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Antiretroviral-based HIV prevention strategies for women

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Abstract

Almost three decades have elapsed since researchers identified HIV as the cause of AIDS, with current estimates from UNAIDS that 33.4 million adults were living with HIV/AIDS in 2008. Two-thirds of this burden of disease is in Sub-Saharan Africa, and 60% of those infected are women. The disease still remains incurable and current prevention strategies including abstinence, male/female condom use and male circumcision are only partially effective. New strategies to curb the epidemic are urgently needed. Scientists are diligently exploring HIV prevention methods that are safe, effective and affordable. These new biological interventions include oral pre-exposure prophylaxis using oral antiretroviral (ARV) drugs, ARV treatment in HIV-infected persons to reduce transmission and topical ARV-based microbicide formulations.

Keywords

antiretroviral agents; biological plausibility; chemoprophylaxis; post-exposure prophylaxis; pre-exposure prophylaxis; topical microbicides

Worldwide, women continue to carry a disproportionate burden of HIV infection, particularly in Sub-Saharan Africa where 67% of people living with HIV/AIDS are women [101]. The WHO estimates that approximately 2.3 million individuals become newly infected with HIV every year, which highlights that the current strategies to control the epidemic by use of condoms and behavioral change are insufficient to limit daily spread of HIV infection. Globally, most new HIV infections are acquired through heterosexual intercourse.

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In Sub-Saharan Africa, which is the epicenter of HIV/AIDS, women's vulnerability to acquisition of HIV infection stems from greater physiological susceptibility to heterosexual transmission and also to social, legal and economic disadvantages they often confront.

While correct and persistent use of condoms has been shown to prevent HIV transmission, this prevention method may not be applicable for women who are trying to get pregnant or who are unable to negotiate condom use with their male partner [1,2]. Advances in developing an effective HIV vaccine have been slow with setbacks and interesting but modest results [3,4]. Male circumcision has proven effective in preventing 50–60% of female-to-male HIV transmission and efforts to scale-up this intervention are underway in many of the epicenter countries [5–7]. While the scale-up of known HIV-preventive methods in women is necessary, there remains a clear need to develop new prevention methods that are affordable and acceptable to women. The introduction of highly active antiretroviral therapy in 1996 has seen a remarkable prolongation and improved quality of life among HIV-infected persons. This article will focus on new oral and topical antiretroviral (ARV)-based biological interventions that are potential HIV prevention strategies for women, as evidenced by completed and ongoing research efforts.

Topical microbicide formulation development

Microbicides are products that can be applied to the vagina or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections, including HIV. In the past decade, approximately 30,000 women worldwide have participated in Phase II/IIb and Phase III clinical trials that tested effectiveness of seven candidate microbicide formulations (Table 1). The first-generation microbicides were based on surfactant formulations (nonoxynol-9 [N-9] sponge, N-9 gel and Savvy® [C31G; Biosyn Inc., Huntington Valley, PA, USA]), which work by destroying the virus envelope. The development of these microbicides experienced setbacks when earlier trials with N-9 formulations paradoxically increased the risk of HIV acquisition instead of reducing it [8]. This increased risk of HIV transmission has been ascribed to the observation that N-9 causes mucosal erosions and ulceration, which create potential entry portals for HIV [9].

The second-generation microbicides are high-molecular-weight anionically charged sulfated polymers (PRO 2000 gel, cellulose sulfate and carageenan). This class of microbicides works by blocking HIV entry at the receptor level. Clinical study results from second-generation microbicide candidates have also been disappointing. A trial of cellulose sulfate suggested that the active gel caused harm owing to the finding of increased HIV infections in the microbicide trial arm compared with placebo [10]. A recent microbicide trial (HPTN 035) that tested 0.5% PRO 2000 gel and buffer gel (a vaginal buffering agent that maintains vaginal pH <4.5 in the presence of semen) showed a modest 30% protection from HIV infection for women in the PRO 2000 arm compared with the control arms [11]. However, this result was not confirmed in a larger trial (MDP 301) where PRO 2000 had similar rates of infection compared with the placebo arm [12].

With conclusive evidence of no significant effectiveness in protecting women from acquiring HIV infection from the first- and second-generation microbicides, researchers

have turned new focus on third-generation ARV-based microbicide formulations. ARVs have been successful in slowing disease progression in HIV-infected individuals and in preventing vertical transmission to infants (prevention of maternal-to-child transmission [PMTCT]) by offering ARV treatment prenatally, intra-partum and post-partum to infected mothers and exposed fetus/newborns. ARVs may also show promise in preventing sexually transmitted HIV infection as evidenced by recent macaque and clinical studies, which are described in detail in the next sections.

