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Preventing HIV in women in Africa

Frances M Cowan[1,2], Maryam Shahmanesh[3], Paul A Revill[4], Joanna Busza[5], Euphemia L Sibanda[1,2], Sungai T Chabata[2], Natsayi Chimbindi[6], Tamara Choola[7], Owen Mugurungi[8], James R Hargreaves[5], Andrew N Phillips[3]

Affiliations:

1 Liverpool School of Tropical Medicine, UK

2 Centre for Sexual Health and HIV AIDS Research (CeSHHAR) Zimbabwe, Zimbabwe

3 Institute of Global Health, University College London, UK

4 University of York, UK

5 London School of Hygiene and Tropical Medicine, UK

6 Africa Health Research Institute, South Africa

7 Afrocab Treatment Access Partnership (AfroCAB)

8 Ministry of Health and Child Care Zimbabwe

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Abstract

HIV incidence is declining globally, but around half of all new infections are in sub-Saharan Africa — where adolescent girls and young women bear a disproportionate burden of new infections. Those who sell sex are at particularly high risk. Despite declining incidence rates and availability of effective biomedical prevention tools, we are not on track, globally or in Africa, to achieve UNAIDS 2025 prevention targets. For those at risk, interventions that strengthen their motivation, capabilities and access to all available HIV prevention technologies are critical — for adolescent girls and women in particular, but also for epidemic control more broadly. Exciting possibilities for scaling up new and highly effective prevention technologies are close, but delivery, implementation and financing models need to be developed and urgently evaluated, in partnership with communities, or these opportunities may be lost. Here, we discuss the evolving landscape of biomedical prevention technologies for women in Africa, their implementation and financing, as well as priorities for HIV prevention research in this setting.

Introduction

Between 2010 and 2023, global HIV incidence decreased by 39% to 1.3 million new infections per annum, (1) far short of UNAIDS' target of 370,000 by 2025. Currently, just under half of all new infections are in Sub-Saharan Africa (SSA). As elsewhere, changes in incidence within SSA vary by region, with slower declines in Western and Central Africa (46%) compared to Eastern and Southern Africa (59%). The absolute number of new infections, however, remains over twice as high in Eastern and Southern Africa (450,0000) than Western and Central Africa (190,000).(2, 3)

Across the African continent, adolescent girls and young women carry a disproportionate burden of new HIV infections. (4) This is in part due to changing demographics; 40% of Africans are aged <15 years.(5) Adolescent girls and women who exchange sex for gifts or money are at particularly high risk.(6) Women at high risk of HIV acquisition also have high prevalence of other sexually transmitted infections (STI) (including chlamydia, gonorrhoea, trichomonas and herpes)(7) as well as for unintended pregnancy, which is often a greater concern than HIV.(8) Enabling all women at high risk of HIV acquisition to protect themselves is critical for the individuals themselves and for epidemic control more broadly.

The global community is not on track to achieve UNAIDS 2025 prevention targets despite availability of highly effective prevention tools including condoms,(9) pre-exposure prophylaxis (PrEP), post exposure prophylaxis (PEP) and tools to enable those with HIV to be rapidly diagnosed and started on antiretroviral therapy. The latter includes cheap point of care HIV lateral flow tests that can be provider or self-delivered, (10) rapid treatment initiation with highly effective drugs that lead to viral suppression (when adhered to) in people living with HIV,(11) which substantially reduces transmissibility(12).

The Global HIV Prevention Coalition has developed a ten step road map(14) to support countries to accelerate progress towards effective prevention coverage. This includes using data to identify gaps and monitor programme coverage and quality in real time, focusing on 'precision prevention' i.e. tailoring services and support to individuals or groups, reducing access barriers and creating an enabling environment. The HIV prevention cascade can be used as a framework to guide effective coverage(15, 16) and can help to identify key reasons for gaps at each step of prevention (**Box 1**). Such guiding frameworks and models can help to inform prevention strategies but need to be informed by, and adapted to, local contexts.

In this Review, we summarize the current epidemiological trends and the effectiveness of ongoing prevention strategies and their implementation among women in Africa. We also

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discuss how the prevention landscape might evolve with the introduction of additional prevention technologies and suggest priorities for future research.

Populations at high risk of HIV acquisition

UNAIDS estimates that 25% of all new infections that occurred across SSA in 2022 were among key populations and their sexual partners(6, 17). UNAIDS defines key populations as those people who are at higher risk of HIV and other health issues due to their behaviours; this includes female sex workers.(18, 19) HIV incidence among female sex workers is nine times higher than among all women, with this difference over twenty times greater in Western and Central Africa and five times greater in Eastern and Southern Africa.(20). Young women who sell sex are especially vulnerable, because they experience relationship power imbalances due to their age as well as their gender. All women who sell sex do so against a background of intense stigma and discrimination, exacerbated by criminalisation of sex work.(21) These challenges are likely to increase as a result of the recent erosion of sexual and reproductive rights in parts of Africa, the impact of climate change, and the rise in conflicts, all of which negatively affect engagement with prevention services.(10)

As HIV epidemics become better controlled across the continent, the relative importance of these 'key' populations is likely to increase. In this scenario, failure to keep sex workers healthy could result in in repeated outbreaks of HIV as a result of direct or indirect transmission through sex work.(22) Modelling suggests that increasing the intensity of HIV prevention programmes for female sex workers in SSA would offer cost-effective and beneficial impact on population incidence. (23)

On the other hand, half of all new infections in SSA are in the general population and while many of the risk factors for incident infection are known (e.g. place of residence, young age, STIs, non-co-habiting with sex partners, selling sex, violence), general population prevention services have struggled to reach those at highest risk who are not easily identifiable. (24, 25) Importantly, not all adolescent girls and women are equally at risk. In an analysis of population-representative surveys conducted across Africa between 1985-2020, the proportion of women reporting ever having sex before age 18 varied by region from under 25% to over 77% (highest in west and central Africa) and the median age of sexual debut was above 18 in both east and southern Africa — the region with highest rate of new infections (although there is considerable within-region variation).(26) Without doubt, new approaches are required. Evidence from the Isisekilo Sempilo

trial in rural South Africa showed that offering home-based sampling for STI testing and integrated sexual and reproductive health combined with HIV mobile services, increased uptake of HIV prevention by 60%(27). Other models offer PrEP and family planning in the same facilities but from different providers. (28, 29) However, these integrated models have not been scaled up for primary HIV prevention delivery in SSA. (30)

Some of those at highest risk are likely individuals who sell sex but do not identify as sex workers (**Figure 1**). A review from the mid-2000s found that when women in Africa were asked (in demographic and health surveys) about exchanging sex for gifts or money in the past 12 months, roughly twice as many women responded affirmatively compared to the number reporting being sex workers.(31) In Zimbabwe, young women who report selling sex but do not identify as sex workers tend to have fewer sex partners than those who do identify as sex workers, but their rate of HIV acquisition is just as high.(32) Similarly, in rural KwaZulu-Natal, South Africa, incidence of HIV infections among young women who sell sex (17% of young women overall) was 8% per annum, three times that of young women who did not report selling sex (33). A comprehensive review of over 300 social science studies exploring transactional sex in SSA observed three overlapping motivations; sex for basic needs, sex for improved social status and sex and material expression of love. Crucially, the associated risks and appropriate mitigation approaches differ between these. (34)

Expanding tailored services for key populations – for example, by introducing peer-led social and sexual network approaches – may reach this population of women who transact sex but who, as a group, are less well characterized than self-identifying female sex workers. In contrast, most current strategies seek to identify and reach high-risk individuals from within 'general population' platforms (which include many people at very low or no risk). We argue that research to explore the relative merits (and cost effectiveness) of both these approaches is needed. In addition, working cooperatively with these groups of women may help researchers to better understand who needs which services and where, and to identify optimal ways to package services, such as STI testing and sexual and reproductive health.

