

# Combination HIV prevention options for young women in Africa

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Although the number of new HIV infections has declined by over 30% in the past decade, the number of people who acquire HIV each year remains unacceptably high. In 2014 the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that there were about 2 million new HIV infections. The virus continues to spread, particularly in key populations, such as men who have sex with men (MSM), transgender individuals, sex workers and people who inject drugs. In Africa, young women have the highest HIV incidence rates. Scaling up known efficacious HIV prevention strategies for these groups at high risk is therefore a high priority. HIV prevention has generally been targeted at HIV-negative individuals or in some instances, entire communities. Prevention efforts are, however, shifting from a narrow focus on HIV-uninfected persons to a continuum of prevention that includes both HIV-negative and HIV-positive individuals. Given that a single HIV prevention intervention is unlikely to be able to alter the epidemic trajectory as HIV epidemics in communities are complex and comprise a mosaic of different risk factors and different routes of transmission, there is need to provide combination prevention. Hence, a mix of behavioural, biomedical and structural HIV prevention options is likely to be needed to alter the course of the HIV epidemic. The combination of HIV prevention interventions needed will vary depending on cultural context, the population targeted and the stage of the epidemic. This paper reviews the available HIV prevention strategies for young women and discusses new HIV prevention approaches in development.

**Keywords:** PrEP, treatment as prevention, condoms, young women

## Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that the number of new HIV infections has declined by 35% since 2000 (UNAIDS, 2015a). The most significant reductions in new HIV infections have been among children below the age of 15 years, with transmission rates from mother-to-child decreasing by 58% since 2000 (UNAIDS, 2014a). Many countries, even those with high HIV burdens, have made significant progress towards eliminating mother-to-child transmission of HIV (UNAIDS, 2015b). Yet despite these encouraging trends, the number of new HIV infections each year remains unacceptably high. In 2014 an estimated 2 million new HIV infections were recorded, translating to about 5 600 people acquiring HIV daily.

HIV continues to spread in key populations, such as sex workers, men who have sex with men (MSM), transgender individuals and people who inject drugs, where the risk of HIV is highest. However, sub-Saharan Africa remains the most heavily burdened area with 66% of all new HIV infections occurring in this region. In this region, adolescent girls and young women aged 16–24 years bear a disproportionate burden of HIV infection. About 380 000 new HIV infections occur in this age group each year (UNAIDS, 2014a) and these young women experience HIV rates up to eightfold higher (UNAIDS, 2010) and acquire HIV infection at least five years earlier than their male peers (Abdool Karim, Abdool Karim, Singh, Short, & Ngxongo, 1992;

Shisana, et al., 2009). One of the most crucial challenges in HIV prevention in Africa is reducing the high infection rates among young women.

In this paper we examine the available behavioural, structural and biomedical HIV prevention options, as well as new prevention technologies under development, with a particular focus on strategies that are appropriate for young women. The potential HIV prevention options that could be combined and tailored for young women are discussed. This paper does not attempt to provide a comprehensive overview of all HIV prevention options available. For example, prevention of vertical transmission and prevention of parenteral transmission are not specifically discussed in this paper.

## Structural and behavioural interventions

### **Abstinence, monogamy and condom use**

Since the beginning of the epidemic, HIV prevention programmes have promoted the “ABC” strategies that encourage sexual abstinence, a reduction in the number of multiple and concurrent sexual partnerships (be faithful) and the use of condoms. Individuals who are sexually abstinent or practice lifelong mutual monogamy have a minimal risk of HIV infection. Unfortunately, women have limited control over whether their male partners remain faithful. Further, as a prevention strategy on its own, the promotion of abstinence has had little to no impact on HIV prevention. One systematic review involving 15 940 youths showed

that sexual abstinence only programmes had no impact on incidence of unprotected vaginal sex, number of partners, condom use or sexual initiation (Underhill, Montgomery, & Operario, 2007).

Male and female condoms are an essential component of HIV prevention programmes. They are inexpensive and, when used correctly and consistently, provide protection against acquisition and transmission of HIV, a variety of other sexually transmitted infections (STIs) and pregnancy (Holmes, Levine, & Weaver, 2004). In HIV sero-discordant studies, condom use has been shown to effectively prevent HIV transmission. Condom promotion programmes, particularly for sex workers, have also had a substantial impact on HIV epidemics in some countries, particularly in the early stages of the epidemic (Rojanapithyakorn, 2006).

However, for condoms to be effective as a prevention option at a population level they need to be widely accessible. Although high condom coverage has been achieved in some countries, in sub-Saharan Africa, only eight condoms on average are estimated to be available per year for each sexually active individual (UNAIDS, 2014a). In South Africa the distribution of male condoms has increased drastically from 376 million units in 2006 to 723 million units in 2014. Although not on the same scale, female condom distribution has increased from 3.6 million units in 2006 to 20 million units in 2014 (National Department of Health, 2015).

