.3%) and women (45.7%) from Botswana[18]. Discontinued on May 31, 2010 for low retention and logistic limitations, TDF2, for which adherence rates of 84% (residual pill count) and 94% (self-reported) have been reported, revealed that daily prophylaxis with oral Truvada® reduced HIV acquisition by 62% for the men and women so treated[17]. The RRE for women (n = 272) was estimated at 49% (statistically

insignificant). However, a secondary analysis of a study sub-cohort known to have a supply of study drugs suggested that Truvada® was effective in reducing the HIV acquisition by women by as much as 76% (p = 0.021)[18]. Going forward, an open-label study for daily oral Truvada® is being planned, the results of which are expected in 2014.

Concluded pre-exposure prophylaxis trials: Recent setbacks

On April 18, 2011, at the recommendation of the Independent Data Monitoring Committee (IDMC), the Feminine PrEP (FEM-PrEP) trial, a large-scale oral PrEP study, was discontinued for futility[24]. A phase III, two-arm, double-blind, randomized, placebo-controlled trial, FEM-PrEP was designed to assess the efficacy and safety of daily prophylaxis with oral Truvada® in heterosexual women[24]. The study randomized 2,120 sexually active, HIV-negative, 18 to 35-year-old women from Kenya, Tanzania, and South Africa[24]. Self-reports as well as pill counts for the treatment and placebo study groups suggested high adherence rates of 95 and 86%, respectively[24]. However, *post hoc* analysis revealed that < 40% of HIV-negative Truvada®-treated women had evidence of recent pill use (i.e. tenofovir concentrations in plasma) at visits that were matched to the HIV-infection window for women with seroconversion[24]. As such, these observations suggest that the failure of FEM-PrEP is due, if only in part, to poor product adherence.

Not long thereafter, on September 16, 2011, at the recommendation of the DSMB, the daily oral tenofovir arm of the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial was discontinued for futility. On November 17, 2011, a similar recommendation was issued for the daily vaginal tenofovir gel arm of the study[25]. Announcement of the failure of the daily oral Truvada® arm followed suit on March 4, 2013[26]. No safety issues were encountered in any of the trial arms. A large-scale oral and vaginal PrEP study, VOICE, also known as MTN-003, was designed as a phase IIb, five-arm, double-blind, randomized, placebo-controlled trial to test the efficacy and safety of daily prophylaxis with oral tenofovir, oral Truvada®, vaginal tenofovir gel (1%), or placebo[27]. To this end, VOICE aimed to enroll 5,029 sexually active, HIV-negative, 18 to 45-year-old women from Uganda, Zimbabwe, and South Africa[27]. Relative to earlier, now completed, studies, VOICE stood out by dint of its large study population and the side by side comparison of several daily oral and vaginal PrEP regimens. The primary reason for the failure of all arms of the VOICE trial was poor product adherence[26]. Indeed, circulating levels of tenofovir associated with the use of oral tenofovir, oral Truvada®, and vaginal tenofovir gel were detectable in only 28, 29, and 23% of the 773 women so tested[28]. Levels of adherence were found to be particularly low in younger women, thereby highlighting the greater challenge posed by adherence in this critical cohort and echoing the outcome of FEM-PrEP[28]. In South African participants, the incidence of HIV acquisition was strikingly higher among unmarried women (7.5 cases per 100-person-years) as compared with married counterparts (0.9 cases per 100-person-years). Similarly, young women < 25 years of age proved highly vulnerable (8.7 cases per 100-person-years) as compared with older women > 25 years of age (4.7 cases per 100-person-years)[28].

Accounting for recent setbacks: The challenge of product adherence

The failure of oral Truvada® (FEM-PrEP and VOICE)[24,28] and of oral and vaginal tenofovir (VOICE)[25,29] initially proved nothing short of puzzling[30,31]. After all, oral Truvada® was deemed effective in the context of Partners PrEP and TDF2[17,18]. Similar efficacy was documented for oral and vaginal tenofovir in Partners PrEP and CAPRISA-004, respectively[16,17]. What was at play in these discordant results?