Other populations with high rates of HIV acquisition in SSA include tertiary education students, who report condomless sex, multiple partnerships, transactional sex, and sex while intoxicated.(35, 36) Pregnant and lactating adolescent girls and young women are another group with high HIV incidence, with new HIV infections associated with higher rates of mother-to-child transmission than preexisting HIV infections.(37) This group are relatively easy to identify and

access through maternal and child health clinics. Although PrEP is recommended for this population(38) and research shows its provision to be feasible and safe,(39) PrEP has not been adequately integrated into antenatal care (40-42).

Primary biomedical prevention strategies for women

PrEP and post-exposure prophylaxis (PEP) agents have been rolled out to varying degrees (and with varying levels of success) in African countries, while recent advances in drug development are generating longer-lasting and more-effective options. In practice, however, prevention choices for women in Africa are often limited to condoms and daily oral PrEP. In the sections below, we discuss the effectiveness, cost-effectiveness and availability of PrEP and PEP options for women in Africa. Other strategies such as preventive vaccines and broadly neutralizing antibodies are also being developed and tested, but these are not currently in a position to have real-world impact, so are not discussed here.

Pre exposure prophylaxis:

Since 2015, the WHO has recommended daily oral PrEP (43) for people at substantial risk of HIV (defined as HIV incidence greater than 3% per annum in their population group). More recently, longer-acting PrEP options – such as the monthly dapivirine vaginal ring (DVR) and injectable long-acting cabotegravir (CAB-LA; administered every 2 months)(44-47) – have been recommended and pre-qualified by WHO, and are being scaled up to varying extents across Africa. Globally, seventy-six countries have national PrEP guidelines in place, with global oral PrEP target set at 10 million individuals initiated by 2025. As of July 2024, only 7.5 million people had initiated oral PrEP globally. (48) According to the Global PrEP tracker, scale up in Africa started in 2016 and by mid 2024, 3.7 million people in Eastern and Southern Africa and 706,000 in Western and Central Africa had started oral PrEP. In South Africa, where more than 5.25 million people are eligible, only 1.35 million (<26%) had received a prescription by June 2024; effective use is likely lower.(49) PrEP roll-out is crucial to achieving targets for HIV prevention but unless careful consideration is given to implementation, for example through service integration and task-shifting, PrEP rollout could overburden already weak health systems.(50)

Qualitative and quantitative data suggest a number of barriers to oral PrEP uptake and effective continuation (**Box 2**).(51, 52) Even among self-reported PrEP users, biomarkers often show low rates of actual protection – for example, among a sample of adolescent girls and young women who were regular PrEP programme attendees in Kenya, fewer than 5% had protective plasma levels of tenofovir disoproxil fumarate (TDF; daily regimen). And among 578 female sex workers in Zimbabwe who reported current PrEP use in an end of trial survey (the AMETHIST trial) only 2 had TDF levels indicative of adherence at 4 or more doses per week. (**Figure 2**) (53-55) There is some evidence that discussing TDF levels with users can reenforce adherence. The randomized, controlled HPTN 082 trial did not show any impact of this approach, although it had only modest power to detect such differences; (56) while the INSIGHT cohort, (57) an uncontrolled study that recruited over 3000 adolescent girls and young women from several countries in Africa, showed high oral PrEP uptake (>95%) and continuation (>85% at 6 months) with this kind of communication. In this study, two-thirds of those tested at 6 months had detectable TDF; self-reported adherence aligned very well with positive results from the TDF test (in this case, a urine test) and over half the girls interviewed at six months reported that their urine TDF test result motivated them to take PrEP.

The DVR offers an alternative strategy — a female-controlled HIV prevention method for women who don't want to take tablets or have injections. It consists of a flexible silicone ring that is inserted in the vagina and slowly releases the antiviral dapivirine over the course of one month. Very little drug is absorbed systemically. In trials, the ring reduced risk of HIV acquisition by 35%, or as much as 45% with optimal adherence.(46, 47) It has been conditionally recommended by WHO since 2021 but is currently only licensed for use in a few African countries, and is not available outside implementation studies. A three-month vaginal ring is currently being evaluated. A Phase I trial to investigate the relative bioavailability of dapivirine with the monthly versus three-monthly DVR found that the latter delivers dapivirine at higher levels than the former.

Injectable PrEP is another long-lasting option that negates the need for daily pill taking. It is highly effective and widely preferred (over daily PrEP) in values and preferences studies.(58) In 2021 and 2022, large trials of injectable CAB-LA (given every 2 months) demonstrated its superiority compared to daily oral TDF in both men(44) and women.(45) Recent safety data from HPTN084 suggest CAB-LA use is safe also in pregnant and lactating women.(59) Since

2022, WHO has recommended that CAB-LA be offered as an additional prevention choice to those at substantial risk of HIV infection. CAB-LA is licensed for prevention in 53 countries worldwide and is starting to be rolled out in 11 countries in Africa.(49) However, supplies are limited and CAB-LA is not available to all who would choose it. To date, 15,000 people globally – but <3000 African women – have been started on CAB-LA.(49)

An important implication of CAB-LA scale up is that infections occurring just before CAB-LA initiation (not detectable at the time of treatment initiation) or while taking CAB-LA are difficult to detect using standard testing algorithms. This is due to altered (clinically silent) presentation of acute HIV infection in people taking CAB-LA, a phenomenon known as 'long-acting early viral inhibition'. Delayed diagnosis is associated with resistance to certain antiretroviral drugs including dolutegravir, a critical part of first-line HIV therapy regimens in most countries in Africa.(60) Modelling the cost effectiveness of CAB-LA in sub-Saharan Africa while taking account of the risk of drug resistance suggests that CAB-LA has the potential to avert more deaths over 50 years than daily oral PrEP, and would be cost effective if delivered at the same cost as oral PrEP.(61) The cost effectiveness of CAB-LA has also been studied in South Africa, which has a much higher gross domestic product per capita than most other countries in the region. CAB-LA was not found to be cost-effective when targeted to those at substantial risk unless the price could be reduced.(61-63) One model of maximum cost at which CAB-LA would be similarly cost-effective to oral PrEP (in South Africa) found a per-dose cost ranging from $9.05-$14.47, which is considerably less than current costs. The extent to which models differ in their findings of PrEP cost effectiveness relate to assumptions about the degree to which it is effectively used by individuals – mostly only during periods in which they are likely to have new condomless partners – which is uncertain. (61-63)