Despite the proven effectiveness and increasing availability, inconsistent use of condoms limits their potential population-level effect. A wide range of factors hinder condom use, the most common being the perception that condoms make sex less pleasurable (Mnyika, Kvale, & Klepp, 1995) and requesting that a partner uses a condom implies self-acknowledgement of HIV infection or a lack of trust in the partner (Bedimo, Bennett, Kissinger, & Clark, 1998). Condom use is often low among married couples and in stable partnerships where pregnancy is desired (Hendriksen, Pettifor, Lee, Coates, & Rees, 2007; Maharaj & Cleland, 2004). Further, because of gender power imbalances, many women find it particularly difficult to negotiate condom use with their partners. A partner's agreement and cooperation is also required to use female condoms. Condoms are therefore a prevention option that is often under the control of a woman's partner.

Other factors associated with inconsistent condom use are alcohol consumption and substance abuse. This trend is particularly problematic because many individuals meet high-risk sexual partners in social settings where alcohol or drugs are available.

Despite these challenges, condoms are highly effective when used consistently and some people do successfully use condoms to prevent both STIs and pregnancy and they should therefore be offered as part of HIV prevention packages for all populations and in all settings.

### **Behaviour change interventions**

Numerous social and behavioural change interventions to prevent HIV have been assessed. Examples include peer education (Medley, Kennedy, O'Reilly, & Sweat, 2009), mass media communication (Bertrand, O'Reilly, Denison, Anhang, & Sweat, 2006), school-based sex education programmes (Fonner, Armstrong, Kennedy, O'Reilly, & Sweat, 2014),

microfinance or skills development projects (Kennedy, Fonner, O'Reilly, & Sweat, 2014), and behavioural counselling (Zajac et al., 2015). Most of the studies find a moderate improvement in behavioural outcomes, for example, increased HIV knowledge, increased condom use, and reduction in high-risk sexual behaviour, but few show a significant impact on biological outcomes such as reduction in HIV incidence. One systematic review in 2010 of 11 behaviour change studies, assessing 8 unique interventions, showed that only 1 study resulted in a reduction of HIV incidence. This study, which was conducted among 541 female sex workers in India and included group educational and motivational sessions over 6 months and was shown to reduce HIV incidence after 1 year of follow-up (incidence rate ratio [IRR] = 0.33, 95% CI: 0.15 to 0.72) (Bhave et al., 1995). More recently the Safe Homes And Respect For Everyone (SHARE) trial, a community-level mobilisation intervention in Uganda to change attitudes, social norms and behaviours related to intimate partner violence was shown to be associated with a 33% reduction in HIV incidence (adjusted incidence rate ratio [aIRR] = 0.67, 95% CI: 0.46 to 0.97,  $p = 0.036$ ) (Wagman et al., 2015). Addressing gender-based violence and encouraging greater male responsibility are critical short- to medium-term interventions. Gender-based violence is often a consequence of the power imbalance between men and women in relationships and compounds a young woman's vulnerability to HIV infection (Abdool Karim, Sibeko, & Baxter, 2010a).

### **HIV counselling and testing (HCT)**

Knowledge of HIV status is a fundamental component of any treatment or prevention programme and should therefore be offered as part of HIV prevention packages for all populations and in all settings. HIV counselling and testing (HCT) is effective in reducing risky sexual behaviours and has been shown to be a cost-effective prevention intervention (Sweat et al., 2000; The VCT Efficacy Study Group, 2000). However, many people remain unaware of their HIV status and estimates from UNAIDS indicate that about 52% of all people living with HIV do not know their status (UNAIDS, 2014a). Denial, stigma, and a lack of understanding of vulnerability and risk contribute to low HIV testing rates. Discrimination and social marginalisation continue to be experienced daily by people who are the most affected by HIV, further contributing to their reluctance to test for HIV (Abdool Karim, 2011).

Ambitious global targets for HIV testing and treatment have been set and aim to have 90% of people living with HIV knowing their HIV status, 90% of people who know their status receiving treatment and 90% of people on HIV treatment having a suppressed viral load by 2020 (UNAIDS, 2014b). Reaching these targets by 2020 will require rapid scale up of HIV testing and innovative ways to reach populations who do not yet know their HIV status. Strategies such as provider-initiated testing (Kennedy et al., 2013), community-based voluntary counselling and testing (Coates et al., 2014) and home-based testing (Sekandi et al., 2011) are some of the initiatives that have been implemented to improve HCT uptake.

### **Cash incentives for HIV prevention**

The use of cash transfers (conditionally or unconditionally) to achieve desired behaviours or health outcomes has been shown to be successful in several different settings. For example, cash incentives programmes have been effective in smoking cessation programmes (Volpp et al., 2009), substitution therapy for drug abuse (Petry et al., 1998; Sindelar, Olmstead, & Peirce, 2007), and improving immunisation coverage and family planning utilisation (Barber & Gertler, 2008; Fernald, Hou, & Gertler, 2008). Cash transfers are also being evaluated for their potential to reduce HIV risk, especially among young women. A systematic review of cash transfer studies in 2012 identified 16 studies, 10 of which had been completed. Most of the studies have been conducted in adolescents and most report reductions in risky sexual behaviour such as delaying sexual debut, staying in school and condom use (Pettifor, MacPhail, Nguyen, & Rosenberg, 2012). One cluster trial in Malawi of cash incentives for school attendance showed that weighted prevalence of HIV at 18 months was lower in the intervention communities (Baird, Chirwa, McIntosh, & Ozler, 2010). A case control study, that assessed the publically funded social grant programme on risk of HIV infection in adolescents from South Africa, showed that cash transfers were associated with a 51% decrease in transactional sex and a 71% reduction in age-disparate sex in girls but had no impact on boys (Cluver et al., 2013).

