Purpose of review
Young women in sub-Saharan Africa bear a disproportionate HIV burden. They urgently require new HIV prevention approaches that they can use. This review provides an overview of the use of antiretrovirals for HIV preexposure prophylaxis (PrEP), highlighting some of the challenges with this technology and explores the potential role of mAbs for HIV prevention in women.

Recent findings
Recent findings on the initial steps in viral entry and establishment of a productive local infectious nidus in the vaginal epithelium has provided important clues for HIV prevention in the female genital tract. Topical and oral formulations of antiretroviral drugs have been shown to prevent HIV infection in women with varying levels of success, depending principally on adherence. Further, several new broad and potent mAbs have been isolated over the last 5 years. Nonhuman primate studies demonstrate that broadly neutralizing HIV mAbs can protect rhesus macaques from simian immunodeficiency virus–HIV chimera (SHIV) infection. These findings have created newfound enthusiasm for passive immunization as a potential prevention strategy for women.

Summary
If potent broadly neutralizing mAbs are effective in preventing HIV infection in women, this outcome could fill an important gap in HIV prevention technologies for young women, especially in Africa.

Keywords
HIV prevention, mAb, passive immunization, young women
many other countries in southern Africa resulting in ‘generalized’ epidemics, as described by UNAIDS. One of the key drivers of the continued spread of HIV infection in this region is the age–sex difference in HIV acquisition between young boys and girls [5]. Temporal trends of the evolving HIV epidemic in this region have been monitored mainly through annual seroprevalence surveys in pregnant women. In South Africa, HIV prevalence among pregnant women has increased from 0.8% in 1990 to 29.5% in 2012 [7]. Despite the rapid scale-up of antiretroviral therapy provision in South Africa from less than 50,000 in 2004 to about 2.6 million in 2012, HIV prevalence among pregnant women utilizing public sector facilities has remained stable at about 29.5% for the past 7 years. In the context of having the largest AIDS treatment programme in the world, South Africa has not yet witnessed an increase in HIV prevalence reflecting the survival benefits of antiretroviral therapy because of the continued high mortality rates, especially in HIV-tuberculosis (TB) coinfected patients. In 2012, HIV prevalence rates among pregnant women exceeded 40% in five subdistricts within South Africa [7]. In one of these high-burden subdistricts, annual cross-sectional surveys of antenatal clinic attendees demonstrate a concerning rise of HIV infection among young women below the age of 20 years, increasing from 13.0% in 2007 to 15.1% in 2010 and 22.1% in 2013. The survey in 2013 revealed that HIV prevalence was 39.7% among pregnant women aged 20–24 years and 63.1% among those aged 25–29 years. Several cohort studies conducted in South Africa between 2002 and 2010 [8–15] demonstrate high HIV incidence rates (Table 2). In the CAPRISA 004 trial, wherein intensive monthly risk reduction counselling was provided, the HIV incidence rate was 9.1 per 100 women-years among 18-to 40-year-old women in the placebo arm [16].

### WHAT MAKES YOUNG WOMEN MORE VULNERABLE TO HIV?

A complex interplay of biology, sex-power disparities, social, political and economic factors contribute to the excess vulnerability of young women to HIV infection compared with men. The per-act probability of acquiring HIV for women is estimated to be 1 per 1000 sexual encounters compared with 1

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### Table 1. HIV prevalence (%) among people 15–24 years old, by sex in selected African countries, 2008–2011

<table>
<thead>
<tr>
<th>Country</th>
<th>HIV prevalence (%)</th>
<th>Fold difference</th>
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<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>South Africa</td>
<td>14.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Lesotho</td>
<td>13.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Mozambique</td>
<td>13.5</td>
<td>10</td>
</tr>
<tr>
<td>Botswana</td>
<td>11.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Zambia</td>
<td>9.4</td>
<td>4.9</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>8.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Malawi</td>
<td>5.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Kenya</td>
<td>5.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Central African Republic</td>
<td>4.8</td>
<td>0.9</td>
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<tr>
<td>Tanzania</td>
<td>4.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Congo</td>
<td>2.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Rwanda</td>
<td>1.8</td>
<td>0.4</td>
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</tbody>
</table>