The injectable antiretroviral capsid inhibitor Lenacapavir is an even longer-lasting PrEP option, requiring subcutaneous injection only every 6 months. The randomised component of a large phase 3 trial (PURPOSE 1) of Lenacapavir in African women was stopped in mid-2024 following a preplanned interim analysis, because there were no incident HIV infections in the lenacapavir arm (follow up of participants continues) — while incidence in two different daily oral PrEP arms was similar to background incidence(64). This has generated excitement about the possibility of a highly effective, twice-yearly prevention technology soon becoming available. The randomised component of a second trial of lenacapavir for HIV prevention in

cis-gender men and transwomen (PURPOSE 2) was also stopped in late 2024 again for preventing incident infections and other trials in the US are due to report in 2025, evaluating Lenacapavir in women (PURPOSE 3) and injecting drug users (PURPOSE 4). One modelling study assessed the cost effectiveness of lenacapavir for HIV prevention among individuals at substantial risk in Western Kenya, Zimbabwe and South Africa.(65) The maximum price at which lenacapavir could be cost effective varied by setting and by the extent to which eligibility was extended beyond those at highest risk. Wider coverage is predicted to avert more infections but lenacapavir would have to be delivered at even lower costs to remain cost effective; lenacapavir rollout to 1.6-4.0% of the population would avert 12.3-18.0% of infections and could be implemented cost effectively at a price per-dose of $106.30 (South Africa), $21.10 (Zimbabwe), and $16.60 (western Kenya). The potential cost per dose of lenacapavir in low- and middle-income countries is not yet known, but below $40 is thought to be achievable. Researchers projecting the minimum lenacapavir pricing based on generic mass production and a Cost-Plus model found it could be manufactured in bulk for <US$100 per person per year.(66)

There is some disquiet that, without coordinated rollout of CAB LA and lenacapavir (as did happen for dolutegravir, the preferred first line antiretroviral treatment) widespread scale up will likely be delayed.(67) The Coalition to Accelerate Access to Long-Acting PrEP, which includes WHO, Global Fund, PEPFAR and other donors/advocates, has developed a plan for accelerated introduction of CAB-LA — but this plan retains the developer (ViiV Healthcare) as sole supplier in the initial period. This is a lost opportunity that advocacy groups are working to address.(68, 69) The developer of lenacapavir (Gilead Sciences, Inc) has issued licences to six generic manufacturers ahead of regulatory approval but this has also led to concerns about access and affordability.(70)

Post exposure prophylaxis (PEP)

HIV PEP as recommended by WHO is a twenty-eight-day course of antiretroviral medication, consisting of tenofovir disaproxil-lamivudine-dolutegravir (TLD)) taken within 72 hours after potential exposure to HIV.(71) (72) PEP works by halting viral replication and preventing persistent infection. There have been no RCTs assessing the efficacy of HIV PEP. Nonhuman primate studies suggest that PEP may reduce the risk of acquiring HIV by around 90%(73), with the efficacy likely to be higher the earlier PEP is initiated after sexual exposure. Based on

studies in macaques, even a single dose of prophylaxis with tenofovir alafenomide (TAF) / emtricitabine (FTC) and an integrase inhibitor (elvitegravir) before or after sex leads to over 90% protection, leading authors to conclude it is a promising HIV prevention strategy. (72) Likewise, Bekerman et al found that two doses of TAF / FTC plus the integrase inhibitor bictegravir initiated within 24 hours of exposure provided over 80% protection, greater than the protection offered with TAF / FTC alone.(74) These studies suggest that HIV PEP can reduce the risk of infection if taken quickly after exposure and for a long enough period. Animal studies suggest that 28 days of PEP may not be required to prevent infection; if PEP is started rapidly (e.g. within a day at most), a much shorter course would likely be effective, although there are no data in humans to confirm this. Also of note, PEP has the potential to act as a 'gateway' to PrEP initiation.(75)

TLD is first-line therapy for millions of people living with HIV across Africa and thus is widely available and considered safe. Although PEP has been recommended by WHO for years, in practice it is not easily accessible. It requires a prescription, and in many settings, it is reserved for people who have experienced sexual assault or an occupational exposure. WHO have recently revised their guidelines to emphasise the importance of expanding access to PEP to all who are potentially exposed to HIV, making it easily available in communities so it can be initiated rapidly after exposure.(71) Monitoring PEP use with HIV self-testing was also recommended.(48) Although there are no RCTs to confirm the impacts of this approach, its potential benefits are considered to outweigh potential harms.

Financing biomedical prevention

The scale of the challenge posed by HIV to African health systems in the 2000s and 2010s was unprecedented, with life expectancies in many countries falling (e.g., to age 45 Malawi and 33 in Zimbabwe in 2002) and wider economies buckling under the strain of the epidemic. The global community coalesced to generate funding to address this challenge. In 2002 the Global Fund for AIDS, TB and Malaria (GFATM) was established and in 2003 the United States President's Emergency Plan For AIDS Relief (PEPFAR) was launched. Today, both institutions account for almost all HIV funding in low-income African countries with high HIV prevalence

(e.g., in Malawi, Zimbabwe, Mozambique), whereas domestic funding for HIV has increased substantially only in relatively wealthier countries (e.g., South Africa, Botswana).

The global response to HIV has been an outstanding success, as evidenced by the fall in HIV infections, but there are concerns that the exceptional levels of international funding for HIV may not be sustained into the future. This is a challenging issue, as global priorities shift towards new concerns such as climate change and pandemic preparedness. International funding for HIV has flatlined in recent years(1, 76) and it is widely expected to fall in future. There are hopes that the fall can be mitigated by increased domestic funding for HIV, but this will not replace donor funding in full since countries face a myriad of other health, social and economic challenges. If funding does fall, this is likely to have adverse implications for HIV prevention, unless domestic funding can fill the gap.

Several countries have experimented with innovative financing mechanisms, such as the use of taxes/levies and debt conversion instruments, to increase the availability of domestic funds for HIV services. The Zimbabwe National AIDS Trust was established in 2000 and receives revenues from a tax on formal sector employers and employees, with 10% of proceeds going to prevention.(77) Cote d'Ivoire and Cameroon have recently agreed schemes with creditors, through the GFATM's Debt4Health Swap, for their debt burdens to be reduced with released funds being committed to national HIV responses.(78) Given the moral imperative for countries to provide antiretroviral therapy to citizens living with HIV for their rest of their lives, it has been recognized that HIV infections create a financial quasi-liability which is comparable in some African countries to management of their debt-to-GDP ratio.(79). In such a context, it makes sense for countries to target available funds to maximally reduce new HIV infections, especially amongst women and those at highest risk. To date, many of the most prominent HIV prevention programmes that focus on women have been financed primarily using international funding.

There are risks that future financing of HIV prevention services will therefore be inadequate unless domestic contributions substantially increase. This requires a combination of science and advocacy. Encouragingly, health leaders across Africa appear to recognize the challenge. For instance, African heads of state committed in 2019 to the African Leaders Meeting (ALM)

Investing in Health Declaration, aiming to increase domestic spending on health, especially to meet the challenges posed by HIV.(80) It is critical that HIV prevention continues to be bolstered, to both ease fiscal challenges and ensure population health improvement.

Accelerating effective coverage of biomedical prevention tools

As described above, we have highly effective tools for preventing acquisition of HIV (all of which have been shown to be safe) and many of these should, by now, be well embedded in health systems. In reality, however, too few people are accessing prevention tools effectively. Randomised trials in East Africa have shown that offering individuals the choice of whichever biomedical prevention method best fits their needs (oral PrEP, long-acting injectable PrEP or condoms and PEP in the event of exposure) and the option to change their choice if their circumstances or preferences change, increases coverage of high risk transmission events and results in substantially more people initiating primary prevention.(81, 82)

The challenge for new technologies, which include new drug delivery mechanisms, is that they be developed in ways that will reduce barriers to their ongoing use, such as by ensuring privacy and ease of use. Many barriers can be mitigated without new technologies but by using the ones we have better. For example, many countries have been reluctant to adopt WHO's recommendation to de-medicalise and monitor PrEP or PEP use via HIV self-tests. Similarly, task shifting of PrEP/PEP prescribing to community cadre, pharmacies and/or selfcare has not been adequate. There is resistance among stakeholders to changing existing prescribing, delivery and monitoring practices and regulations. Although such regulations are in place to ensure population safety, they are often maintained by vested interests (e.g. health care professionals' concerns about 'losing control' over certain aspects of care).(83)