Two trials that directly assessed HIV incidence as the main outcome found no impact of cash transfers on HIV incidence. The HPTN 068 Swa Koteka study ( $n = 2\,448$ ), which provided a cash incentives for school attendance, showed that there was no difference in HIV acquisition between the young women who received the cash transfer and those that did not (Pettifor et al., 2015). The CAPRISA 007 cluster randomised controlled trial (CAPRISA 007), which was undertaken with 3 217 consenting male ( $n = 1\,517$ ) and female ( $n = 1\,700$ ) students in grades 9 and 10 in 14 schools in rural KwaZulu-Natal, South Africa, showed that conditional cash incentives for meeting any combination of four conditionalities (annual HIV testing, school performance, participation in a HIV prevention programme and participation in a community project) was associated with a 30% reduction in herpes simplex virus type 2 (HSV-2) incidence, but did not have sufficient statistical power to demonstrate an impact on HIV incidence (Abdool Karim et al., 2015) (Table 1).

The implementation of behavioural interventions or cash transfer programmes for HIV prevention in young women would need to be evaluated in the specific context and should be complemented by other effective HIV prevention strategies.

### **Biomedical prevention options**

#### **Oral pre-exposure prophylaxis**

Since 2010 the evidence for the protective benefits of oral pre-exposure prophylaxis (PrEP) has been consistently growing and includes a range of settings and populations. Results from several randomised double-blinded placebo-controlled trials of tenofovir-containing PrEP for the prevention of sexual transmission of HIV, provide consistent evidence of efficacy in men (Baeten et al., 2012; Grant et al.,

2010; McCormack et al., 2016; Molina et al., 2015; Thigpen et al., 2012), but not in women (Marrazzo et al., 2015; Van Damme, et al. 2012). Daily oral PrEP has also been shown in one study to be effective in a population of people who inject drugs (Choopanya et al., 2013).

In women, although two trials (Partners PrEP and Botswana TDF2) demonstrated effectiveness of oral PrEP ranging from 66% to 75%, two other trials (the FEMPrEP (Van Damme et al., 2012) and VOICE (Marrazzo et al., 2015) trials) showed no protective effect of PrEP in this group (Table 1). Analysis of drug concentrations revealed that <30% of the women in these trials were able to adhere to the prescribed intervention (Marrazzo et al., 2015; Van Damme et al., 2012). Therefore, just like condoms, consistent use is essential for the intervention to be effective.

In 2015 the World Health Organization (WHO) released guidelines for oral PrEP (World Health Organization, 2015). The guidelines recommend that “oral PrEP (containing Tenofovir Disoproxil Fumarate [TDF]) should be offered as an additional prevention choice for people at substantial risk of HIV infection (defined as HIV incidence >3%) as part of combination prevention approaches” (World Health Organization, 2015, p. 14). These guidelines combined with the approval of tenofovir-containing PrEP for HIV prevention by several countries including the USA, France, South Africa and Kenya, has made the use of PrEP for HIV prevention a possibility. PrEP is a particularly important HIV prevention option for women, as it is one of the few strategies that can be directly controlled by a woman.

The challenge now is to determine how best to implement PrEP in the populations that would benefit most, while still maintaining high levels of adherence.

Long-term, high adherence is essential for PrEP to be successful. Poor adherence may lead not only to sub-optimal protection, but may also have an impact on drug resistance. While clinical trials may achieve high adherence, the same may not pertain to “real world” settings where PrEP may be implemented in under-developed public healthcare facilities without adequate attention to adherence support. Evidence from a clinical practice setting in the US, however, shows that PrEP scale-up with high adherence is possible and none of the 653 MSM followed for a mean of 7.2 months after initiating PrEP have acquired HIV (Volk et al., 2015). Clinical trials of PrEP among young women in Africa, a group that is at particularly high risk of HIV have encountered significantly more challenges with adherence than trials in MSM. Data on effective PrEP adherence strategies in young women are limited, making it difficult for programmatic scale-up to use proven evidence-based approaches for adherence in this group.

The concerns about adherence to PrEP should certainly not hinder its implementation; similar concerns were raised when antiretroviral therapy (ART) first became available as treatment and was actually used as an argument against the implementation of these life-saving drugs in Africa. The scale up of ART roll-out programmes to over 15 million people has demonstrated that high levels of adherence are possible, even in resource-constrained settings. Further, the product’s effectiveness may serve as strong motivation for adherence (Amico & Stirratt, 2014). Regardless, adherence is likely to be a challenge that will require a concerted effort