The issue of adherence is inevitably central to the utility of PrEP in the primary prevention of HIV in at-risk women. In retrospect, this notion was first evident in the CAPRISA-004 trial, wherein high (> 80%) levels of adherence were associated with a RRE as high as 54%[32]. In contrast, low (< 50%) levels of adherence were associated with a RRE of 28%[32]. Equally compelling clues were provided in the course of the Partners PrEP trial, wherein daily prophylaxis with oral tenofovir or Truvada® have been found to reduce HIV acquisition by female partners by 71 and 66%, respectively[27]. However, carefully documented adherence (i.e. measurement of the circulating levels of tenofovir) revealed RREs as high as 86 and 90% for oral tenofovir and Truvada®, respectively[27]. Finally, note must be made of the *post hoc* analysis of FEM-PrEP, wherein the primary prevention failure appears to have been associated with the observation that < 40% of HIV-negative Truvada®-treated women displayed measurable levels of circulating tenofovir[24]. The VOICE trial was similarly plagued by poor product adherence. Indeed, only 29, 28, and 23% of participants in the oral Truvada®, oral tenofovir, and tenofovir gel arms, respectively, displayed

Table 3. Pre-exposure prophylaxis: Ongoing clinical trials

Trial	Location	Intervention	Participants (age range)	1.º Outcome	Status
FACTS 001	SA	Peri-coital vaginal tenofovir gel (1%)	2,600 HIV(–) women (18-40)	Seroconversion	Results anticipated in 2014
ASPIRE (MTN-020)	SA, Malawi, Uganda, Zambia, Zimbabwe	Monthly vaginal dapivirine ring	3,500 HIV(–) women (18-45)	Seroconversion	Results anticipated in late 2014
IPM 027	SA, Rwanda, Malawi	Monthly vaginal dapivirine ring	1,650 HIV(–) women (18-45)	Seroconversion	Results anticipated in 2014
CDC 4730	Thailand	Daily oral tenofovir tablets	2,413 HIV(–) injection drug users (20-60)	Seroconversion	Results anticipated in 2013
CAPRISA-008	SA	Peri-coital vaginal tenofovir gel (1%)	700 HIV(–) participants of CAPRISA-004 (18-40)	Seroconversion	Results anticipated in 2015

SA: South Africa.

detectable circulating levels of tenofovir[33]. It is now clear that the failure of the FEM-PrEP and VOICE trials was attributable to poor product adherence. While other unforeseen countervailing forces may also be at play, intermittent or absent drug exposure appeared to constitute the root cause of trial failures.

Precise reasons for variable adherence to PrEP among trial participants are still speculative in nature, with theories ranging from the side effects of the drugs, the duration of the studies ("study fatigue"), the failure to refill drug supplies due to skipped appointments, the youthful perception of invincibility, the lingering stigma of HIV, the presumption of assignment to a placebo arm, and the practices of pill-sharing and diversion. Compliance with long-term primary prevention paradigms has been described as a core, intrinsic difficulty of HIV prevention[34]. These sorts of challenges appear to have plagued efforts at daily prophylaxis with vaginal tenofovir in the VOICE study. In addition, a phase II VOICE cross-over study (MTN-001) found that 40% of African women stated a preference for oral tablets over vaginal gel, a finding suggestive of the possibility that vaginal tenofovir may have failed the tests of simplicity, convenience, and acceptability[35].

Above and beyond the preceding considerations, adherence may have been significantly affected by the diversity of the populations of women under study. It has been well-established that casual sexual behavior patterns amongst partners of unknown HIV status, likely predominant in the CAPRISA-004, TDF2, FEM-PrEP, and VOICE trials, are unlikely to foster optimal adherence[36]. In contrast, couples of known HIV status who are committed to long-term relationships (Partners PrEP) have been found to be highly motivated to comply[36]. Pre-exposure prophylaxis may also be beneficial in the context of family planning for HIV-serodiscordant couples[37,38]. A recent sub-study within the Partners PrEP trial appears to support this view by documenting 100% efficacy for daily oral PrEP in the face of verified (e.g. unannounced home pill counts) adherence rates in excess of 80%[39].

Going forward, some have proposed that future trials be designed with active, prospective, and real-time adherence monitoring in mind with the goal of readily identifying and addressing issues of adherence in a timely fashion[40].