Biological plausibility of oral & topical pre-exposure prophylaxis using selected ARVs

Nonhuman primate studies

The initial indication that pre-exposure prophylaxis (PrEP) could play a role in biomedical prevention in HIV-uninfected persons was provided by the finding that macaque infants were protected from infection if given zidovudine prior to virus inoculation [13]. Further evidence from macaque studies showed that systemic PrEP using tenofovir (TFV) or the combination drug TFV/ emtricitabine (FTC; Truvada® [Gilead Sciences Inc., Foster City, CA, USA]) was associated with significant reductions in risk of simian immunodeficiency virus (SIV) infection [14,15].

To date, efficacy studies in macaques have primarily involved TFV, a highly potent nucleotide reverse transcriptase inhibitor. Although the viral inoculum, challenge type and route of ARV administration have varied, these studies have demonstrated the important proof of concept that a single ARV, when administered close to the time of infection (before and after), is sufficient to prevent infection in controlled conditions.

Rectal and vaginal use of TFV gel has been evaluated in two separate macaque studies. Compared with a placebo gel, rectal administration of a 1% TFV gel resulted in significant protection (67%) in macaques challenged rectally with a single high dose of $SIV_{mac251/32H}$. Of those macaques that did become infected, two out of three had modified outcomes, including intermittent detection of virus and delayed viremia [16]. Vaginal administration of TFV alone or in combination with FTC conferred protection to all macaques against repeat low-dose vaginal challenge with a simian– human immunodeficiency virus ($SHIV_{SF162p3}$) [17]. Although study conditions differed, these data suggest that complete protection from infection by vaginal application is theoretically possible, but more potent drugs or combinations of ARVs may be needed for rectal use. Rectal tissue has greater vulnerability to irritation, tearing and infection during sex, and the penetrability of rectal mucosa differs significantly from vaginal mucosa. Chenine and colleagues found that rectal challenges require less virus than vaginal challenges, even when the same strain ($SHIV_{1157ipd3N4}$, a SHIV encoding a primary R5 HIV clade C env) is used [18]. These data also caution against making assumptions about anticipated rates of protection afforded by the same formulation used rectally or vaginally.

Studies of chemoprophylaxis for SIV/SHIV prevention have explored both pre- and post-exposure ARV use. Early work with cynomolgus and rhesus macaques demonstrated that a regimen of 28 days of subcutaneous TFV initiated 24 h after SIV exposure was required to

prevent infection. Waiting until 48 h or reducing the duration of treatment led to a decrease in efficacy [14,19,20]. Similarly, timing of oral TFV dosing is also critical for pre- and post-exposure prophylaxis. Garcia-Lerma and colleagues conducted a series of experiments in a repeat exposure macaque model of rectal transmission with single or double oral doses of TFV given at time points ranging from 3 days prior to challenge up to 26 h post-inoculation. They found that treatment was needed both before and after exposure for maximum protection, and that the best outcome occurred when TFV was given up to 3 days prior to inoculation and followed with a second dose 2 h post-inoculation. Even better protection is seen when drug levels are increased by using combinations of the potent drugs TFV and FTC at twice the oral dose, or by administering the drugs subcutaneously to ensure uptake. This suggests that sufficient drug levels are needed prior to HIV exposure in order to prevent infection [21,22]. By contrast, daily oral TFV alone did not protect against $SHIV_{162P3}$ infection in Chinese rhesus macaques, which was attributed to variability in drug levels [15].

The macaque models have been complemented by humanized mice models [23]. Table 2 focuses on preclinical macaque data with TFV and FTC to date, and expands on work by Garcia-Lerma, including studies of vaginal and rectal administration [24]. Several general conclusions can be derived from this body of work. First, timing of exposure is important. Animals were less likely to be protected when PrEP was administered relatively close to the time of viral challenge. Second, post-exposure prophylaxis (PEP), the provision of antiviral drug after viral challenge, enhanced the likelihood of protection; this suggests that maintenance of a baseline steady-state level of ARV, present before and after a given exposure is important. Third, the likelihood of protection is, not surprisingly, directly related to drug dose. The major implication of these findings for use of PrEP in humans is that the drug needs to reach a threshold (as yet undefined) intracellular concentration well in advance of exposure to HIV, and similarly maintain that concentration immediately after exposure. This suggests that regular dosing to maintain a steady state at the site of exposure (generally, the cervicovaginal epithelium) will be important. How such dosing might be timed with sexual exposure that is anticipated to be intermittent (e.g., women who may be sexually active on a weekend, or 1 week a month) – an approach known as pericoital dosing – remains to be determined.