**Table 1:** Evidence for behavioural and biomedical HIV prevention interventions in reducing HIV infection in women

Intervention	Target	Evidence	Effect for HIV prevention (95% CI)	Dosing	Comment
<i>Behavioural</i>					
Condoms	HIV-uninfected and HIV-infected, men & women	Multiple observational studies	–	Correct and consistent use for every sex act	Prevents HIV, pregnancies and other STIs
Knowledge of sero-status/ counselling and testing	HIV-uninfected and HIV-infected, men & women	1 RCT	Project Accept: 14% (–2 to 27) 30% (10 to 46) in women $\geq$ 24 years	Community-based voluntary counselling and testing	HIV testing rates were increased by 25% overall
Conditional cash transfer	HIV-uninfected women	3 RCTs	Malawi: OR: 0.36 (0.14–0.91) for HIV prevalence HPTN 068 study: HR: 1.17 (95% CI 0.80–1.71) CAPRISA 007: HIV: IRR: –26% (–139 to 44) HSV-2: 30% (14 to 43) 57–0.86	Cash incentives for school attendance Conditional cash transfers for school attendance Conditional cash incentives for meeting any combination of four conditionalities (annual HIV testing, school performance, participation in an HIV prevention program and participation in a community project)	Cash transfer programmes for HIV prevention would need to be evaluated in the specific context
<i>Biomedical</i>					
Oral PrEP	HIV-uninfected men* and women	4 RCTs	Botswana TDF2: 75%* (24 to 94) Partners PrEP: 71%* (37 to 87) 66%* (28 to 84) FemPrEP: 6% (–52 to 41) MTN003 VOICE trial: –4% (–49 to 27) –49% (–129 to 3)	Daily oral FTC/TDF Daily oral FTC/TDF or TDF Daily oral FTC/TDF Daily oral FTC/TDF or TDF	High efficacy in individuals with high adherence
Topical PrEP (microbicides)	HIV-uninfected women and MSM	3 RCTs	CAPRISA 004: 39% (6 to 60) MTN003 VOICE: 15% (–21 to 40) FACTS 001: 0% (–40 to 30)	Peri-coital tenofovir gel Daily tenofovir gel Peri-coital tenofovir gel	No microbicide available for implementation — ongoing studies assessing a rectal gel
Intravaginal rings	HIV-uninfected women	2 RCTs	Aspire trial: 27% (1% to 46%) Ring Study: 31% (1% to 51%)	Monthly intravaginal dapivirine ring	Open label post-trial access studies planned
ART provided to HIV+ persons, to reduce infectiousness of HIV positive individual	HIV-infected men and women	1 RCT and several observational studies	HPTN 052: 93%	Early ART initiation in HIV-positive partner	ART is highly effective for prevention of sexual transmission of HIV in discordant couples. Observational studies show 79–100% reduction
Treatment of curable STIs	HIV-uninfected and HIV-infected, men and women	1 RCT	Mwanza trial: 42% (21 to 58)	Improved STI case management at primary health care level	8 additional trials show no impact on HIV
Vaccine	HIV-uninfected men and women	1 RCT	RV144 Thai trial: 31.2%	ALVAC-HIV [VCP1521] plus AIDSVAX B/E boost	Demonstrated moderate protection but not available / licensed

\*Although oral PrEP is effective in men, only the trials that included women have been included here

\*Point estimate for women only

to overcome and PrEP programmes will need to include practical and proven adherence support programmes.

There are several other factors that may hinder PrEP implementation. Firstly, given that PrEP is a new HIV prevention strategy for many countries, the implementation of PrEP will need to be accompanied by advocacy and community outreach to increase awareness and knowledge. Several studies in the US have shown that PrEP awareness among physicians is suboptimal (Mimiaga, White, Krakower, Biello, & Mayer, 2014) and there is limited immediate uptake by individuals who could benefit from PrEP (Liu et al., 2008; Rucinski et al., 2013). Secondly, before PrEP can be initiated, the HIV status of the individual must be established and ongoing access to HIV testing will be an important component of any PrEP roll-out programme. Thirdly, when resources are scarce, it is necessary to rationalise and prioritise certain high risk groups for access to interventions over others. Determining who would benefit most will vary from country to country and while some groups, like MSMs, are easily identifiable, determining who should have access or be prioritised in generalised epidemics is more complex. In South Africa, for example, although young women are considered to be a group at high risk of HIV infection, sex workers have been prioritised for the implementation of PrEP (Department of Health, 2016) and it may take several years before PrEP is available to young women through the public sector.

However, the ongoing demonstration projects in a range of populations will help inform scale up of PrEP in populations like young women. Initiatives like the PEPFAR-funded DREAMS initiative, which aims to help adolescent girls develop into determined, resilient, empowered, AIDS-free, mentored and safe women, will provide the necessary resources for scaling up PrEP in this vulnerable group.

### **Microbicides for the prevention of HIV**

Microbicides, which are topical agents applied in the genital tract or rectum to prevent HIV infection, have been in development since the early 1990s. A safe and effective microbicide is a particularly important HIV prevention strategy for women because it offers them the opportunity to control their own HIV risk. Over the past 23 years, 12 advanced clinical trials of 7 candidate products (some tested as multiple doses and formulations) have been completed. The CAPRISA 004 tenofovir gel trial (Abdool Karim et al., 2010b), was the first to demonstrate a significant reduction in HIV acquisition in women. This trial showed that tenofovir gel, when used before and after sex, reduced HIV acquisition by 39% and HSV-2 by 51% (Abdool Karim et al., 2010b).