One way to make PEP more widely available is to provide TLD (WHO-recommended PEP) in communities for anyone to access without prescription. This approach would need to be coupled with community education to promote PEP following condomless sex. Freely available TLD might end up being used as either PrEP by people wanting to prevent infection or by people living with HIV as treatment, allowing them to circumvent the need to go to a clinic (even though these would not be the intended uses). Phillips et al (84) modelled effectiveness and cost effectiveness of this approach; assuming a high uptake of TLD, they projected a mean reduction in general population HIV incidence in Eastern and Southern

Africa of 31% over 20 years. Non-prescription, community-based TLD was cost-effective in 90% of scenarios and cost-saving (in terms of disability-adjusted life-years) in 58% of scenarios. A range of implementation research projects are currently underway to make PEP more easily available including through pharmacies, vouchers, community cadres and 'PEP in Pocket' but none yet test removing all barriers to TLD access.(85, 86)

Multi-purpose prevention technologies combining antiretrovirals and contraception are a promising intervention for women who want to prevent HIV and pregnancy simultaneously(87). Although reported acceptability and adherence to a dual PrEP/contraceptive pill was high among adolescent girls and young women in Zimbabwe, mean adherence was too low for protection, which did not differ between the dual PrEP/contraceptive pill and taking two pills separately.(88) Ongoing studies investigating a co-formulated smaller pill may give a better picture of adherence and impact.(89) A three-month combined dapivirine-levonorgestrel vaginal ring was well tolerated with plasma and cervicovaginal levels that compared well with a dapivirine-only ring and other levonorgestrel contraceptives. (90) Other future approaches under development include a subdermal implant that can be refilled by transcutaneous injection for ultra-long-acting delivery of antiretrovirals for pre-exposure prophylaxis, as well as long acting oral prevention (91).

A major challenge is to identify and test population impact of scalable implementation strategies, to ensure effective use of available technologies while advocating for coordinated introduction of new innovations (see **Box 3** for implementation priorities). Proactively engaging communities of women will increase understanding that HIV is genuinely preventable and worth preventing. In Mysore India, for example, within the Ashodaya Samithi sex worker collective, sex workers designed and implemented PrEP roll out as an integral part of their broader sexual health and social support programme. Importantly, sex workers living with HIV were at the heart of community mobilisation for PrEP, and were able to discuss the value of remaining uninfected with HIV-negative sex workers. In stark contrast to the numerous other demonstration programs run over that period, over 90% of all potential PrEP users opted to initiate PrEP; 86% of those were retained after 16 months of whom 87% had protective levels of PrEP.(92) (93)

Separately, there has been concern about 'risk compensation' among those using biomedical prevention, whereby condom use is reduced and rates of STIs rise. Evidence for this is limited (94) as levels of condomless sex and STIs are already high in Africa and the high levels of

efficacy for HIV prevention outweigh the potential behavioural impact. PrEP services are an opportunity to provide sexual health promotion, STI testing and treatment to those at highest risk of HIV and STI acquisition.

Future research priorities

The immediate challenge for prevention research is to determine how to deploy the highly effective prevention tools already available (or near available) to ensure effective coverage among women who are at a substantial risk of infection. Evaluation of new biomedical tools including preventive vaccines will of course be required in the longer term if the goal of eradicating HIV infection is to become a reality. To maximize the impact of available and emerging technologies in the near future, equal priority must be given to efficacy and implementation research. Below, we outline key considerations for research in both these areas.

Determining the efficacy of biomedical prevention products

While the falling global incidence of HIV and growing availability of effective primary prevention tools is a cause for celebration, it has implications for research aimed at assessing the efficacy of new biomedical prevention tools. Falling incidence rates mean that trials need to recruit more people to demonstrate impact, and they must be large enough to detect benefit or equivalence compared to existing products, rather than placebo. An additional complication is that the effectiveness of oral PrEP – a likely comparator to new innovations – is highly dependent on adherence, making it difficult to estimate efficacy. All of this poses challenges to the use of traditional randomised clinical trials that require impractically large sample sizes and noninferiority designs. A consensus group of academic researchers, regulators, pharmaceutical innovators, and other stakeholders (the Forum HIV Prevention Trial Design Project) proposed estimating HIV incidence in people not on PrEP as an external counterfactual, measured using a recency infection testing algorithm — to which on-PrEP incidence in trial participants could then be compared.(95)

This approach was adopted by the recent PURPOSE-1 trial(64) which tested effectiveness of 6-monthly injectable lenacapavir and TAF by comparing prospectively-measured HIV incidence for each investigational agent to background HIV incidence among all those

screened to take part in the trial (a cross-sectional incidence cohort). HIV incidence in each drug arm was also compared to that in an active internal control group receiving daily oral TDF. This novel approach was able to demonstrate the efficacy of lenacapavir, but also confirmed the difficulty women have in taking daily oral PrEP. Therefore, it is likely that this approach be used to assess emerging antiretroviral-based products.

A similar approach could potentially be used to assess the efficacy of new vaccines or broadly neutralizing antibodies, although it is more likely that these trials will use a placebo arm but allow access to standard-of-care PrEP in all trial arms, for anyone who chooses it. Additionally, investigators might combine trial resources to determine efficacy of different agents simultaneously — as happened in PrEPVacc study, which combined trials of HIV vaccines with a trial of a novel oral PrEP agent (TAF) in women.(96)

Implementation research to develop and test models of prevention delivery

Implementation research is critical to scaling up efficacious prevention approaches in a way that provides effective coverage for those at risk of HIV acquisition. Having an effective prevention product is not in itself a guarantee of uptake. There is growing consensus that prevention needs to be demedicalised; people who use it are, after all, not ill. Thus, research on how best to remove barriers to access and use (**Box 2**) can help identify changes required at different levels of health programming. Furthermore, implementation research can investigate how advances in diagnostics and digital technologies can support shifting prevention delivery to selfcare or community cadre, safely and integrated within health programming (97-100).

Box 4 summarises priorities for future HIV prevention research that can scale up effective technologies among African women. Communities should be at the centre of prioritising, designing, implementing and evaluating interventions. Citizen science can play an important role in determining why and how deployment is failing or succeeding, as well as helping tailor deployment strategies to specific settings and populations.(101)

Conclusion

Accelerating prevention of new HIV infections among African women and their sexual partners is a global health priority. Recent declines in HIV incidence have been driven by both treatment

expansion and combination prevention, underpinned by a growing toolbox of prevention commodities combined with strong understanding of patterns of risk, and how to reach those with the greatest need.

The next phase of the response will be driven by three key pillars. First, is to strengthen the implementation of HIV prevention. Implementation research will be needed to drive innovation in developing community leadership models, strengthening delivery platforms, expanding choice (both of products and delivery platforms) and tailoring strategies to address gaps. Second, is to develop and test new products and integrate them within the prevention toolbox. Ongoing research on new longer-acting formulations of antiretrovirals, candidate vaccines and other approaches such as BNAbs will need innovative methodologies to adapt to the new prevention landscape. Third, is work to both reduce the prices of emerging products and to ensure long term financing of the response. This must be underpinned by country-specific priorities, co-financing, modelling and cost-effectiveness research to drive decision making.