Data adapted from [5].
per 2000 encounters for the male partner in peno-vaginal sex [17]. Thus, women appear to be biologically more likely to become infected than men. Factors such as intimate partner violence [18] and early sexual debut [19] have also been shown to be associated with an increased risk of acquiring HIV in women. Sexual debut also marks the initial exposure to a number of sexually transmitted pathogens, including viruses such as herpes simplex virus type-2 and human papilloma virus that also increase the risk of HIV acquisition [20–23]. Teenage pregnancy rates are also high in sub-Saharan Africa, leading to girls dropping out from school, which itself is a risk factor for HIV acquisition [24]. Although controversial, some studies have suggested that the long-acting injectable hormonal contraceptive, Depo-Provera (DMPA), may be associated with an increased HIV risk [25], and this effect may be further amplified in younger women. Data from several African countries have shown that young women who have sexual partners who are 5–10 years older than them are at an increased risk for acquiring HIV [26–30]. In some cases, young women, particularly those from impoverished backgrounds, form relationships with older men for financial and social security [31]. Young people are also more likely to be inexperienced in sexual risk-taking and they may not be able to negotiate condom use with older partners.

### EXISTING HIV PREVENTION TECHNOLOGIES

Several effective prevention strategies are already available but are often not being implemented at the necessary scale and magnitude to those most in need. For example, although condoms are highly effective in preventing HIV, UNAIDS estimates that in sub-Saharan Africa, each sexually active individual only has access to about eight male condoms per year [1].

Further, traditional behaviour change prevention programmes, based on the ABCC (Abstinence, Be faithful, Condoms and Circumcision) approach, have had a little, if any, impact in women in sub-Saharan Africa. Programmes promoting abstinence have been unsuccessful in delaying the age of sexual debut. Data from a national HIV prevalence, incidence and behaviour survey in South Africa show that rates of reported early sexual debut, that is, before the age of 15 years, has remained almost

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**Table 2. HIV incidence rates from cohort studies that have been conducted in South Africa between 2002 and 2010**

<table>
<thead>
<tr>
<th>Years of study conduct</th>
<th>Population (age range in years)</th>
<th>Location</th>
<th>HIV Incidence rate (per 100 person-years) [95% CI]</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.0 in women ≤24 years old</td>
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<td></td>
<td></td>
<td></td>
<td>6.0 in women 25–34 years old</td>
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<td></td>
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<td></td>
<td>3.6 in women ≥35 years old</td>
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<td></td>
<td></td>
<td></td>
<td>5.3 [2.7–9.2] in Durban</td>
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<td></td>
<td></td>
<td></td>
<td>6.2 [3.4–10.5] in Hlabisa</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>6.9 [4.8–9.6] ≥18 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.4 [2.6–13.2] in urban women</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>17.2 [2.1–62.2] in urban women &lt;20 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.7 [4.1–13.2] in Hlabisa</td>
</tr>
<tr>
<td>2007–2008</td>
<td>598 sexually active HIV-negative women (18–35)</td>
<td>North-West Province and Western Cape, South Africa</td>
<td>6.0 [3.0–9.0] in North-West</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.5 [1.8–7.1] in Western Cape</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3.0 [0.4–10.8] in Rustenburg</td>
</tr>
</tbody>
</table>

CI, confidence interval.
stable at 10% between 2002 and 2012 [6]. Further, abstinence is an inappropriate prevention strategy for women in relationships or who are married. Sexual inequality and the threat of sex-based violence also limits a woman’s ability to convince her male partner to use condoms, to remain faithful or have an HIV test. Medical male circumcision, which is a proven HIV prevention strategy for men [32], has a little immediate direct benefit to the woman [33]. Although male circumcision could potentially impact on HIV incidence rates in women in the long-term through diminished exposure to HIV because of lower HIV levels among circumcised men, this prevention option is not controlled by women.

The development of women initiated HIV prevention strategies could make a potentially important impact in this ‘key population’, as it offers women who are unable to negotiate safer sex with their partner an option to remain HIV uninfected. Two promising HIV prevention options that could be of direct benefit to women are topical (microbicides) and oral antiretroviral drugs administered as preexposure prophylaxis (PrEP).