Despite these encouraging results, two other trials, which also assessed tenofovir gel, failed to show a protective effect. The Follow-on African Consortium for Tenofovir Studies (FACTS) trial (Rees, et al., 2015) of peri-coital gel reported 0% (95% CI: -40;30) protection and the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial (Marrazzo et al., 2015) of daily gel reported an estimate of 15% (95% CI: -21;39). Suboptimal adherence was the main reason for the variability in HIV outcomes across these trials. An analysis of drug levels revealed that only 25% of women assigned to tenofovir gel in the VOICE trial (Marrazzo et al., 2015) and about half of the women in the FACTS trial (Rees et al., 2015) had detectable drug levels.

Although research on tenofovir gel is continuing, including its potential as a rectal microbicide in MSM in several countries, the microbicide field has shifted its focus towards developing products that are less dependent on user compliance and products that can meet multiple sexual reproductive health needs. Data from two efficacy trials evaluating the long-acting antiretroviral dapivirine intravaginal ring were recently released. These studies showed that the dapivirine vaginal ring reduced HIV incidence by 27% (95% CI: 1% to 46%) in the ASPIRE (A Study to Prevent Infection with a Ring for Extended Use) trial and by 31% (95% CI: 1 to 51%) in the Ring trial (Baeten et al., 2016; International Partnership for Microbicides, 2016). While the effectiveness of the dapivirine vaginal ring in preventing HIV is considerably lower than anticipated and hoped for, the success of the two trials in achieving high levels of adherence (82% in ASPIRE and 73% in the Ring Study) and regular monthly vaginal ring insertions, is encouraging. However, the results show that protection differed by age; with no protection observed in young women below the age of 21 years. An analysis of drug levels in plasma samples shows that adherence in the younger women was two- to fourfold lower than in women older than 21 years (Baeten et al., 2016). More research is needed to fully understand and overcome the remaining challenges for sustained adherence in this high-risk population. An open label post-trial access study is now planned, which will include focus group discussions with the women, and will hopefully contribute to our understanding of the contextual factors that have an impact on adherence in young women.

In addition to new formulations and delivery devices, future microbicide development is likely to focus on a combination of antiretroviral drugs and products that meet multiple sexual and reproductive health needs, for example, combinations of antiretroviral agents with contraceptives.

### **Prevention benefits of antiretroviral treatment**

Remarkable progress has been made in scaling up ART as a treatment for AIDS. By mid-2015, a total of 15.8 million people living with HIV were receiving ART. In addition to averting an estimated 7.8 million deaths globally between 2000 and 2014 (UNAIDS, 2015a), there is compelling evidence that treatment of HIV infected individuals can prevent sexual transmission of HIV. Several studies have demonstrated that heterosexual HIV transmission is closely correlated with viral load (Fideli et al., 2001) and that the risk of transmission is very low when the HIV-infected individuals receiving ART have a suppressed viral load. A systematic review and meta-analysis of studies that included 5 021 heterosexual couples and 461 HIV-transmission events showed that there were no transmission events from seropositive partners who had a viral load <400 copies/ml on ART (Attia, Egger, Müller, Zwahlen, & Low, 2009). Observational data from the PARTNERS study, which included HIV serodiscordant heterosexual and MSM couples, show that when the HIV-positive partner's viral load was below 200 copies/ml there were zero linked transmission events (Rodger et al., 2014).

The HPTN 052 trial provides the most compelling evidence of the prevention benefits of ART (Table 1). In this trial interim results showed that early ART initiation (CD4 cell

count  $>350$  cells/mm<sup>3</sup>) in the HIV-positive partner led to a 96% reduction in HIV transmission among HIV discordant couples from 9 countries (Cohen et al., 2011). Following the release of these results, all participants in the deferred arm were offered immediate ART and the trial cohort was followed up for a further four years. Final results show that there was an overall 93% reduction in transmission among those on ART (Cohen & the HPTN 052 study team, 2015). The findings demonstrate the sustained protection against transmission provided by ART and the vital importance of ensuring treatment adherence and viral suppression.

If implemented on a large enough scale, the treatment as prevention strategy has the potential to alter the HIV epidemic. Evidence from one rural community in KwaZulu-Natal shows that a modest 30–40% ART coverage resulted in a 38% reduction in new HIV infections between 2004 and 2011 (Tanser, Barnighausen, Grapsa, Zaidi, & Newell, 2013). However, women have little control over whether their HIV-positive male partners will have an HIV test, agree to take ART and to take their ART with high adherence.

### **Medical male circumcision**

Voluntary medical male circumcision (VMMC) is an important biomedical HIV prevention option for heterosexual men and has been shown to reduce the risk of female-to-male transmission of HIV by up to 66% (Siegfried, Muller, Deeks, & Volmink, 2009), with three independent randomised controlled trials in South Africa (Auvert et al., 2005), Kenya (Bailey et al., 2007) and Uganda (Gray et al., 2007) showing consistent findings. Although VMMC may provide some indirect benefits to women over time by reducing exposure to HIV, there is limited epidemiological evidence showing a direct protective effect of male circumcision on reducing HIV in women (Weiss, Hankins, & Dickson, 2009).

VMMC has become a priority component of HIV prevention programmes and is being scaled up in 14 priority countries that have a high HIV burden. About 10 million men in Eastern and Southern Africa are estimated to have undergone VMMC for HIV prevention since its implementation in 2009.