Macaque studies offer valuable insights on the potential of specific compounds for use in HIV prevention; however, the data may incompletely predict outcomes in human studies, which are subject to greater variability. Although the macaque studies vary by challenge method and dose, all currently use a subtype B variant of SHIV in the absence of semen or semen-derived factors. Furthermore, inoculations are typically performed only with cell-free virus on intact mucosa in the absence of conditions known to increase risk of acquisition such as genital ulcers, bacterial vaginosis or other coinfections. Despite these limitations, the macaque model enables detailed study of breakthrough infection, which would not be possible in humans.

Human studies & clinical trials

Among the first indications for the biological plausibility of oral PrEP was the marked reduction in perinatal HIV transmission among HIV-infected women taking oral ARVs.

PMTCT is now a widely promoted and established strategy. Moreover, PrEP as a general concept is supported by its routine use for several infectious diseases, including malaria and *Pneumocystis jirovecii* pneumonia. Tenofovir disoproxil fumarate (TDF) and TDF/FTC (Truvada) were logical candidates for PrEP because of their potent inhibition of the HIV-1 reverse transcriptase, generally good safety and tolerability profiles in HIV-infected persons, high barrier to HIV-1 resistance and favorable pharmacokinetics (once daily dosing that need not occur with food intake). Importantly, when taken orally, these drugs achieve concentrations in the genital secretions that are two- to sixfold that of blood plasma [25–27]. In order for TFV to be active, it must be taken up by relevant mononuclear cells and phosphorylated to its active form, TFV-diphosphate (TFV-DP). Data are emerging to support the fact that levels of extracellular TFV measured in genital secretions are directly proportional to intracellular concentrations of TFV-DP [28]. The intracellular half lives of both TDF and FTC are long (40 to >100 h), again providing support that substantial concentrations of these drugs in the genital tract could theoretically provide adequate activity against ‘incoming’ HIV.

To date, only one clinical trial of oral PrEP has been published [29]. In this Phase II safety study, 936 female sex workers in Cameroon, Ghana and Nigeria were randomized to daily oral TFV (300 mg) or corresponding placebo tablets. The incidence of adverse events did not differ between the two groups. Because only eight women acquired HIV on trial, estimating the extent to which TFV may have reduced participants’ risk of HIV acquisition was not possible. It is worth noting, however, that six HIV infections occurred in the group assigned to take placebo tablets, and two occurred in the group assigned to take TFV.

Since that study was completed, several other trials of oral and topical PrEP have been initiated (Table 3). A Phase IIb study of pre- and postcoital dosing of vaginal 1% TFV gel (CAPRISA) was recently completed this year [30]. A Phase II study of 400 men who have sex with men (MSM) is nearing completion in the USA, with results expected in 2011. Groups participating in these studies comprise the persons most vulnerable to HIV acquisition, including reproductive-age women and men in Sub-Saharan Africa, MSM, intravenous drug users, and HIV-uninfected sex partners of HIV-infected persons (discordant couples). A complete list of trials, along with their updated status, is available at [102].

Post-exposure prophylaxis

The US CDC last provided a comprehensive overview of recommendations for non-occupational PEP for HIV in 2005 [31]. Those recommendations emphasize that PEP should be provided within 72 h of the exposure, but the sooner the better (ideally within 24 h). Preferred regimens listed included zidovudine (AZT)/lamivudine (3TC) or TDF/FTC with either lopinavir/ritonavir or efavirenz. Since that time, the superior tolerability of TDF/FTC over AZT/3TC, and concerns about emergent resistance to the class of NNRTIs after even transient exposure, has led many experts to consider TDF/FTC, with or without a protease inhibitor-based regimen such as lopinavir/ritonavir, the preferred regimen.