Microbicides, which are chemical products designed to prevent the sexual acquisition of HIV, have been in development since the early 1990s. Although no microbicides are licensed or available yet, the CAPRISA 004 tenofovir gel trial [16] provided proof-of-concept that topical antiretroviral microbicides, when used before and after sex, can reduce sexual transmission of HIV and herpes simplex type-2 (HSV-2). The overall protective effect of tenofovir gel against HIV was a modest 39%, with the most adherent women achieving 54% protection and those with genital tenofovir concentrations in excess of 1000 ng/ml demonstrating 74% protection [34]. A confirmatory study of the effectiveness of tenofovir gel, the FACTS 001 [35] trial, is currently underway and the results are anticipated in the first quarter of 2015. A successful outcome from the FACTS 001 trial could lead to licensure of tenofovir gel as the first microbicide for HIV prevention.

Oral antiretrovirals as PrEP have also been shown in clinical trials to reduce the risk of HIV acquisition in HIV-negative partners in discordant couples [36], MSM [37], at-risk men and women [38], and people who inject drugs (PWID) [39,40] between 44 and 75%. The initial studies tested daily oral antiretrovirals for PrEP. In late 2014, a trial in the UK and one in France testing coital dosing of oral PrEP announced that their Data Safety Monitoring Boards had recommended the trials stop as participants in the active arms had shown significant benefits that the placebo groups could no longer be justified. Despite the potential impact that PrEP could have on the epidemic, only the USA has approved the oral antiretroviral, Truvada, as an HIV prevention option [41]. Scale-up of this option has, however, been suboptimal.

Apart from the unavailability of PrEP in most countries, several other challenges could hinder the rapid scale-up of PrEP. The most significant challenge in using antiretrovirals either as microbicides or as oral PrEP is inadequate adherence to the prescribed dosing regimen. Several microbicide and PrEP trials, testing the same products, have produced vastly different findings. The failure to demonstrate a protective effect in some of the trials has been ascribed to suboptimal adherence. For example, in the FEM-PrEP trial [42], only 24% of the women allocated to the daily oral Truvada [a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC)] group had detectable drug levels. Similarly, in the VOICE trial, only 25, 29 and 30% of women allocated to the daily tenofovir gel, daily oral TDF and daily oral TDF/FTC groups, respectively, had detectable drug levels [43]. Even in successful trials, the degree of adherence directly impacts on the effectiveness of the intervention. In the CAPRISA 004 trial for example, the effectiveness of tenofovir gel increased to 54% when women used the gel according to the dosing strategy in more than 80% of all sexual encounters but was only 28% when the gel was used less than 50% of the time [16]. A case-control study of the iPrEx trial showed that effectiveness was increased to 90% [95% confidence interval (95% CI) 71–98, P < 0.001] in those with a detectable drug [44].

In addition to impacting on the effectiveness, suboptimal adherence could also lead to increased resistance. Thus far, the concerns about resistance have not been demonstrated empirically, but are likely to occur in programmatic scale-up. An additional concern relates to therapeutic success rates in patients with breakthrough infections following PrEP. Data from seroconverters in CAPRISA 004 demonstrate no impact of topical antiretrovirals used as PrEP on disease progression [45] or therapeutic success rates. A separate concern about resistance is the use of the same drugs (e.g. tenofovir) in therapy and prevention and some consideration about setting aside a class (or classes) of antiretrovirals for use in prevention only is warranted. A wider array of HIV prevention options and ones that overcome the adherence challenges are required. Long-acting, slow release products that are less dependent on user compliance compared with oral or gel formulations are already in development. Examples of such products include the monthly intravaginal ring containing the antiretroviral drug,
dapivirine, and the long-acting injectable antiretroviral agents such as rilpivirine and cabotegravir, which are administered every 2–3 months. The monthly dapivirine ring studies underway by MTN and IPM are in advanced stages of clinical trial testing and offer another potential HIV prevention option for women who are unable to use products that require daily or intermittent dosing. Results from these studies are anticipated in the second half of 2015.