Current and upcoming phase III pre-exposure prophylaxis trials

To further confirm and expand the findings of CAPRISA-004, the Follow-on African Consortium for Tenofovir Studies (FACTS), an initiative funded by the South African government and the U.S. Agency for International Development, has launched the FACTS 001 trial (Table 3)[26]. Results are expected in 2014[41]. Pivotal to potential regulatory approval, FACTS 001 was designed as a phase III version of CAPRISA-004 in the hope of confirming the efficacy and safety of peri-coital prophylaxis

with the vaginal tenofovir (1%) gel in the primary prevention of HIV (and herpes simplex virus-2)[41]. In addition, FACTS 001, a large scale, two-arm, double-blind, randomized, placebo-controlled trial, aims to assess the impact of this vaginal PrEP regimen on sexual risk behavior and the wellbeing of hepatitis B-positive subjects in heterogeneous demographic settings[41]. With these goals in mind, an effort is being made to enroll a minimum of 2,600 sexually active, HIV-negative, 18 to 40-year-old women in South Africa[41]. If successful, FACTS 001 stands to play a critical role in supporting the licensing prospects of the first ever vaginal microbicide.

In May 2012, a follow-up phase IIIb trial to CAPRISA-004 received approval from the South African Medicines Control Council (MCC) to study the safety, efficacy, and practicability of peri-coital vaginal administration of a 1% tenofovir gel through South African family planning services[43]. The trial (CAPRISA-008*)* in question is presently enrolling 700 sexually active, HIV-negative former participants in the CAPRISA-004 trial with an eye towards assessing the vaginal tenofovir gel in a "real-life service delivery setting"[44]. Results are anticipated in 2015.

Yet another key vaginal PrEP trial, A Study to Prevent Infection with a Ring for Extended use (ASPIRE), is presently underway[45]. Results are anticipated in late 2014[45]. Also known as MTN-020, this phase III, two-arm, double-blind, randomized, placebo-controlled trial is designed to evaluate the efficacy and safety of prophylaxis with a long-acting vaginal ring capable of slow and sustained release of the pyrimidine analog (diarylpyrimidine) dapivirine (TMC120)[46]. The latter, a non-nucleoside RTI (NNRTI), the subject of a successful phase I study, is an investigational microbicide deemed unsuitable for oral use due to limited solubility and poor systemic absorption. Viewed as an alternative to peri-coital or daily prophylaxis with a vaginal gel, the coitally-independent, dapivirine-releasing, silicone elastomer is designed to be replaced monthly. Peri-cervical in location, the inconspicuous vaginal ring, developed by the International Partnership for Microbicides (IPM), represents an alternative way of addressing the putative adherence challenges that appear to have plagued earlier PrEP trials. At present, ASPIRE aims to enroll approximately 3,500 sexually active, HIV-negative, 18 to 45-year-old women from Malawi, Uganda, South Africa, Zambia, and Zimbabwe[46].

Finally, and parallel to ASPIRE, The Ring Study, also known as IPM 027, is presently underway[45]. As such, this trial builds on a substantial body of preliminary clinical trials focused on safety and acceptability. Results are anticipated late in 2014 or early in 2015[45]. This phase III study, not unlike ASPIRE, will evaluate the efficacy and safety of prophylaxis with the long-acting dapivirine-releasing vaginal ring[47]. At present, the study aims to enroll 1,650 sexually active, HIV-negative, 18 to 45-year-old women from Rwanda and South Africa[47]. Assuming a favorable outcome for ASPIRE and The Ring Study, it is the hope of IPM to make the vaginal ring widely available for use in the primary prevention of HIV in at-risk women (Table 3).

Pre-exposure prophylaxis: Concerns for negative public health externalities

Pre-exposure prophylaxis and the prospect of drug resistance

The specter of PrEP-associated drug resistant viral mutants remains an ongoing concern for the undiagnosed seroconverter as well as for his/her sexual partners. Attributable to the incomplete therapeutic impact of PrEP, unrecognized infection at the time of PrEP initiation, non-adherence, and infrequent HIV testing, drug resistance could well give rise to significant challenges in the context of subsequent therapy. Such a scenario is less likely to apply to trial participants whose HIV status is regularly monitored and whose PrEP regimen stands to be discontinued prior to the development of drug resistance. Indeed, none of the heretofore completed PrEP trials (CAPRISA-004, Partners PrEP, TDF2, FEM-PrEP, and iPrEx) observed the emergence of clinically significant drug resistance (Table 4)[16-18,24,48].

