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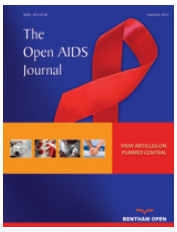

# HIV Infection and AIDS in Sub-Saharan Africa: Current Status, Challenges and Opportunities

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**Abstract:** Global trends in HIV infection demonstrate an overall increase in HIV prevalence and substantial declines in AIDS related deaths largely attributable to the survival benefits of antiretroviral treatment. Sub-Saharan Africa carries a disproportionate burden of HIV, accounting for more than 70% of the global burden of infection. Success in HIV prevention in sub-Saharan Africa has the potential to impact on the global burden of HIV. Notwithstanding substantial progress in scaling up antiretroviral therapy (ART), sub-Saharan Africa accounted for 74% of the 1.5 million AIDS related deaths in 2013.

Of the estimated 6000 new infections that occur globally each day, two out of three are in sub-Saharan Africa with young women continuing to bear a disproportionate burden. Adolescent girls and young women aged 15-24 years have up to eight fold higher rates of HIV infection compared to their male peers. There remains a gap in women initiated HIV prevention technologies especially for women who are unable to negotiate the current HIV prevention options of abstinence, behavior change, condoms and medical male circumcision or early treatment initiation in their relationships.

The possibility of an AIDS free generation cannot be realized unless we are able to prevent HIV infection in young women. This review will focus on the epidemiology of HIV infection in sub-Saharan Africa, key drivers of the continued high incidence, mortality rates and priorities for altering current epidemic trajectory in the region. Strategies for optimizing the use of existing and increasingly limited resources are included.

**Keywords:** Antiretroviral therapy, Biomedical interventions, HIV epidemic, HIV prevention, Sub-Saharan Africa.

## INTRODUCTION

With more than thirty years of the HIV epidemic, there is still no cure or an effective vaccine, however, there have been major advances in treating HIV [1 - 3] as the availability and rapid scale up of antiretroviral therapy (ART) has transformed what was inevitably a fatal disease to a chronic, manageable condition leading to notable declines in the worldwide rates of AIDS related deaths and new infections. Whilst research into HIV vaccines and vaginal microbicides continue, major breakthroughs in the prevention of HIV include voluntary male medical circumcision [4 - 6] and antiretrovirals for the prevention of mother to child transmission [7], for preventing transmission [8] and as pre-exposure prophylaxis [8] has been achieved [9, 10].

Furthermore, focusing on high transmission areas and key populations, together with the implementation of evidence-based combination prevention strategies has the ability to substantially reduce HIV transmissions and achieve epidemic control, potentially transforming the pandemic to low level endemic epidemics [11]. Notwithstanding the major advances in the delivery of HIV prevention and treatment to attain epidemic control, initiatives to prevent sexual

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transmission of HIV, indeed the major mode of transmission in sub-Saharan Africa remains a challenge to the possibility of an AIDS free generation.

## ESTIMATES OF HIV IN SUB-SAHARAN AFRICA

In 2013 an estimated 35.0 [33.2-37.2, (range around estimate)] million people were living with HIV worldwide. Sub-Saharan Africa is home to only 12% of the global population, yet accounts for 71% of the global burden of HIV infection. Ten countries, mostly in southern and eastern Africa, *viz*. South Africa (25%), Nigeria (13%), Mozambique (6%), Uganda (6%), Tanzania (6%), Zambia (4%), Zimbabwe (6%), Kenya (6%), Malawi (4%) and Ethiopia (3%), account for almost 80% of all people living with HIV [12].

The trends in new HIV infections across countries in sub-Saharan Africa have shown a decline by more than 33% from an estimated 2.2 (2.1-2.3) million in 2005 to 1.5 (1.3-1.6) million in 2013, but remain high. The scale up and widespread coverage of ART has led to substantial declines in new HIV infections. For example, HIV uninfected individuals living in a community with high ART coverage (30 to 40% of all HIV-infected individuals on ART) were 38% less likely to acquire HIV than those living in communities where ART coverage was low (<10% of all HIV-infected individuals on ART) [13]. Despite these declines, HIV incidence rates remain unacceptably high with the largest number of new infections coming from South Africa (23%), Nigeria (15%), Uganda (10%), Mozambique (8%) and Kenya (7%) [12]. The epidemics in Botswana, Namibia and Zambia appear to be declining, whilst the epidemics in Lesotho, Mozambique and Swaziland seem to be plateauing [12].