References

1. Joint United Nations Programme on HIV/AIDS. The urgency of now: AIDS at a crossroads. . Geneva: CC BY-NC-SA 3.0 IGO; 2024. Available from: https://www.unaids.org/en/resources/documents/2024/global-aids-update-2024
2. UNAIDS. West and Central Africa regional profile — 2024 global AIDS update The Urgency of Now: AIDS at a Crossroads 2024 [Available from: https://www.unaids.org/en/resources/documents/2024/2024-unaids-global-aids-update-western-central-africa.
3. Joint United Nations Programme on HIV/AIDS. Eastern and Southern Africa regional profile — 2024 global AIDS update The Urgency of Now: AIDS at a Crossroads 2024 [Available from: https://www.unaids.org/en/resources/documents/2024/2024-unaids-global-aids-update-eastern-southern-africa.
4. Joint United Nations Programme on HIV/AIDS. Geneva: Joint United Nations Programme on HIV/AIDS;; 2023. https://www.unaids.org/en/resources/documents/2023/global-aids-update-2023
5. Canning D, Raja S, Yazbeck A. Africa's Demographic Transition : Dividend or Disaster? : World Bank; 2015. Available here: https://documents.worldbank.org/en/publication/documents-reports/documentdetail/802811468187135148/africa-s-demographic-transition-dividend-or-disaster
6. Korenromp EL, Sabin K, Stover J, Brown T, Johnson LF, Martin-Hughes R, et al. New HIV Infections Among Key Populations and Their Partners in 2010 and 2022, by World Region: A Multisources Estimation. J Acquir Immune Defic Syndr. 2024;95(1s):e34-e45.
7. World Health Organization. Implementing the global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022–2030: report on progress and gaps 2024. Geneva: World Health Organization; 2024. Contract No.: licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/publications/i/item/9789240094925
8. Miller LE, Zamudio-Haas S, Otieno B, Amboka S, Odeny D, Agot I, et al. "We Don't Fear HIV. We Just Fear Walking around Pregnant.": A Qualitative Analysis of Adolescent Sexuality and Pregnancy Stigma in Informal Settlements in Kisumu, Kenya. Stud Fam Plann. 2021;52(4):557-70.
9. Stover J, Teng Y. The impact of condom use on the HIV epidemic. Gates Open Res. 2021;5:91.
10. World Health Organization. Consolidated guidelines on differentiated HIV testing services. Geneva: World Health Organization; 2024. Availabe at: https://www.who.int/publications/i/item/9789240096394
11. World Health Organization. Consolidated Guidelines on HIV Prevention, Testing, Treatment, Service Delivery and Monitoring: Recommendations for a Public Health Approach [Internet]. Geneva: World Health Organisation; 2021. https://www.who.int/publications/i/item/9789240031593
12. Cohen M, Chen Y, McCauley M, Gamble T, Hosseinipour M, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. 2011;10.1056/NEJMoa1105243.
13. HIV Prevention Coalition 2024 [Available from: https://hivpreventioncoalition.unaids.org/en.
14. Global HIV Prevention Coalition. HIV Prevention 2020 Road Map: Accelerating HIV prevention to reduce new infections by 75%. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS). 2017. Available at: https://digitallibrary.un.org/record/3946062?ln=fr&v=pdf

15. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: A unifying framework to replicate the successes of treatment cascades. The lancet HIV. 2019;6(1):e60-e6.
16. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implementation Science. 2011;6(1):42.
17. Joint United Nations Programme on HIV/AIDS. In Danger: UNAIDS Global AIDS Update 2022. Geneva; 2022. https://www.unaids.org/en/resources/documents/2022/in-danger-global-aids-update
18. Boily MC, Pickles M, Alary M, Baral S, Blanchard J, Moses S, et al. What really is a concentrated HIV epidemic and what does it mean for West and Central Africa? Insights from mathematical modeling. J Acquir Immune Defic Syndr. 2015;68 Suppl 2:S74-82.
19. Steen R, Hontelez JA, Veraart A, White RG, de Vlas SJ. Looking upstream to prevent HIV transmission: can interventions with sex workers alter the course of HIV epidemics in Africa as they did in Asia? . 891-899, editor: AIDS; 2014.
20. Jones HS, Anderson RL, Cust H, McClelland RS, Richardson BA, Thirumurthy H, et al. HIV incidence among women engaging in sex work in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2024;12(8):e1244-e60.
21. The Lancet Public Health. Sex workers health: time to act. Lancet Public Health. 2023;8(2):e85.
22. Garnett GP. Reductions in HIV incidence are likely to increase the importance of key population programmes for HIV control in sub-Saharan Africa. Journal of the International AIDS Society. 2021;24(S3):e25727.
23. Bansi-Matharu L, Revill P, Taramusi I, Steen R, Chabata ST, Busza J, et al. The effect on HIV transmission and cost-effectiveness of programmes for female sex workers in East, Central, and Southern Africa: a modelling study. The Lancet Global health. 2024;12(9):e1436-e45.
24. Jia KM, Eilerts H, Edun O, Lam K, Howes A, Thomas ML, et al. Risk scores for predicting HIV incidence among adult heterosexual populations in sub-Saharan Africa: a systematic review and meta-analysis. Journal of the International AIDS Society. 2022;25(1):e25861.
25. Risher KA, Cori A, Reniers G, Marston M, Calvert C, Crampin A, et al. Age patterns of HIV incidence in eastern and southern Africa: a modelling analysis of observational population-based cohort studies. The lancet HIV. 2021;8(7):e429-e39.
26. Nguyen VK, Eaton JW. Trends and country-level variation in age at first sex in sub-Saharan Africa among birth cohorts entering adulthood between 1985 and 2020. BMC Public Health. 2022;22(1):1120.
27. Shahmanesh M, Chimbindi N, Busang J, Chidumwa G, Mthiyani N, Herbst C, et al. Effectiveness of integrating HIV prevention within sexual reproductive health services with or without peer support among adolescents and young adults in rural KwaZulu-Natal, South Africa (Isisekelo Sempilo): 2 × 2 factorial, open-label, randomised controlled trial. The lancet HIV. 2024;11(7):e449-e60.
28. Stewart J, Baeten JM. HIV pre-exposure prophylaxis and sexually transmitted infections: intersection and opportunity. Nat Rev Urol. 2022;19(1):7-15.
29. Ramraj T, Chirinda W, Jonas K, Govindasamy D, Jama N, McClinton Appollis T, et al. Service delivery models that promote linkages to PrEP for adolescent girls and young women and men in sub-Saharan Africa: a scoping review. BMJ Open. 2023;13(3):e061503.
30. Gotsche CI, Steyn PS, Narasimhan M, Rodolph M, Baggaley R, Kiarie JN. Integrating pre-exposure prophylaxis of HIV infection into family planning services: a scoping review. BMJ Sex Reprod Health. 2023;49(3):210-8.
31. Vandepitte J, Lyerla R, Dallabetta G, Crabbe F, Alary M, Buve A. Estimates of the number of female sex workers in different regions of the world. . Sexually transmitted infections 2006;82((Suppl III)):iii18- iii25.