Pre-exposure prophylaxis and the prospect of risk compensation

The notion of PrEP-attributable risk compensation, also known as "behavioral disinhibition", revolves around the possibility of an increase in high-risk sexual behavior and/or decline in utilization of other established preventive measures such as condom use. Intuitively sound and presumably driven by a false sense of security, this socio-behavioral change remains the subject of ongoing evaluation. Thus far, PrEP trial-derived data appear reassuring. First, self-reported condom use during the CAPRISA-004 trial proved comparable for the active and placebo arm of the study[16]. Second, self-reported unprotected sex during the Partners PrEP trial decreased in all study arms from 27% at enrollment to 10% or less by the end of the 30-month study period[17]. Third, self-reported breach of monogamy and condom migration did not differ significantly between

Table 4. Pre-exposure prophylaxis: viral drug resistance mutations

Completed clinical trial	Seroconverters tested	Major drug resistance mutation(s)
CAPRISA-004	35	None to tenofovir (K65R or K70E)
Partners PrEP	27	None to tenofovir or tenofovir/emtricitabine
TDF2	4	One to tenofovir (K65R and A62V) and one to emtricitabine (M184V)*
FEM-PrEP	33	Four to emtricitabine (M184Vx3 & M184Ix1)
iPrEx	38	None to tenofovir/emtricitabine

*All three mutations were identified in a patient retrospectively found to harbor a wild-type HIV infection acquired prior to trial enrollment.

the treatment and placebo arms[17]. A recent review of five completed PrEP trials proved confirmatory though cautionary, given the fact that available data are largely subjective in nature.

Oral and vaginal pre-exposure prophylaxis: The state of regulatory approval

On December 15, 2011, Gilead Sciences announced that it had filed a supplemental New Drug Application (NDA) with the FDA for the once-daily use of Truvada® for PrEP for the prevention of HIV in uninfected adults[49]. On February 13, 2012, the review of the latter application was granted priority[50]. On May 10, 2012, the FDA Advisory Committee recommended approval of Truvada® for PrEP for the primary prevention of HIV[51]. The decision was not unanimous[52,53], but on July 16, 2012, the FDA approved Truvada® for daily use in PrEP paradigms[54]. In so doing, the FDA noted that Truvada® constituted the "first drug approved to reduce the risk of HIV infection in uninfected individuals who are at high risk of HIV infection and who may engage in sexual activity with HIV-infected partners"[51]. In the final analysis, approval of Truvada® for PrEP was granted largely on the strength of the Partners PrEP and iPrEx trials and the efficacy and safety data thereof[17,48]. Still, mindful of the risks and uncertainties of the PrEP paradigm, the FDA was quick to note that "Truvada® is approved for use as part of a comprehensive HIV prevention strategy that includes other prevention methods, such as safe sex practices, risk reduction counseling, and regular HIV testing"[1]. The FDA went on to say that "Truvada® for PrEP must only be used by individuals who are confirmed to be HIV-negative prior to prescribing the drug and at least every three months during use"[51]. Finally, note was made of the fact that "Truvada® for PrEP is being approved with a risk evaluation and mitigation strategy (REMS) to minimize the risk to uninfected individuals of acquiring HIV infection and to reduce the risk of development of resistant HIV-1 variants"[51].

The path forward for the regulatory approval of a vaginal tenofovir gel for PrEP is less clear. On the one hand, the notion of a tenofovir-based vaginal PrEP product for the prevention of HIV in women has been dramatically buoyed by the results of the CAPRISA-004 trial[16]. On the other hand, the momentum so generated has been set back by the subsequent failure of daily vaginal prophylaxis with the same tenofovir gel in the VOICE trial[25]. It follows that independent confirmation of CAPRISA-004 now must await the successful conclusion of the FACTS 001 and CAPRISA-008 trials in early 2014 and 2015, respectively[41-43]. After all, it was the collective promise of CAPRISA-004 and VOICE that led the FDA to raise the prospect of fast tracking the approval of a tenofovir-based vaginal PrEP product[55]. Should FACTS 001 and CAPRISA-008 confirm the observations made by CAPRISA-004, it is possible that the combined efficacy and safety data thereof, possibly along with the safety data gathered during the VOICE trial, will enable the submission of an NDA for a tenofovir-based vaginal PrEP product.