The evidence base for PEP remains relatively thin, and particularly rests on data in two areas: PEP after occupational exposure (typically, needle-sticks in healthcare providers) and in sexual assault victims. These data indicate that PEP may reduce the risk of HIV acquisition by approximately 80% overall. Thus, persons with unprotected sexual exposure to partners with known or suspected HIV infection should be considered as candidates for potential PEP. A comprehensive review has recently been published [32] and emphasizes consideration of classes of ARV agents beyond that defined in the most recent (2005) CDC recommendations. In particular, integrase inhibitors (such as raltegravir) would seem to be appropriate for this purpose; maraviroc, a CCR5 inhibitor, has also been considered. In particular, raltegravir attains high levels in the genital tract after oral dosing [33] and the combination of TDF/FTC/raltegravir was safe in a study of post-sexual exposure PEP in MSM [34].

ARV treatment of HIV-infected individuals to reduce transmission

Modeling studies of a generalized heterosexual South African HIV/AIDS epidemic suggest that if all adults are tested for HIV annually and all infected adults start combination therapy immediately after diagnosis, annual HIV incidence and mortality could be reduced to less than one case per 1000 people within 10 years. Furthermore, prevalence could be reduced to less than 1% within 50 years [35,36]. However, the annual cost of this strategy could exceed US$1.7 billion per year, and despite considerable effort by the WHO in increasing universal access to ARVs, only 42% of those in need of therapy actually receive it [103–105].

The impact of ARV use on the epidemic can also be influenced by the stringency of guidelines set for eligibility of treatment in infected persons. In high-resource settings, treatment success is often measured by monitoring plasma HIV-1 RNA in conjunction with CD4-positive T-cell counts, and adjusting treatment regimens to manage drug resistance and to ensure that viral load remains undetectable, generally, below 50 copies/ml using sensitive assays [105]. When monitoring relies solely on CD4-positive T-cell counts, the proportion of HIV-positive people eligible for ART decreases if the threshold for ART eligibility is set too low. The United States Department of Health (DHHS) guidelines indicate treatment initiation in persons with CD4 counts below 350 cells/mm^3 and recommends it in those with counts between 350 and 500 cells/mm^3 [105], while WHO guidelines indicate treatment initiation in those with less than 200 CD4 cells/mm^3 with treatment not recommended for those with more than 350 cells/mm^3 [103,104]. Starting ART at higher CD4 counts results in a 74% reduction in risk of death [37] and the impact of ART in reducing transmission is greater with the DHHS guidelines compared with the WHO guidelines [38]. Similarly, decreasing community viral load can also avert new HIV infections [39].

As with other prevention methods, community viral load reduction through treatment alone is insufficient to have a major impact on transmission. In a US-based community sample of HIV-positive people, just believing that an undetectable viral load leads to lower infectiousness was associated with contracting a new sexually transmitted infection. An increased number of sexual partners by HIV-positive people could also counter the beneficial impact of treatment, by putting HIV-negative people at greater risk for other sexually transmitted infections that could enhance the possibility of HIV acquisition [40].

Although expanding HIV treatment is a promising strategy for reducing transmission, it must be paired with continued efforts in education and behavioral intervention.

Challenges of implementing ARV-based HIV prevention strategies in women: potential introduction of HIV-resistant strains during chemoprophylaxis

A major concern regarding ARV-based prevention is the possibility that the use of ARVs by those who are unknowingly already infected could select for drug-resistant HIV-1. Drug resistance can also develop in an infected person who is exposed to ARVs in doses insufficient to sustain complete suppression of HIV replication. ARV resistance is a concern both for treatment and prevention; high rates of drug resistance in a population could facilitate spread of drug resistance and eventually compromise the effectiveness of ARVs, both as treatment for HIV-positive individuals and as prevention in HIV-negative persons.

In macaque studies, Garcia-Lerma and colleagues have looked at resistance emergence in PrEP failures by continuing drug treatment after infection in animals who seroconverted on ARV study arms [22]. Compared with untreated infected macaques, those that had failed PrEP had decreases in peak viremia, and breakthrough infections were typically initiated with wild-type SIV. Although four out of six macaques in this study did not have evidence of drug resistance by both sensitive and standard testing up to a median of 23 weeks of treatment, one out of six (FTC treated) had the FTC-resistance mutation M184V 10 weeks after the first detectable RNA, and one out of six (FTC/TDF treated) had M184I 3 weeks after the first detectable RNA. K65R, the mutation primarily responsible for TFV resistance, was not detected in any macaque [21]. These data suggest that the transmitted variant is wild-type and that residual virus replication in cells not protected by drugs may have caused infection rather than a rapid selection and infection by a drug-resistant virus. Resistance may also occur with the continued use of incompletely suppressive drug.