32. Hensen B, Chabata ST, Floyd S, Chiyaka T, Mushati P, Busza J, et al. HIV risk among young women who sell sex by whether they identify as sex workers: analysis of respondent-driven sampling surveys, Zimbabwe, 2017. Journal of the International AIDS Society. 2019;22(12):e25410.
33. Magut F, N. C, Mazibuko L, Mthiyane N, Harling G, Baisley K, et al. High HIV and HSV-2 incidence among Young women who sell sex and Young Men who buy sex in Rural South Africa. AIDS 2024, the 25th International AIDS Conference; Munich2024.
34. Stoebenau K, Heise L, Wamoyi J, Bobrova N. Revisiting the understanding of "transactional sex" in sub-Saharan Africa: A review and synthesis of the literature. Soc Sci Med. 2016;168:186-97.
35. McHaro RD, Kisinda A, Njovu L, McHaro M, Mbwilo F, Mihale G, et al. Prevalence of and risk factors associated with HIV, Herpes Simplex Virus-type 2, Chlamydia trachomatis and Neisseria gonorrhoeae infections among 18-24 year old students attending Higher Learning Institutions in Mbeya-Tanzania. PLoS One. 2022;17(5):e0266596.
36. Othieno CJ, Okoth R, Peltzer K, Pengpid S, Malla LO. Risky HIV sexual behaviour and depression among University of Nairobi students. Ann Gen Psychiatry. 2015;14:16.
37. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis. PLoS Med. 2014;11(2):e1001608.
38. WHO Technical brief: Preventing HIV during pregnancy and breastfeeding in the context of pre-exposure prophylaxis (PrEP). Geneva: World Health Organisation; 2017. Available from: https://www.who.int/publications/i/item/WHO-HIV-2017.09
39. Joseph Davey DL, Pintye J, Baeten JM, Aldrovandi G, Baggaley R, Bekker LG, et al. Emerging evidence from a systematic review of safety of pre-exposure prophylaxis for pregnant and postpartum women: where are we now and where are we heading? Journal of the International AIDS Society. 2020;23(1):e25426.
40. Kinuthia J, Pintye J, Abuna F, Mugwanya KK, Lagat H, Onyango D, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. The lancet HIV. 2020;7(1):e38-e48.
41. Mugwanya KK, Pintye J, Kinuthia J, Abuna F, Lagat H, Begnel ER, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: A feasibility programmatic evaluation in Kenya. PLoS Med. 2019;16(9):e1002885.
42. Pintye J, Drake AL, Kinuthia J, Unger JA, Matemo D, Heffron RA, et al. A Risk Assessment Tool for Identifying Pregnant and Postpartum Women Who May Benefit From Preexposure Prophylaxis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2017;64(6):751-8.
43. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly K R, Koechlin FM, et al. Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis. Aids. 2016.
44. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med. 2021;385(7):595-608.
45. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399(10337):1779-89.
46. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, et al. Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women. New England Journal of Medicine. 2016;375(22):2121-32.
47. Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, et al. Safety and Efficacy of a Dapivirine Vaginal Ring for HIV Prevention in Women. N Engl J Med. 2016;375(22):2133-43.

48. World Health Organization. Countries take up new WHO recommendations on self-testing for PrEP and PEP 2024 [Available from: https://www.who.int/news-room/feature-stories/detail/countries-take-up-new-who-recommendations-on-self-testing-for-prep-and-pep.
49. The Global PrEP Tracker [cited 2024 26/09/24]. Available from: https://data.prepwatch.org/.
50. Were DK, Musau A, Atkins K, Shrestha P, Reed J, Curran K, et al. Health system adaptations and considerations to facilitate optimal oral pre-exposure prophylaxis scale-up in sub-Saharan Africa. The lancet HIV. 2021;8(8):e511-e20.
51. Zuma T, Busang J, Hlongwane S, Chidumwa G, Gumede D, Luthuli M, et al. A mixed methods process evaluation: understanding the implementation and delivery of HIV prevention services integrated within sexual reproductive health (SRH) with or without peer support amongst adolescents and young adults in rural KwaZulu-Natal, South Africa. Trials. 2024;25(1):448.
52. Nagai H, Adiibokah E, Tagoe H, Tun W, Pilgrim NA, Ankomah A, et al. Policymakers' and healthcare providers' perspectives on the introduction of oral pre-exposure prophylaxis for key populations in Ghana. BMC Public Health. 2023;23(1):1065.
53. Tapsoba JdD, Cover J, Obong'o C, Brady M, Cressey TR, Mori K, et al. Continued attendance in a PrEP program despite low adherence and non-protective drug levels among adolescent girls and young women in Kenya: Results from a prospective cohort study. PLOS Medicine. 2022;19(9):e1004097.
54. Cowan FM, Machingura F, Ali MS, Chabata ST, Takaruza A, Dirawo J, et al. A risk-differentiated, community-led intervention to strengthen uptake and engagement with HIV prevention and care cascades among female sex workers in Zimbabwe (AMETHIST): a cluster randomised trial. The Lancet Global health. 2024;12(9):e1424-e35.
55. Pintye J, Kinuthia J, Abuna F, Anderson PL, Dettinger JC, Gomez L, et al. HIV pre-exposure prophylaxis initiation, persistence, and adherence during pregnancy through the postpartum period. Aids. 2023;37(11):1725-37.
56. Celum C, Hosek S, Tsholwana M, Kassim S, Mukaka S, Dye BJ, et al. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence among young women in southern Africa: Results from HPTN 082, a randomized controlled trial. PLoS Med. 2021;18(6):e1003670.
57. Mirembe BG, M. K, Zwane Z, Bukusi E, R. P, C. L, et al., editors. High PrEP Uptake and Adherence Measured Objectively Among Young African Women in the INSIGHT Cohort. Conference on Retroviruses and Opportunistic Infections; 2024; Denver.
58. Lorenzetti L, Dinh N, van der Straten A, Fonner V, Ridgeway K, Rodolph M, et al. Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition. Journal of the International AIDS Society. 2023;26 Suppl 2(Suppl 2):e26107.
59. Delany-Moretlwe S, F' V, Saidi F, team. Hs, editors. Initial evaluation of injectable cabotegravir (CAB-LA) safety during pregnancy in the HPTN 084 open-label extension. AIDS 2024 - 25th International AIDS Conference; 2024; Munich.
60. Landovitz RJ, Delany-Moretlwe S, Fogel JM, Marzinke MA, Piwowar-Manning E, Richardson P, et al. Features of HIV Infection in the Context of Long-Acting Cabotegravir Preexposure Prophylaxis. N Engl J Med. 2024.
61. Smith J, Bansi-Matharu L, Cambiano V, Dimitrov D, Bershteyn A, van de Vijver D, et al. Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. The lancet HIV. 2023;10(4):e254-e65.
62. Bozzani FM, Terris-Prestholt F, Quaife M, Gafos M, Indravudh PP, Giddings R, et al. Costs and Cost-Effectiveness of Biomedical, Non-Surgical HIV Prevention Interventions: A Systematic Literature Review. Pharmacoeconomics. 2023;41(5):467-80.