Even less clarity exists at this time as to the potential regulatory approval of the oral tenofovir option. While highly effective in the context of Partners PrEP[17], daily prophylaxis with oral tenofovir during VOICE was discontinued for futility. Taken together, these observations suggest that approval of a tenofovir-based oral PrEP product is unlikely at this time.

Conclusion

The imperative of treatment as the cornerstone of the global response to HIV remains paramount. At the same time, however, the improbabilities of mutual

monogamy and consistent condom use all but demand that women-initiated and controlled prevention paradigms be designed, evaluated, and implemented. At the time of this writing, these all-important efforts must be viewed as work in progress[56]. Of the 10 advanced clinical trials of PrEP for the primary prevention of HIV in women, three were successfully completed (CAPRISA-004, Partners PrEP, and TDF2), two have failed (FEM PrEP and VOICE), and five are ongoing (FACTS 001, CAPRISA-008, CDC 4370, ASPIRE, IPM 027). All but one (CDC 4370) were or are being conducted in sub-Saharan Africa. Overall, RRE estimates ranged from 0-71% and 0-39% for oral and vaginal PrEP, respectively. However, variable adjustments for the level of adherence may well extend the upper end of the ranges in question to 90 and 54%, respectively.

The promise of vaginal PrEP presently rests entirely on the shoulders of a single successful trial (CAPRISA-004), the results of which are yet to be independently confirmed[16]. It follows that the viability of the vaginal PrEP paradigm hinges on the outcome of four key ongoing trials: FACTS 001, CAPRISA-008, ASPIRE, and IPM 027. In contrast, the promise of oral PrEP in women draws on the combined strength of two successful trials: Partners PrEP and TDF2[17,18]. Looking ahead, new data are expected in early 2014 (FACTS 001) and 2015 (ASPIRE, IPM 027, CAPRISA-008).

As can be true of many disruptive technologies, the notion of PrEP for the primary prevention of HIV in at-risk women raised more questions than answers. Residual questions include but are not limited to the optimal population target, the overall impact on disease burden, the implementation logistics in "real-world" settings, and the cost-effectiveness thereof. Perhaps most importantly, questions remain as to the optimal balance between PrEP and TasP in the context of combination HIV prevention[57,58]. While several clinical trials have proved that PrEP is accomplishable, it is not yet clear if it can be fully protective, or for that matter, fully substitutive to other prevention strategies.

Will PrEP become an integral component of the HIV prevention armamentarium? At this time, the final verdict is still out on both oral and vaginal PrEP for the primary prevention of HIV in at-risk women. It follows that debates over the future of PrEP will continue until and likely beyond the next round of completed clinical trials.

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Conflict of Interest Disclosures

Aaron Kofman and Eli Y. Adashi declare no conflict of interest.