In South Africa VMMCs have increased from just 5 190 in 2008 to approximately 2.1 million by January 2015 (Careworks, 2016). In the Orange Farm district, the scale up of VMMC from 12% in 2007 to 53% in 2010 has led to a 19% reduction in HIV prevalence and up to 61% reduction in incident HIV infection (Auvert et al., 2013), providing evidence of a population level impact of circumcision.

Despite these remarkable achievements, more needs to be done to reach the ambitious global target of 20 million circumcisions (80% coverage) by 2020 (UNAIDS, 2014a, b). Targeting of VMMC to young men, demand creation for and uptake of VMMC by early adopters are some of the innovative approaches being utilised in sub-Saharan Africa to increase uptake of VMMC (Montague et al., 2014). Other innovative strategies being implemented to help countries accelerate access to VMMC services include simplified procedures and new circumcision devices, which may facilitate task-shifting of circumcisions from doctors to mid-level health professionals, including nurses (Mutabazi et al., 2014; Sokal et al., 2014).

### **Treatment of sexually transmitted infections**

STIs are a major contributor to the global burden of disease, causing substantial illness, severe medical complications and infertility. The presence of STIs, particularly those that cause genital ulceration or inflammation has been shown to play an important role in the transmission of HIV by increasing the infectiousness of people living with HIV and the susceptibility of HIV-negative individuals (Chen et al., 2007; Cohen, 1998; Wald & Link, 2002). HSV-2, for example, has been shown to be associated with a 2.8 and 3.4-fold increased risk of HIV acquisition in men and women respectively (Glynn, Biraro, & Weiss, 2009). Accumulating data indicates that human papillomavirus (HPV), one of the most common STIs worldwide, may also be an important cofactor in HIV acquisition in men and women. A systematic review and meta-analysis in 2012 showed that the overall risk of HIV acquisition in women doubled when they had a prevalent HPV infection (hazard ratio [HR] = 2.06 (95% CI: 1.44–2.94) (Houlihan et al., 2012). The presence of bacterial vaginosis has also been linked to an increased risk of HIV infection. A meta-analysis of studies that included 30,739 women shows that bacterial vaginosis infection was associated with a 1.6-fold increased risk of HIV infection (Atashili, Poole, Ndumbe, Adimora, & Smith, 2008). The burden of these STIs is particularly severe in sub-Saharan Africa and especially in young women.

An improved STI case management intervention, which was implemented in the early stages of the HIV epidemic, was shown in one community randomised controlled trial (The Mwanza trial) in rural Tanzania to reduce incident HIV infections among 12 537 individuals by 42% (Grosskurth et al., 1995). Eight subsequent STI treatment trials were unable to replicate this finding, possibly due to the maturing HIV epidemic and lower-risk behaviours in the populations participating in the trials (Korenromp et al., 2005). Nevertheless, treatment of STIs remains an important public health priority whether it affects HIV transmission or not, in epidemiological settings that have subpopulations with a substantial burden of curable STIs. Since STIs and HIV have a common route of transmission, STI treatment should be included as part of HIV prevention programmes for both men and women in these settings.

### **HIV prevention combinations for young women**

Several evidence-based behavioural, structural and biomedical HIV prevention interventions are available and are described above. Currently, limited data are available on how these separate interventions will work when implemented together. It is therefore challenging to define what an effective combination HIV prevention package should look like across contexts.

Given that HIV epidemics in communities are complex and comprise a mosaic of different risk factors and different routes of transmission, a single “one size fits all” approach to HIV prevention is unlikely to be able to alter the epidemic trajectory. Rather, a mixture of prevention strategies that combines biomedical, behavioural, and structural interventions and are tailored for specific key locations and priority populations is needed. The optimal combination will vary by population and location and different combinations

may be needed even in the same country. Several trials are currently underway to study various combinations of strategies in different populations and settings will expand the evidence base for impact (Table 2).

Based on available evidence, an HIV prevention package for a young woman in Africa, could include HCT with linkage to ART (if positive), prevention of mother-to-child programmes (if pregnant) or PrEP (if negative), condom promotion, treatment of STIs (in regions with a high burden of STIs), behaviour change communication that reinforces key sexual risks such as having multiple partners and age-disparate sex, social protection interventions including cash transfer or other economic empowerment strategies in some settings, gender-based violence education and VMMC (for her male partner) (Figure 1). As with contraceptive choices, the package of HIV prevention options ultimately adopted by a woman will depend on her personal situation and may even change throughout her life course or her relationship status.

Despite the growing number of HIV prevention options available, the number of strategies that empower women to directly control their risk of HIV remain limited. Therefore, ongoing research for new HIV prevention technologies, particularly ones that can be controlled by women, remains an essential tool in the fight against the HIV epidemic in sub-Saharan Africa.