63. Jamieson L, Johnson LF, Nichols BE, Delany-Moretlwe S, Hosseinipour MC, Russell C, et al. Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. The lancet HIV. 2022;9(12):e857-e67.
64. Bekker LG, Das M, Abdool Karim Q, Ahmed K, Batting J, Brumskine W, et al. Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women. N Engl J Med. 2024.
65. Wu L, Kaftan D, Wittenauer R, Arrouzet C, Patel N, Saravis AL, et al. Health impact, budget impact, and price threshold for cost-effectiveness of lenacapavir for HIV pre-exposure prophylaxis in eastern and southern Africa: a modelling analysis. The Lancet HIV. 2024;11(11):e765-e73.
66. Hill A, Levi J, Fairhead C, Pilkington V, Wang J, Johnson M, et al. Lenacapavir to prevent HIV infection: current prices versus estimated costs of production. J Antimicrob Chemother. 2024;79(11):2906-15.
67. Venter WDF, Gandhi M, Sokhela S, Sikwese K, Bygrave H, Gama LD, et al. The long wait for long-acting HIV prevention and treatment formulations. The lancet HIV. 2024.
68. Afrocab. "Long overdue long-acting products" A call to action to accelerate access to LEN! 2024 [Available from: http://www.afrocab.info/2024/06/long-overdue-long-acting-products-a-call-to-action-to-accelerate-access-to-len/.
69. Medicins sans frontiers. Advocating for access to long-acting medicines for HIV prevention. 2024. p. https://www.msfaccess.org/hiv-aids.
70. International AIDS Society. IAS statement: IAS calls for global access as Gilead announces lenacapavir licensing 2024 [Available from: https://www.iasociety.org/ias-statement/ias-calls-global-access-gilead-announces-lenacapavir-licensing.
71. World Health Organization. Guidelines for HIV post-exposure prophylaxis. Geneva; 2024. Available at: https://www.who.int/publications/i/item/9789240095137
72. Massud I, Ruone S, Zlotorzynska M, Haaland R, Mills P, Cong ME, et al. Single oral dose for HIV pre or post-exposure prophylaxis: user desirability and biological efficacy in macaques. EBioMedicine. 2020;58:102894.
73. Irvine C, Egan KJ, Shubber Z, Van Rompay KK, Beanland RL, Ford N. Efficacy of HIV Postexposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2015;60 Suppl 3:S165-9.
74. Bekerman E, Cox S, Babusis D, Campigotto F, Das M, Barouch DH, et al. Two-dose emtricitabine/tenofovir alafenamide plus bictegravir prophylaxis protects macaques against SHIV infection. J Antimicrob Chemother. 2021;76(3):692-8.
75. Zhang L, Collins S, Fox J, von Kleist M. Modelling the impact of initiation delay, duration and prior PrEP usage on the prophylactic efficacy of FTC/TDF-containing post-exposure prophylaxis. medRxiv. 2024:2024.07.22.24310798.
76. Wexler A, Kates J, Oum S, Joint United Nations Programme on HIV/AIDS (UNAIDS). Donor government funding for HIV in low-and middle-income countries in 2021. Joint United Nations Programme on HIV/AIDS. Accessed 19 Jan 20252022 [Available from: https://www.kff.org/global-health-policy/report/donor-government-funding-for-hiv-in-low-and-middle-income-countries-in-2023/
77. Atun R, Silva S, Ncube N, Vassall A. Innovative financing for HIV response in sub-Saharan Africa. Journal Global Health. 2016:010407.
78. The Global Fund. The Global Fund, 2023 Update:

2023 [Available from: https://www.theglobalfund.org/en/updates/2023/2023-11-06-spain-debt-swap-improved-health-indicators-cameroon-ethiopia-drc/

79. Collier P, Sterck O. The moral and fiscal implications of antiretroviral therapies for HIV in Africa. Oxford Economic Papers. 2018;70(2):353-74.
80. AIDS Watch Africa. ALM Declaration. 2019 [Available from: https://aidswatchafrica.org/alm-declaration/.
81. Kabami J, Koss CA, Sunday H, Biira E, Nyabuti M, Balzer LB, et al. Randomized Trial of Dynamic Choice HIV Prevention at Antenatal and Postnatal Care Clinics in Rural Uganda and Kenya. J Acquir Immune Defic Syndr. 2024;95(5):447-55.
82. Koss CA, Ayieko J, Kabami J, Balzer LB, Kakande E, Sunday H, et al. Dynamic choice HIV prevention intervention at outpatient departments in rural Kenya and Uganda. Aids. 2024;38(3):339-49.
83. Spotlight. Courts to decide whether pharmacists can start HIV medicines without a doctor's script South Africa2023 [Available from: https://www.spotlightnsp.co.za/2023/05/09/courts-to-decide-whether-pharmacists-can-start-hiv-medicines-without-a-doctors-script/.
84. Phillips AN, Bansi-Matharu L, Shahmanesh M, Hargreaves JR, Smith J, Revill P, et al. Potential cost-effectiveness of community availability of tenofovir, lamivudine, and dolutegravir for HIV prevention and treatment in east, central, southern, and west Africa: a modelling analysis. The Lancet Global Health. 2023;11(10):e1648-e57.
85. S. R, Omollo V, Mogere P, Asewe M, Gakuo S, Banerjee P, et al. Pharmacy-based PrEP delivery in Kenya: findings from a pilot study extension. Conference on Retroviruses and Opportunistic Infections; Denver, Colarado2024.
86. Kiptinness C, Naik P, Thuo N, Malen RC, Dettinger JC, Pintye J, et al. Online HIV prophylaxis delivery: Protocol for the ePrEP Kenya pilot study. Front Public Health. 2023;11:1054559.
87. Minnis AM, Browne EN, Boeri M, Agot K, van der Straten A, Ahmed K, et al. Young Women's Stated Preferences for Biomedical HIV Prevention: Results of a Discrete Choice Experiment in Kenya and South Africa. Journal of acquired immune deficiency syndromes (1999). 2019;80(4):394-403.
88. Friedland B, Zieman B, Mathur S, Bruce I, Dandadzi A, Musara P, et al. A Dual Prevention Pill for HIV and Pregnancy Prevention: A Pilot Study Among Young Women in Zimbabwe. Conference on Retroviruses and Opportunistic Infections; Denver, Colarado2024.
89. Haddad LB. Multipurpose Prevention Technologies: HPTN 104. HPTN Anual Meeting; Washington2022. https://www.hptn.org/news-and-events/featurestories/future_of_mpts
90. Achilles SL, Kelly CW, Hoesley CJ, Blithe DL, Brown J, Richardson BA, et al. Phase 1 randomized trials to assess safety, pharmacokinetics, and vaginal bleeding associated with use of extended duration dapivirine and levonorgestrel vaginal rings. PLoS One. 2024;19(6):e0304552.
91. Agrahari V, Anderson SM, Peet MM, Wong AP, Singh ON, Doncel GF, et al. Long-acting HIV pre-exposure prophylaxis (PrEP) approaches: recent advances, emerging technologies, and development challenges. Expert Opin Drug Deliv. 2022;19(10):1365-80.
92. Reza-Paul S, Lazarus L, Doshi M, Hafeez Ur Rahman S, Ramaiah M, Maiya R, et al. Prioritizing Risk in Preparation for a Demonstration Project: A Mixed Methods Feasibility Study of Oral Pre-Exposure Prophylaxis (PREP) among Female Sex Workers in South India. PLoS One. 2016;11(11):e0166889.
93. Reza-Paul S, Lazarus L, Maiya R, Haldar P, Rewari BB, Venugopal MS, et al. The Ashodaya PrEP project: Lessons and implications for scaling up PrEP from a community-led demonstration project among female sex workers in Mysore, India. Glob Public Health. 2020;15(6):889-904.
94. von Schreeb S, Pedersen SK, Christensen H, Jørgsensen KM, Harritshøj LH, Hertz FB, et al. Questioning risk compensation: pre-exposure prophylaxis (PrEP) and sexually transmitted