THE POTENTIAL OF BROADLY NEUTRALIZING MABS FOR HIV PREVENTION

The use of mAbs to treat human diseases, particularly cancer, is a rapid expanding therapeutic strategy with substantial new commercial potential. To date, only one mAb, Palivizumab (trade name, Synagis), has been licensed for an infectious disease and is used to prevent lung disease caused by respiratory syncytial virus. Given the difficulties in designing an HIV vaccine able to stimulate protective antibodies, the mass-production of mAbs opens up the possibility of testing them as passive immunotherapy. mAbs are also being tested as a drug for treating HIV infection.

Large numbers of highly potent and broadly cross-reactive neutralizing antibodies (bNAbs) have been isolated from several HIV-infected donors over the past 5 years [46**]. Collectively, these mAbs target five to six conserved neutralization-sensitive epitopes on the HIV-1 envelope including sites on gp120, the CD4+ binding site (CD4bs), glycans on the V1, V2 and V3 loops, the membrane proximal external region (MPER) of gp41 and epitopes that span gp120 and gp41 [47**]. Those that target V3 and V1V2 glycans show the highest potency (IC50 of 0.01–1 μg/ml) while those targeting the MPER and CD4bs are generally broader (neutralize >90% of global isolates).

Several challenge studies have shown that broadly neutralizing mAbs can both protect rhesus macaques from simian immunodeficiency virus (SIV)–HIV chimera (SHIV) infections as well as treat, and possibly cure, macaques with SHIV infections. Studies using the SHIV model in macaques have shown that these mAbs can provide sterilizing immunity against both high-dose and repeated low-dose challenge [48,49]. In particular, PGT121, an antibody that targets glycans in and around the V3 region, demonstrated protection from a single high-dose vaginal challenge with SHIV SF162P3 [50]. All animals that received 1 mg/kg and more than half that received 0.2 mg/kg were protected, consistent with the high potency of PGT121 [50]. Other studies have highlighted the potential for using bNAbs in passive immunization strategies, with immunotherapy in some cases resulting in durable viral control [51*,52**]. These findings provide a strong rationale for human passive protection and therapeutic trials using mAbs and a number of such studies are planned. Several of the mAbs are currently being cloned and produced for preclinical and early clinical testing.

WHY MABS COULD BE A SUITABLE HIV PREVENTION OPTION FOR WOMEN

If mAbs are shown to be well tolerated and efficacious in humans, they could be long-acting HIV-specific prevention strategies as an alternative to current antiretroviral strategies that require daily or intermittent administration. As mAbs may provide protection for a few months after a single administration, this could be a more effective option, as it will not depend on adherence to the same extent as daily pill-taking or coital gel applications. This strategy would be cost effective and patients would only need to visit the clinic every few months to receive their treatment/prophylaxis. Another advantage that a long-acting antibody product offers is that its administration would be unrelated to sex. Further, an mAb could potentially be formulated for systemic or topical application. A topical formulation would produce a product with fewer side effects and could result in much higher levels of mAbs at the site of infection. An injectable product leads to detectable antibodies in the genital tract at a level sufficient in monkeys to protect even against high-dose genital challenge.

A further advantage of mAbs for HIV prevention is that regardless of antiretroviral drugs being used for treatment, these mAbs could be effective against all viruses, including antiretroviral-resistant viruses. To reduce the potential development of resistance to mAbs, combinations of antibodies would be preferable and different antibodies could be used for prevention and treatment.

CONCLUSION

Given the high burden of HIV infection among young women in sub-Saharan Africa and the limited prevention options available, the development of novel HIV prevention technologies such as mAbs, which could be administered as a once-monthly topical application or a three-monthly injection,
Antibodies for prevention and therapy

could be a game changer in the HIV epidemic in Africa.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
• of outstanding interest


This study explores passive immunotherapy in animal models and suggests that bNAbs may become a valuable addition to the armamentarium of drugs that work against HIV-1.

This study describes a set of human mAbs that recognize a glycan-dependent epitope on the prefusion conformation of gp41.


This study shows that immunotherapy or a combination of immunotherapy as well as conventional antiretroviral drugs might be useful as a treatment for chronically HIV-1 infected individuals experiencing immune dysfunction.

This study demonstrated a profound therapeutic effect of potent neutralizing HIV-1 specific mAbs in SHIV-infected rhesus monkeys as well as an impact on host immune responses.