## HIV prevention strategies under development

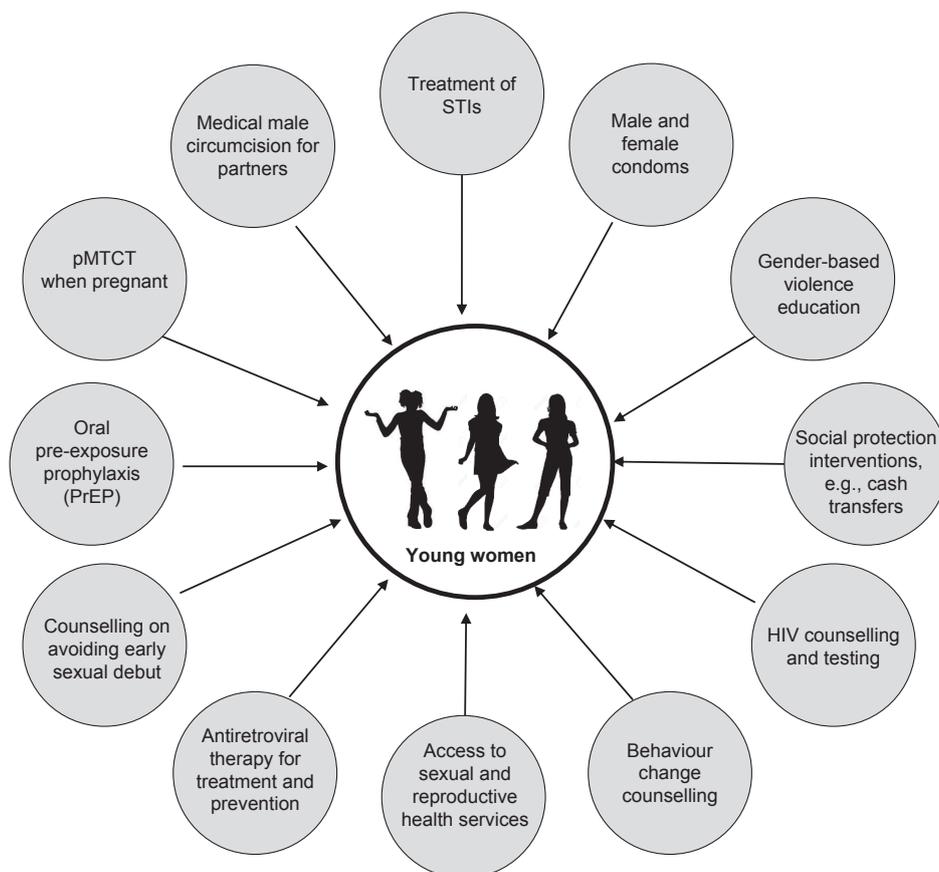
### Long-acting biologicals

Other promising HIV prevention strategies being explored are long-acting biologicals. Long-acting antiretroviral injectable agents such as rilpivirine (TMC278) and cabotegravir (GSK1265744), which can be administered every 2 to 3 months, are in early stages of clinical testing as potential microbicide/PrEP agents. Several potent and broadly neutralising antibodies (bNAbs) such as VRC01, PGT121 and CAP256-VRC26.25, which have been shown to prevent infection and reduce viral load in non-human primates, are also being developed as a passive immunisation prevention strategy in humans.

If these new products are shown to be effective, they have the potential to overcome the adherence challenges of topical and oral PrEP and could substantially expand HIV prevention options, particularly for young women.

### Vaccines

A safe and efficacious vaccine to prevent HIV infection remains an important global goal but its development has proved challenging. Glimmers of hope that an HIV vaccine is possible emerged with the findings from the RV144 trial in Thailand (Rerks-Ngarm et al., 2009) (Table 1), which showed a protective effect of 31.2% (95% CI, 1.1 to 52.1;  $P = 0.04$ ). Since the RV144 trial, important progress is being



**Figure 1:** HIV prevention for young women — examples of prevention options that could be used in combination (as appropriate) to prevent HIV infections in young women