More is known about resistance emergence during TFV monotherapy in macaques infected with SIV or SHIV. In rhesus macaques treated daily with subcutaneous phosonomethoxypropyl adenine (PMPA) for 28 weeks beginning 2 weeks postinfection, Taber and colleagues found an average viremia of more than 10^5 RNA copies/ml was required to maintain the TFV-resistant mutation K65R and compensatory mutation N69S/T [41]. In another study, 12 reverse transcriptase-SHIV-infected rhesus macaques were administered 10 mg/ml once-daily subcutaneous TFV beginning at 20 weeks postinfection. Using sensitive real-time PCR testing, the K70E mutation in reverse transcriptase was detected in plasma viral RNA of all 12 macaques within 1–4 weeks (median 2 weeks) after initiating TFV treatment, while the K65R mutation was detected in all 12 macaques by 2–12 weeks (median 4 weeks) post-TFV initiation [42].

A better understanding of resistance emergence during ARV-based prevention is needed, and such data are not yet available in humans. Further studies in macaques may include testing a resistant strain of SIV/SHIV in the repeat challenge model to provide insight on the level of protection ARVs may offer against transmitted drug resistance. High virus

replication may facilitate the selection of drug resistance. The risk of drug resistance may be reduced if blunted viremias are seen in ARV-based gel or PrEP failures [21]. The key to preventing resistance will be to closely monitor people using ARV-based prevention through frequent HIV testing, and to stop ARV use as soon as infection is suspected [21]. Continuing the prevention regimen with the addition of additional ARVs is not recommended, in order to avoid maintaining selection pressure if drug-resistant mutants are present. In addition, current guidelines for eligibility of treatment of acute HIV infection are based on CD4-positive T-cell levels, and the benefits of initiating treatment when CD4-positive T-cell counts are high are unknown.

Novel agents & future directions for ARV microbicide formulations

The aim of application of topical intravaginal ARV microbicides is to block replication of HIV RNA inoculums in the vaginal–cervical mucosa where its transmission occurs via entry into target epithelial lymphocytes (dendritic cells, Langerhans cells, $CD4^+$ T cells and macrophages) for its initial replication [43]. ARV-based topical products, which specifically target HIV by blocking replication in the female genital tract, are a biologically plausible strategy for HIV prevention with the potential to have an effective product on the market within the next 3–5 years. CAPRISA 004 tested 1% TFV gel in which participants were instructed to insert gel within 12 h before sexual intercourse and insert a second dose as soon as possible within 12 h after intercourse, using only two doses over 24 h regardless of the frequency of intercourse. Use of coitally dependent TFV gel was shown to significantly reduce the rate of HIV acquisition (by 39%) and, surprisingly, of herpes simplex virus type 2 acquisition (by 51%) [30]. Other confirmatory studies such as VOICE (MTN 003) currently testing non-coitally-dependent 1% TFV gel or a larger Phase III trial will probably be required before a product can undergo an approval process by relevant drug regulatory authorities.

The goal of Phase II/IIb trial study designs is to assess safety and efficacy in a tightly controlled setting where investigations try to minimize factors such as imperfect adherence to regimens, changes in risk behavior and changes in risk of exposure to HIV. Phase III trials are effectiveness trials that assess how well the intervention would perform in the real world where there is no rigorous control of adherence and risky behavior. These efficacy trials are undertaken as a ‘proof of concept’ to determine if the intervention, if taken as designed, can lower the risk of becoming infected from an exposure to HIV. Phase IIb and Phase III trials generally have a similar study duration, but Phase II trials typically enroll a quarter to a third of the sample size of Phase III studies. The Phase IIb design allows researchers to screen for low efficacy of intervention that will not require further testing of the product under study. Intermediate or stronger efficacy results will require a confirmatory Phase III trial that will evaluate effectiveness in the real-world environment. In the event of extremely positive efficacy results from a Phase IIb trial design, investigators may submit for approval without further testing [44].