References

1. Karim S, Karim Q. Antiretroviral prophylaxis for HIV prevention reaches a key milestone. Lancet. 2012;379:2047-8.
2. Stein Z. HIV prevention: the need for methods women can use. Am J Public Health. 1990;80:460-2.
3. World Health Organisation/UNAIDS/UNICEF. Progress report 2011: Global HIV/AIDS response. 2011. http://www.who.int/hiv/pub/progress_report2011/en/index.html [accessed Jan 5, 2013].
4. UNAIDS. World AIDS Day Report 2011. http://www.unaids.org/en/resources/publications/2011/name,63525,en.asp [accessed Jan 5, 2013].
5. UNAIDS. Report on the Global AIDS Epidemic 2010. http://www.unaids.org/globalreport/global_report.htm [accessed Jan 5, 2013].
6. UNAIDS. Data Tables 2011. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2225_UNAIDS_datatables_en.pdf [accessed Jan 5, 2013].
7. UNAIDS. AIDSinfo Database. http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/ [accessed Jan 5, 2013].
8. UNAIDS. Women, girls, gender equality and HIV. 2012. http://www.unaids.org/en/media/unaids/contentassets/documents/factsheet/2012/20120217_FS_WomenGirls_en.pdf [accessed Jan 5, 2013].
9. Boily M, Baggaley R, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis. 2009;9:118-29.
10. Morrison C, Skoler-Karpoff S, Kwok C, et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. AIDS. 2012;26:497-504.
11. Aziz M, Smith K. Treating women with HIV: is it different than treating men? Curr HIV/AIDS Rep. 2012;9:171-8.
12. Vermund S, Van Damme L. HIV prevention in women: next steps. Science. 2011;331:284.
13. Karim S, Karim Q. Antiretroviral prophylaxis: a defining moment in HIV control. Lancet. 2011;378:e23-5.
14. Aaron E, Cohan D. Preexposure prophylaxis for the prevention of HIV transmission to women. AIDS. 2013;27:F1-5.
15. Okwundu C, Uthman O, Okoromah C. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. Cochrane Database Syst Rev. 2012;7:CD007189.
16. Abdool Karim Q, Abdool Karim S, Frohlich J, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010;329:1168-74.
17. Baeten J, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367:399-410.
18. Thigpen M, Kebaabetswe P, Paxton L, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367:423-34.
19. Supervie V, Blower S. Predicting effect of pre-exposure prophylaxis on HIV epidemics. Lancet. 2012;379:2423.
20. McCoy S, Watts C, Padian N. Preventing HIV infection: turning the tide for young women. Lancet. 2010;376:1281-2.
21. Cohen M, Baden L. Preexposure prophylaxis for HIV--where do we go from here? N Engl J Med. 2012;367:459-61.
22. Cohen M, Chen Y, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;365:493-505.
23. Matthews L, Sibeko S, Mansoor L, Yende-Zuma N, Bangsberg D, Karim Q. Women with pregnancies had lower adherence to 1% tenofovir vaginal gel as HIV preexposure prophylaxis in CAPRISA 004, a phase IIB randomized-controlled trial. PloS One. 2013;8:e56400.
24. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367:411-22.
25. National Institute of Allergy and Infectious Disease (NIAID). "NIH Discontinues Tenofovir Vaginal Gel in 'VOICE' HIV Prevention Study; Product Safe but No More Effective Than Placebo". Nov 25 2011. http://www.niaid.nih.gov/news/newsreleases/2011/Pages/VOICEdiscontinued.aspx [accessed Jan 5, 2013].
26. National Institues of Health (NIH). Daily-use HIV prevention approaches prove ineffective among women in NIH study. 2013. http://www.nih.gov/news/health/mar2013/niaid-04a.htm [accessed Mar 4, 2013].
27. Microbicide Trials Network. VOICE (MTN-003) Backgrounder. http://www.mtnstopshiv.org/news/studies/mtn003/backgrounder [accessed Jan 5, 2013].
28. Marrazzo J. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). Presentation at 2013 CROI. Atlanta, USA.
29. National Institute of Allergy and Infectious Disease (NIAID). NIH Modifies 'VOICE' HIV Prevention Study in Women; Oral Tenofovir Discontinued in Clinical Trial. Sep 28 2011. http://www.nih.gov/news/health/sep2011/niaid-28.htm [accessed Jan 5, 2013].