**Table 2:** Examples of ongoing combination HIV prevention trials in sub-Saharan Africa

Country	Sample size / population	Project	Combination intervention being assessed
Kenya	1 215 men and women	Gender-specific HIV packages for male and female youth delivered using community-based mobile health teams	<ul style="list-style-type: none"> <li>• HTC (males and females)</li> <li>• Facilitated linkage to care for HIV+: ART/pMTCT (males and females)</li> <li>• Contraception (females)</li> <li>• PrEP (females)</li> <li>• Conditional cash transfers (females)</li> <li>• Condoms (males)</li> <li>• VMMC (males)</li> <li>• Mobile HTC</li> <li>• Facilitate access to treatment and retention in care</li> <li>• Sensitivity training for HIV clinical care providers</li> <li>• Text messages to promote adherence to care and ART</li> <li>• Venue-based peer education and condom distribution</li> <li>• A community drop-in-centre to promote cohesion and collective action to reduce stigma and discrimination.</li> </ul>
Tanzania	500 women	Community-based Combination HIV Prevention in Tanzanian Women	<ul style="list-style-type: none"> <li>• Condom-compatible lubricant choices</li> <li>• Couples HIV counselling and testing (CVCT)</li> <li>• Staff and provider MSM and LGBT sensitisation training</li> <li>• HCT</li> <li>• Linkage to care</li> <li>• PrEP</li> </ul>
South Africa and Zambia	100 MSM	Comprehensive HIV Prevention Package for MSM in Southern Africa	<ul style="list-style-type: none"> <li>• ART for prevention (CD4 &lt;500) plus couples counselling</li> <li>• Couple-focused counselling for decreasing sexual risk behaviour and enhancing adherence with ART</li> <li>• VMMC</li> <li>• PrEP</li> <li>• HCT</li> <li>• Condoms,</li> <li>• Contraceptive counselling</li> </ul>
Lesotho	HIV sero-discordant heterosexual couples	Enhance Prevention in Couples (EPIC)	<ul style="list-style-type: none"> <li>• HCT services during 2 annual HCT campaigns</li> <li>• ART for adults according to local standard of care</li> <li>• Expanded ART for adults (above and beyond the local standard of care)</li> <li>• VMMC</li> </ul>
South Africa	150 HIV-uninfected adolescents (15 to 19 years)	CHAMPS: Choices for Adolescent Methods of Prevention in South Africa	<ul style="list-style-type: none"> <li>• Strengthening of PMTCT services, including Option B+</li> <li>• Universal HCT</li> <li>• Active linkage to care for individuals diagnosed as HIV-infected, with immediate eligibility for ART</li> <li>• Promotion of VMMC and PMTCT services</li> <li>• Provision of condoms</li> <li>• Strengthening of HIV testing and services at health facilities and other venues</li> <li>• Strengthening of VMMC and pMTCT services available in the community</li> <li>• Treatment of STIs</li> <li>• Home-based HIV testing</li> <li>• Targeted referrals for VMMC</li> <li>• ART</li> <li>• STI treatment</li> <li>• Couples counselling</li> <li>• Oral PrEP plus topical PrEP (if effective)</li> </ul>
Botswana	Community-based sample from 30 communities and HIV-infected persons in Combination Prevention communities who are not yet on ART	Evaluation of the impact on HIV incidence of expanding population coverage of an integrated set of HIV prevention interventions	
South Africa and Zambia	52 500	PopART/HPTN 071: A strategy linking household-based HIV testing to universal community-based HIV treatment	
South Africa and Uganda	2 075	Methods for Prevention Packages Programme	

Source: www.AVAC.org. Adapted from AVAC Report 2012 and data from clinicaltrials.gov

made in the vaccine field. Specifically, scientific advances in understanding the types of immune responses that may contribute to a vaccine's protective effect (Corey et al., 2015; Liao et al., 2013; Moore et al., 2012), discovery of new sites for neutralisation, including a site at the gp120-gp41 interface, isolation of several new potent neutralising monoclonal antibodies (Doria-Rose et al., 2014), and highly effective new strategies to deliver HIV vaccines (Hansen et al., 2013) have been identified. Pre-clinical studies have also shown that bNAbs may also have therapeutic benefits (Barouch et al., 2013).

In 2015 the Pox-Protein Public Private Partnership (P5) launched a trial in South Africa that will assess a modified version of the RV144 vaccine strategy. Several early phase I and II vaccine trials are underway testing a variety of candidates and vaccine concepts (AVAC, 2015). Research on bNAbs is also accelerating, with potential promise for future prevention, treatment and cure strategies.

### Scaling up prevention interventions

To realise the goal of ending the AIDS epidemic as a public health threat by 2030, the number of new HIV infections globally will need to be drastically reduced to fewer than 500 000 by 2020 (UNAIDS, 2014b). To achieve this ambitious target, proven HIV prevention strategies will need to be rapidly scaled up and focused on the populations and locations in greatest need.

Mathematical modelling of data from Kenya shows how the impact of combination HIV prevention can be enhanced through prioritisation of the population and locations in greatest need. The universal implementation of a combination HIV prevention package in Kenya that includes VMMC, behaviour change communication, early ART and PrEP could reduce the total number of new HIV infections by 40% during a 15-year period. However, when the HIV prevention package was tailored to reflect patterns in local epidemiology, the overall impact was increased by 14% during the 15 years (Anderson et al., 2014).

The estimated resources required to achieve the ambitious goal of ending the AIDS epidemic as a public health threat by 2030 are substantial. UNAIDS estimates that domestic and international investment in HIV programmes will need to increase from an estimated US\$19.2 billion available in 2014 to US\$26.2 billion by 2020 (UNAIDS, 2016). Whether low- and middle-income countries will be able to meet the estimated 450% and 530% increase in funding needed is questionable.

### Conclusion

Despite substantial progress in reducing HIV infections, the epidemic continues to spread in some locations and mainly in key and vulnerable populations. A range of behavioural, structural and biomedical HIV prevention options are available. Scaling up these proven HIV prevention strategies in combination will be the most effective way to reduce the number of new HIV infections to fewer than 500 000 by 2020 (Piot et al., 2015). The combination of HIV prevention interventions needed will vary depending on cultural context, the population targeted, the location and the stage of the epidemic.

Appropriate HIV prevention strategies for young women in Africa include HCT, with linkage to ART (if positive) or PrEP (if negative), condom promotion, treatment of STIs, behaviour change communication, social protection interventions including cash transfer or other economic empowerment strategies in some settings as well as ART for HIV-positive male partners, gender-based violence education and VMMC (for her male partner). The development of new long-acting biologicals for HIV prevention as well as a safe and effective HIV vaccine will substantially advance the progress towards eliminating HIV as a public health threat.

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