Although TFV is the first ARV-based proof of concept microbiocide product, it is essential to pursue other compounds as future PrEP or microbicide candidates, particularly those that are not also used for treatment and those that are active at different stages in the replication

cycle of HIV. Newer reverse transcriptase inhibitor formulations under early development include UC-781 gel (CONRAD, VA, USA) and TMC 120 gel (CONRAD). Another emerging class of microbicide under very early development are the fourth-generation ARV formulations that prevent fusion between pathogens and the mucosal wall (CCR5 inhibitors), and the fusion inhibitory peptide T-1249, which showed dose-dependent protection against high-dose SHIV challenge. Maraviroc gel (International Partnership for Microbicides [IPM], MD, USA) is also a promising leading candidate in the CCR5 inhibitor class. Another developing concept includes combination delivery methods such as TFV-UC 781 gel (CONRAD), dapivirine–maraviroc ring (IPM) and dapivirine–maraviroc gel (IPM).

The current ARV-based microbicide formulations target a specific stage of HIV viral replication and can be used independent of coitus timing. Researchers are also testing novel delivery routes that include gels, rings, films and suppositories. Microbicide formulations that will test new delivery pathways (IPM) include once-daily gels that are not coitally dependent, once-monthly rings with sustainable release and once-daily films and tablets for ease and comfort of use. Further discussion on ongoing and completed microbicide trials can be obtained from [106–109].

Expert commentary & five-year view

Now that we have a robust result from an ARV-based microbiocide [30], the spectrum of ARV-based prevention strategies are expected to have a more significant impact on the reduction of new HIV infections than HIV prevention strategies from the past 25 years that have focused on behavioral changes and condom use alone. However, implementation of ARV-based products must occur in combination with continued efforts using behavioral interventions and promotion of condom use when feasible. The growing HIV epidemic is more concentrated in young women as evidenced in South Africa, where women make up 90% of the HIV-infected population of 15–24-year-olds [101], resulting in a concerted effort to target research efforts in female-controlled methods. The HIV burden in South African men occurs in older age groups compared with their female counterparts [101].

The development curve for ARV-based prevention products is long and complex with only a few candidates that eventually enter the Phase IIb/III clinical trials. Many seemingly promising compounds are rejected due to safety concerns and futility. Researchers narrow the product pipeline by using evidence from *in vitro* tissue culture-based studies followed by *in vivo* validation of protection by undergoing pre-clinical safety and efficacy testing in animal models. Classical Phase I studies are then conducted for early safety signals in a small group of human participants followed by extended safety in Phase II trials. Thus far, only TFV alone or in combination with FTC has progressed to the anxiously awaited effectiveness Phase IIb/III clinical trials as oral PrEP.

Most of the current HIV prevention research on ARV-based regimens is confined to Sub-Saharan Africa using multicenter, multi-country, randomized, placebo-controlled, double-blind clinical trials on seronegative women 18–40 years of age at high risk of acquiring HIV infection during the study period. Researchers have chosen sites that demonstrate high HIV

incidence rates (>2.0%), to allow for an adequate sample size that will demonstrate the effectiveness of a new intervention within the timeline defined by the protocol [45].

ARV-based topical products, which specifically target HIV by blocking replication in the female genital tract, are a biologically plausible strategy for HIV prevention with the potential to have an effective product on the market within the next 3–5 years. TFV gel is the product that is expected to be available on the market in the coming 3 years now that the CAPRISA results are out [30]. We are now likely to see bridging studies of 1% TFV gel in vulnerable populations such as pregnant women, young adolescents (15–18 years of age), and breastfeeding women who have not been included in completed and ongoing clinical trials. In the coming years, we are also likely to see results of safety and effectiveness of dapivirine ring and dapivirine gel from IPM.

In the next few months the trial landscape includes study results of once-daily oral TFV in 2010 (CDC 4370) and in 2011 (iPrEX). In 2012, results should be available from Partners PrEP, FEM PrEP and in 2013 VOICE (MTN 003) (see [102]). ARV-based HIV prevention strategies in women will have a meaningful public health impact when these new biological interventions are integrated into existing behavioral interventions in order to achieve synergy and avoid disinhibition. The public health impact will largely depend on acceptability, accessibility, availability and affordability of the new interventions. The impact will be greatest in programs that have optimum coverage and are of high quality.