infections among men who have sex with men, capital region of Denmark, 2019 to 2022. Euro Surveill. 2024;29(13).
95. Parkin N, Gao F, Grebe E, Cutrell A, Das M, Donnell D, et al. Facilitating Next-Generation Pre-Exposure Prophylaxis Clinical Trials Using HIV Recent Infection Assays: A Consensus Statement from the Forum HIV Prevention Trial Design Project. Clin Pharmacol Ther. 2023;114(1):29-40.
96. Ruzagira E, editor Final vaccine efficacy results from PrEPVacc: A phase IIb HIV prophylactic vaccine trial of two active regimens each compared to placebo AIDS 2024 - 25th International AIDS Conference; 2024; Munich.
https://programme.aids2024.org/Programme/Session/207
97. Adeagbo O, Herbst C, Blandford A, McKendry R, Estcourt C, Seeley J, et al. Exploring People's Candidacy for Mobile Health-Supported HIV Testing and Care Services in Rural KwaZulu-Natal, South Africa: Qualitative Study. J Med Internet Res. 2019;21(11):e15681.
98. Turbe V, Herbst C, Mngomezulu T, Meshkinfamfard S, Dlamini N, Mhlongo T, et al. Deep learning of HIV field-based rapid tests. Nat Med. 2021;27(7):1165-70.
99. Gibbs J, Solomon D, Jackson L, Mullick S, Burns F, Shahmanesh M. Measuring and evaluating sexual health in the era of digital health: challenges and opportunities. Sex Health. 2022;19(4):336-45.
100. Gibbs A, Gumede D, Luthuli M, Xulu Z, Washington L, Sikweyiya Y, et al. Opportunities for technologically driven dialogical health communication for participatory interventions: Perspectives from male peer navigators in rural South Africa. Soc Sci Med. 2022;292:114539.
101. Lauer KJ, Soboyisi M, Kassam CA, Mseu D, Oberth G, Baptiste SL. Defining community-led monitoring and its role in programme-embedded learning: lessons from the Citizen Science Project in Malawi and South Africa. Journal of the International AIDS Society. 2024;27 Suppl 2(Suppl 2):e26277.
102. Busza J, Machingura F, Kujeke T, Makamba M, Madimutsa G, Matambanadzo P, et al. What happened with PrEP uptake among female sex workers in Zimbabwe? Implications for future prevention programmes. AIDS (in press). 2025.

Figure Titles and Legends

Figure 1: Women and men on the edge of sex work. The figure shows the distribution of new HIV infections across key population groups in sub-Saharan Africa in 2022 (data from UNAIDS Global AIDS Update 2024(1)). Women who sell sex but don't identify as 'sex workers' (eg when they first start selling sex, sell sex only sporadically or are transitioning into and out of sex work) may make up a substantial proportion of infections, so that this group may be larger than the data suggest (see panel with blue diagonal lines). Their male sex partners may also may make up a substantial proportion of new infections in men (see panel with red diagonal lines). .

Figure 2. A PrEP cascade. The figure shows the percentage of HIV-negative female sex workers – recruited to the endline survey of the AMETHIST trial(54, 102) – who engaged with each step of the cascade, highlighting the substantial challenges to successful PrEP rollout.

Box 1: The HIV prevention cascade

The HIV prevention cascade offers a framework to capture the steps needed to achieve optimal effective coverage with prevention products, in this case antiretroviral-based primary prevention products, among women in Africa. The prevention cascade is more complex than the treatment cascade for a range of reasons; for example, there are many prevention options and the risk of infection (and therefore need for preventive tools) are highly variable between place, person and time. Consequently, many different cascades have been proposed and there is no single agreed model — and it is unlikely there will be one in the future. One proposed 'unifying' approach to the prevention cascade has quite strong overlaps with the COM-B model of behaviour, which outlines capability, opportunity, and motivation as the three crucial determinants of behaviour change. In the context of HIV prevention, these can be described as motivation to adopt the prevention tool (Pillar 1), access to any particular commodities required (Pillar 2), and capabilities for effective use (Pillar 3). It identifies key reasons between gaps in the cascade- these include, but are not limited to, insufficient knowledge, risk perception or norms for motivation; limited availability, affordability, or acceptable provision for access; and limited capabilities, self-efficacy or skills for effective use.

Box 2. Barriers to uptake and continuation of PrEP/PEP
Barriers are listed below, grouped according to three prevention cascade pillars — motivation and intention, access, and capability.

Cascade pillar 1: Motivation and intention to use PrEP and PEP

- low perception of risk
- low awareness about PrEP and its potential to prevent HIV acquisition; even lower awareness of PEP
- prevention a low priority compared to other challenges of daily life — and often for those at highest risk, a sense of inevitability of HIV acquisition
- perception of PrEP use as stigmatising
- perceived or experienced side effects
- scepticism about effectiveness
- distrust between sexual partners

Cascade pillar 2: Access to PEP and PrEP

- rapid scale up of facilities providing PrEP in some countries but very limited or no access in many settings
- limited integration of PrEP into sexual reproductive health and antenatal services
- universally poor access to PEP
- Personal and social barriers to accessing available health services (including distance, waiting times, stigma and fear of being recognised or treated poorly at health facilities)

Cascade pillar 3: Capabilities for effective use

- inconvenience of carrying pills and returning for refills
- fear that taking PrEP might be misconstrued as taking antiretroviral therapy or might inadvertently expose the persons' sexual activity to family and friends
- lack of clear guidance for both providers and clients on how to approach discontinuation and reinitiation of PrEP

Box 3: Priorities for implementation of existing HIV prevention technologies

Cascade pillar 1: Motivation / Intention to use PrEP and PEP

- Facilitate community-led education and empowerment to reduce stigma
- increase awareness of sexual rights and improve knowledge and self-efficacy of prevention technologies and where and how to access them.

Cascade pillar 2: Access to PEP and PrEP

- Coordinate introduction of injectable PrEP with the aim of lowering costs and increasing volumes available.
- Ensure PEP is easily and widely available throughout communities and that people are empowered to use it
- Facilitate and promote self-care in communities through access to self-testing and community delivery of interventions, thereby lowering the barriers to access for all PrEP technologies
- Maximise the choice of prevention technologies as currently available.

Across the cascade continuum

Address the following – regard to motivation, intention, access, and capability – as required for each setting and population group:

- Improve quality and effective coverage of STI management
- Intensify and strengthen programmes targeting key populations, particularly sex workers.
- Ensure adolescents have the motivation, access and capability to use effective and comprehensive sexual and reproductive health services.
- Improve effective treatment coverage among men, particularly mobile men and those who are hard to reach (including men who pay for sex).

Box 4 Future research priorities

1. Find ways to demedicalise HIV prevention — such as 'task shifting' provision of preventive technologies to community members and moving it away from clinics.
2. Develop capacity for citizen science initiatives focused on HIV prevention and community-led monitoring of services and policies.
3. Evaluate models for safety, acceptability and effectiveness of 'PEP in pocket' i.e. providing PEP prior to exposure for individuals at high risk of acquiring HIV.
4. Evaluate use of community-wide, freely available TLD to lower access barriers for PEP, potentially incorporating a test of 7-day PEP.
5. Determine the role of social media, electronic clinical management systems, digital diagnostics and other digital technologies (including AI-enabled toolkits) to support self-management and community cadre supported care.
6. Determine the role of sexual and reproductive services (including for STIs) and maternal and child health services as a hook to attract sexually active populations into prevention services — where risk stratification can target products to those who need them most.
7. Evaluate the role of community-based cadres in tailoring prevention packages to individual needs and the extent to which this contextual knowledge is adaptive to changing epidemiology
8. Identify levers to support intrinsic motivation (perceived self-benefit) and extrinsic motivation (external reward or benefit) for effective use and how or whether it is cost effective to deploy these
9. Determine the impact of biomedical HIV prevention on STIs and their treatment, and any knock on impact on antimicrobial resistance of *Neisseria gonorrhoea* in Africa.
10. Explore how HIV prevention activities can be delivered within limited health system capacities, cost effectively and equitably
11. Determine the optimal mix of funding sources for HIV prevention, including for populations / interventions seen as lower priority for some governments.
12. Collaborate with policy makers to understand the evidence requirements to lower barriers to prevention technology access.