30. Kashuba A, Patterson K, Dumond J, Cohen M. Pre-exposure prophylaxis for HIV prevention: how to predict success. Lancet. 2012;379: 2409-11.
31. van der Straten A, Van Damme L, Haberer J, Bangsberg D. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS. 2012;26:F13-9.
32. Baeten J, Celum C. Systemic and topical drugs for the prevention of HIV infection: Antiretroviral pre-exposure prophylaxis. Annu Rev Med. 2013;64:219-32.
33. Microbicide Trials Network. VOICE (MTN-003) Fact Sheet. http://www.mtnstopshiv.org/node/2003 [accessed Mar 31, 2013].
34. Grobler A, Abdool Karim S. Design challenges facing clinical trials of the effectiveness of new HIV-prevention technologies. AIDS. 2012;26:529-32.
35. Minnis A, Gandham S, Richardson B, et al. Adherence and acceptability in MTN 001: A randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. AIDS Behav. 2013;17:737-47.
36. Ware N, Wyatt M, Haberer J, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012;59:463-8.
37. Barreiro P, Castilla J, Labarga P, Soriano V. Is natural conception a valid option for HIV-serodiscordant couples? Hum Reprod. 2007;22:2353-8.
38. Barreiro P, Duerr A, Beckerman K, Soriano V. Reproductive options for HIV-serodiscordant couples. AIDS Rev. 2006;8:158-70.
39. Bangsberg D, Haberer J, Psaros C, et al. High adherence and high effectiveness observed in HIV discordant couples: Partners PrEP Study, Adherence Monitoring and Counseling Substudy. CROI 2012. Seattle, WA, USA. [Abstract 1067].
40. Koenig L, Lyles C, Smith D. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. Am J Prev Med. 2013;44(Suppl 2):S91-8.
41. Contraceptive Research and Development Program (CONRAD). Safety and Effectiveness of Tenofovir Gel in the Prevention of Human Immunodeficiency Virus (HIV-1) Infection in Women and the Effects of Tenofovir Gel on the Incidence of Herpes Simplex Virus (HSV-2) Infection. In: ClinicalTrials.gov [Internet]. Bethesda (MD). National Library of Medicine (US). Nov 29 2012. http://www.clinicaltrials.gov/ct2/show/NCT01386294?term=FACTS+001&rank=1 [accessed Jan 5, 2013].
42. FACTS Consortium. FACTS-001 Study Design. http://www.facts-consortium.co.za/?page_id=83 [accessed Jan 5, 2013].
43. Karim S. CAPRISA 008 trial receives go-ahead. 1 June 2012. http://www.caprisa.org/Lists/Announcements/AllItems.aspx.
44. CAPRISA 008 - Executive Summary. 1 June 2012. http://www.caprisa.org/Lists/Announcements/AllItems.aspx.
45. International Partnership for Microbicides. IPM 027 (The Ring Study) Backgrounder. http://www.ipmglobal.org/the-ring-study [accessed Jan 5, 2013]. http://www.clinicaltrials.gov/ct2/show/NCT01363037?term=IPM+026&rank=1 [accessed Jan 5, 2013].
46. International Partnership for Microbicides. Phase 3 Safety and Effectiveness Trial of Dapivirine Vaginal Ring for Prevention of HIV-1 in Women (ASPIRE). In: ClinicalTrials.gov [Internet]. Bethesda (MD). National Library of Medicine (US). Nov 27 2012. http://www.clinicaltrials.gov/ct2/show/NCT01617096?term=ASPIRE&rank=20 [accessed Jan 5, 2013].
47. International Partnership for Microbicides. Safety and Efficacy Trial of a Dapivirine Vaginal Matrix Ring in Healthy HIV-Negative Women. In: ClinicalTrials.gov [Internet]. Bethesda (MD). National Library of Medicine (US). Aug 20 2012. http://www.clinicaltrials.gov/ct2/show/NCT01539226?term=IPM+027&rank=2 [accessed Jan 5, 2013].
48. Grant R, Lama J, Anderson P, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363:2587-99.
49. Gilead. Press Release: Gilead Sciences Submits Supplemental New Drug Application to U.S. Food and Drug Administration for Truvada® for Reducing the Risk of Acquiring HIV. Dec 15 2011. http://www.gilead.com/pr_1640306 [accessed Jan 5, 2013].
50. Gilead. Press Release: U.S. FDA Grants Priority Review for Truvada® for Reducing the Risk of Acquiring HIV Infection". Feb 13 2012. http://www.gilead.com/pr_1660616 [accessed Jan 5, 2013].
51. Cohen J. FDA Panel recommends anti-HIV drug for Prevention. Science. 2012;336:792.
52. Feinberg J. Truvada PrEP: why I voted "yes". Ann Intern Med. 2012; 157:521-2.
53. Wood L. Why I voted "no" to Truvada PrEP. Ann Intern Med. 2012;157:519-20.
54. U.S. Food and Drug Administration. News Release: FDA approves first drug for reducing the risk of sexually acquired HIV infection. Jul 16 2012. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm [accessed Jan 5, 2013].
55. CONRAD. Press Release: FDA and CONRAD Chart U.S. Regulatory Path for 1% Tenofovir Gel for HIV Prevention. 25 October 2010. http://www.conrad.org/news-pressreleases-56.html [accessed Jan 5, 2013].
56. Shelton J. HIV/AIDS. ARVs as HIV prevention: a tough road to wide impact. Science. 2011; 334:1645-6.
57. Chang L, Serwadda D, Quinn T, Wawer M, Gray R, Reynolds S. Combination implementation for HIV prevention: moving from clinical trial evidence to population-level effects. Lancet Infect Dis. 2013;13:65-76.
58. Colbert J. Clinical decisions. Preexposure prophylaxis for HIV prevention--polling results. N Engl J Med. 2012;367:e22.