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Key issues

- There still remains an urgent need to develop effective HIV prevention methods that women find acceptable, affordable and accessible in order to control the HIV epidemic that has had a devastating effect particularly in Sub-Saharan Africa where women comprise up to 60% of the disease burden.
- Antiretroviral (ARV) agents in animal models administered as oral chemoprophylaxis or as topical vaginal gels have demonstrated adequate protection when given both before and/or after exposure in order to achieve maximum protection. A baseline steady-state level of ARV maintenance seems to be essential before and after exposure of the viral inoculum. These studies have been confined to macaque species using subtype B variants of simian immunodeficiency virus or simian–human immunodeficiency virus in the absence of semen-derived factors and other genital comorbidities that increase the risk of HIV acquisition.
- Efficacy results from trials of oral pre-exposure prophylaxis using the ARV drug tenofovir (TFV) alone or combined with emtricitabine (TFV/FTC; Truvada®) are expected to be released in 2011. Positive results should signal large efforts for bridging studies and potential drug regulatory authority registration.
- Seven clinical trials of first- and second-generation topical microbicides have not shown protection against HIV infection. The first trial results of ARV-based topical 1% TFV gel demonstrated 39% effectiveness in preventing HIV in women, which has opened discussions of a roadmap to have this microbicide gel on the market within the next 3–5 years, after confirmatory study results that will allow accelerated registration process of 1% TFV gel.
- The fourth-generation ARV microbicide formulations that include CCR5 inhibitors and combination formulations (dapivirine–maravoric ring and dapivirine–maravoric gel) as well as new delivery pathways including rings, tablets and once-daily films will be on the horizon once data on safety and accessibility are available.

Table 1

Microbicide effectiveness trials.

Sponsor	Product	Number of women enrolled	Status	Outcome of trial	Ref.
Agency for International Development, the Mellon Foundation/NIH	N-9 film	1292	Completed	No harm or benefit	[46]
UNAIDS/Columbia Laboratories	N-9 gel (COL-1492 gel)	1005	Completed 2000	Stopped with evidence of harm	[8]
FHI/USAID	Savvy®	4284	Completed 2007	Stopped due to futility, no evidence of harm	[47]
FHI/USAID/CONRAD	Cellulose sulfate	2160	Completed 2007	Stopped prematurely due to concerns from parallel trial interim results	[48]
Population Council	Carraguard®	6300	Completed 2007	No harm or benefit	[49]
CONRAD/USAID/Bill and Melinda Gates Foundation	Cellulose sulfate	1398	Completed 2007	Evidence of harm at interim analysis	[10]
NIAD	Buffer gel 0.5% PRO 2000	3100	Completed 2008	0.5% PRO 2000 showed 30% effectiveness: buffer gel did not have an effect	[11]
MDP/MRC	PRO 2000	10,000	Completed 2009	0.5% PRO 2000: no harm, no benefit	[12]
LIFE Lab/FHI/USAID/ CONRAD/South African government	1% Tenofovir	889	Completed 2009	39% effectiveness in HIV prevention	[30]
NIAD	1% Tenofovir	5000 to be enrolled	Ongoing, enrollment started in September 2009	Aim for completion June 2012	[Unpublished data]

FHI: Family Health International; MDP: Microbicides Development Program; MRC: Medical Research Council UK; N-9: Nanoxynol-9; NIAD: National Institute of Allergies and Infectious Diseases; UNAIDS: Joint United Nations Programme on HIV/AIDS; USAID: United States Agency for International Aid.

Table 2

Summary of preclinical macaque data with tenofovir and emtricitabine.