In sub-Saharan Africa, the main mode of HIV transmission is through heterosexual sex with a concomitant epidemic in children through vertical transmission. As such, women are disproportionately affected accounting for 58% of the total number of people living with HIV, have the highest number of children living with HIV and the highest number of AIDS related deaths.

With increasing access to ART, the number of AIDS related deaths have steadily declined and in sub-Saharan Africa these decreased by 39% between 2005 and 2013 [12]. In South Africa alone the decline was 51% whereas in Ethiopia it was 37% and in Kenya it was 32%. Several empiric studies from South Africa, Uganda, Tanzania, Rwanda and Malawi have demonstrated that the impact of modest ART coverage at CD4 cell counts ranging from <200 to 500 cell per μl resulted in significant declines in mortality with life expectancy increasing by an additional 10 years [14 - 21]. These studies provide evidence on the benefits of early ART initiation to HIV positive individuals.

Despite these benefits of ART, in 2013 the region still accounted for 74% of deaths from AIDS related illnesses. Whilst the achievements of the Millennium Development Goals (MDG) specifically "to halt and begin to reverse the HIV epidemic" have begun to show a downward trend in HIV infection, it is critical that the Sustainable Development Goals (SDGs) of 2015 dedicated to improving the well being of present and future generations have far reaching, profound and sustained impact on health and increases in life expectancy by reaching out to HIV positive individuals irrespective of CD4 cell counts [2, 22, 23].

## PRIORITY POPULATIONS FOR HIV PREVENTION

Globally, 15% of women living with HIV are aged 15-24 years, of whom 80% live in sub-Saharan Africa. In this region where just over 70% of all new HIV infections occur, young women bear a disproportionate burden of HIV infection. Not only do young women aged 15-24 years have HIV rates higher than their male peers, they acquire HIV infection 5-7 years earlier than their male peers. Although there are some declining trends in the 15-24 year age group, HIV prevalence is consistently higher among young women compared to young men throughout eastern and southern Africa [12] (Table **1**).

The disproportionately high HIV prevalence throughout the region suggest the lack of appropriate interventions to protect young women and to meet their sexual and reproductive health needs as they prepare for adulthood [12]. Furthermore, marked male female differences in sexual debut, age disparate sex, transactional sex, multiple partners and partner concurrency, low condom use and sexually transmitted infections contribute to adolescent girls and young women's vulnerability to HIV [25 - 31].

In the region, there is a paucity of research in marginalized groups such as men who have sex with men, people who inject drugs and sex workers, however, emerging data suggests that HIV prevalence is significantly higher in these groups than in the general population [32]. Studies from South Africa and Kenya show that HIV prevalence was almost three fold higher in men who had sex with men than in men who had sex with women only [33, 34]. Similarly, HIV

incidence rates have also been three to four fold higher at 35.2 [95% confidence interval (CI) 23.8-52.1] per 100 person years (py) among men who have sex with men only, compared to 5.8 (95% CI 4.2-7.9) per 100 py among men who have sex with men and women [34].

The data on people who inject drugs are even sparser, however, studies from Kenya and Tanzania show a similar high HIV prevalence of 36% and 35% respectively [35, 36] compared to the 6.0% and 5.0% in the general population [12]. Injecting drug use is a growing concern across the region compounded by reports of high risk sexual behaviors in these individuals. The absence of harm reduction programs and persistent high risk behaviors has implications for transmission of HIV.

Sex work has been the key driver of the epidemic in the region and the burden of HIV remains disproportionately high amongst female sex workers. Even in countries with generalized epidemics, HIV prevalence is at least two fold higher in this group than in the general population and the pooled HIV prevalence among female sex workers in sub-Saharan Africa was 30.7% (95% CI 30.2-31.3) and the odds ratio for infection was 11.6 (95% CI 9.1-14.8) [37]. Whilst the number of life time sex partners, risky sex acts or behavioral practices impact on HIV acquisition, sex workers within sexual networks play a role in sustaining transmission.