Macaque	Virus		Drug				Number protected	Ref.
	Strain/dose	*Challenge route*	*Drug*	*Dose*†	*Administration*	*Dosing schedule*‡		
Long-tailed	SIV_{mne}	Subcutaneous	TFV	20–30	Subcutaneous	48 h pre + QD for 4 weeks	15/15	[14]
	10^3 $TCID_{50}$					4 h post + QD for 4 weeks	5/5	
						24 h post + QD for 4 weeks	5/5	
Long-tailed	SIV_{mne}	Subcutaneous	TFV	30	Subcutaneous	24 h post + QD for 28 days	4/4	[19]
	10^3 $TCID_{50}$					48 h post + QD for 28 days	0/4	
						72 h post + QD for 28 days	1/4	
						24 h post + QD for 10 days	2/4	
						24 h post + QD for 3 days	0/4	
Rhesus	$SHIV_{162p3}$	Repeat low-dose	TDF	22	Oral	2 h post + QD for 36 weeks	1/5	[15]
	10 $TCID_{50}$	rectal				2 h post + QW for 36 weeks	0/5	
Rhesus	$SHIV_{162p3}$	Repeat low-dose	FTC	20	Subcutaneous	2 h pre + QD for 18 weeks	2/6	[21]
	10 $TCID_{50}$	rectal	FTC/TDF	20/22	Oral	2 h pre + QD for 18 weeks	4/6	
			FTC/TDF	20/22	Subcutaneous	2 h pre + QD for 18 weeks	6/6	
			FTC/TDF	20/22	Subcutaneous	2 h pre + 24 h post	6/6	
Rhesus	$SHIV_{162p3}$	Repeat low-dose	FTC/TDF	20/22	Subcutaneous	2 h pre	4/6	[22]
	10 $TCID_{50}$	rectal	FTC/TDF	20/22	Oral	2 h pre + 22 h post	3/6	
Rhesus	$SHIV_{162p3}$	Repeat low-dose	FTC/TDF	20/22	Oral	2 h post + 26 h post	3/6	[22]
	10 $TCID_{50}$	rectal	FTC/TDF	40/44	Oral	2 h pre + 24 h post	5/6	
			FTC/TDF	20/22	Oral	22 h pre + 2 h post	5/6	
			FTC/TDF	20/22	Oral	3 days pre + 2 h post	5/6	
			FTC/TDF	20/22	Oral	7 days pre + 2 h post	4/6	
Pig-tailed	SIV_{mac239}	Repeat low-dose	TFV	1%	Vaginal	30 min pre	6/6	[17]
	10 $TCID_{50}$	vaginal	FTC/TFV	5/1%	Vaginal	30 min pre	6/6	

Macaque	Virus		Drug				Number protected	Ref.
	Strain/dose	*Challenge route*	*Drug*	*Dose*†	*Administration*	*Dosing schedule*‡		
Rhesus	$SIV_{mac251/32H}$	Single high-dose	TFV	1%	Rectal	15 min pre	4/6	[16]
	18,974 $TCID_{50}$	rectal	TFV	1%	Rectal	2 h pre	2/3	
			TFV	1%	Rectal	2 h post	1/3	

†Doses are mg/kg unless otherwise indicated.

‡Pre refers to drug administration prior to virus challenge, while post refers to drug administration after virus challenge.

FTC: Emtricitabine; QD: Once daily; QW: Once weekly; TCID: Tissue culture infective dose; TDF: Tenofovir disoproxil fumarate (oral); TFV: Tenofovir.

Adapted with permission from [24].

Table 3

Pre-exposure prophylaxis trials in humans.

Study	Sponsor	Product	Population	Countries	Enrollment started	Status/ anticipated results
West Africa TDF Trial	FHI	Daily oral TDF	936 heterosexual women	Ghana, Cameroon, Nigeria	2004	Completed
US Extended TDF Safety Trial	CDC	Daily oral TDF	400 MSM	USA	2005	Completed
Bangkok TDF Study	CDC	Daily oral TDF	2400 IDUs	Thailand	2005	Fully enrolled/2010
TDF-2	CDC	Daily oral TDF/FTC (switched from TDF in 2007)	1200 heterosexual men and woman	Botswana	2007	Fully enrolled/2011
iPrEX	NIH, BMGF	Daily oral TDF/FTC	3000 MSM	Peru, Ecuador, Brazil, USA, Thailand, South Africa	2007	Fully enrolled/2011
Partners PrEP	BMGF	Daily oral TDF Daily oral TDF/FTC	3900 heterosexual HIV-discordant couples	Kenya, Uganda	2008	Enrolling/2012
FEM PrEP	FHI, USAID	Daily oral TDF/FTC	3900 high-risk heterosexual women	Malawi, Uganda, South Africa, Zambia, Zimbabwe	2009	Enrolling/2012
VOICE (MTN 003)	NIH	Daily oral TDF Daily oral TDF/FTC Daily vaginal TFV gel	4950 heterosexual women	Malawi, South Africa, Uganda, Zambia, Zimbabwe	2009	Enrolling/2013

BMGF: Bill & Melinda Gates Foundation; CAPRISA: Centre for the AIDS Programme of Research in South Africa; FHI: Family Health International; FTC: Emtricitabine; IAVI: International AIDS Vaccine Initiative; IDU: Intravenous drug user; iPrEX: Pre-exposure prophylaxis initiative; MSM: Men who have sex with men; MTN: Microbicide Trial Network; TDF: Tenofovir disoproxil fumarate; TFV: Tenofovir; VOICE: Vaginal and oral interventions to control the epidemic.

Adapted from [24].