Despite the impact of combination prevention interventions that target high risk marginalized populations, the major challenges in the region are the discriminatory environments and in-country legislation that not only sustain, but fuel the epidemics resulting in extraordinarily high prevalence [38]. Major challenges exist in maintaining the declining rates of HIV infections. It is imperative that structural, behavioral and biomedical interventions are evidence and rights based, are non-discriminatory and gender transformative [38]. Furthermore, the programs should aim to decriminalize sex work, men who have sex with men and reduce intimate partner violence [39, 40] as these impact on HIV prevention efforts. Ideally, access to comprehensive sexual reproductive health services for HIV prevention should focus on maximizing on coverage of interventions [12].

**Table 1. HIV prevalence (%) among people 15-24 years old, by sex in selected sub-Saharan African countries in 2013. Adapted from [12, 24].**

| Country | HIV prevalence (%) | | Fold difference |
|---|---|---|---|
| | Females | Males | |
| South Africa | 13.1 | 4.0 | 3.3 |
| Swaziland | 12.4 | 7.1 | 1.7 |
| Lesotho | 10.5 | 5.8 | 1.8 |
| Zimbabwe | 6.6 | 4.1 | 1.6 |
| Mozambique | 6.1 | 2.7 | 2.3 |
| Botswana | 6.0 | 3.5 | 1.7 |
| Zambia | 4.5 | 4.4 | 1.0 |
| Uganda | 4.2 | 2.4 | 1.8 |
| Malawi | 3.8 | 2.4 | 1.6 |
| Kenya | 2.8 | 1.7 | 1.6 |
| Tanzania | 2.2 | 1.4 | 1.6 |
| Central African Republic | 1.5 | 0.9 | 1.7 |
| Congo | 1.2 | 0.7 | 1.7 |
| Rwanda | 1.2 | 0.9 | 1.3 |

## HIV PREVENTION STRATEGIES

Intensifying prevention activities requires a thorough understanding of the HIV epidemic typologies, modes of transmission and populations affected as these inform the extent to which evidence based modalities can be customized and combined to substantially reduce HIV transmission which is critical in continuing the path to altering epidemic trajectory [41 - 43].

The evolving epidemic has been characterized into several typologies to capture the dominant characteristic at regional and or country level. However, a key feature of the epidemic is variation in disease burden not only across population and countries but across districts and sub districts. Countries characterized as having *low-level epidemics*, where adult HIV prevalence has not spread to significant levels in the general population nationally, nor in any sub-

population, suggests that sexual networks of risk are diffuse and driven by low levels of partner change or concurrent sexual relationships or that the virus may have been recently introduced.

In such settings, information on the most vulnerable and at risk populations is needed to understand risk behaviors, social sexual networks and factors such as rates of sexually transmitted infections (STIs) that could potentially impact on the spread of HIV. Many West African countries such as Benin (1.1%), Burkina Faso (0.9%), Gambia (1.2%), Ghana (1.3%), Guinea (1.7%), Liberia (1.1%), Mali (0,9%), Niger (0.4%), Senegal (0.5%), and Sierra Leone (1.6%) experience low level epidemics [12, 44]. Thus, prevention planning should track the epidemic and entail knowledge of HIV trends.

In *concentrated epidemic* settings, HIV has spread rapidly in one or more populations but is not well established in the general population. Adult HIV prevalence is high enough in one or more sub-populations, such as men who have sex with men (MSM), people who inject drugs (PWID) or sex workers and their clients who maintain the epidemic in this sub-population, but the virus has not spread in the general population. In several countries, HIV prevalence is nearly 20 times higher amongst high risk sub-populations such as MSM and sex workers compared to adult HIV prevalence in the general population.

In Burundi, HIV prevalence in sex workers is 26.5% compared to 1.0% in the general adult population, whilst in Côte d'Ivoire amongst MSM and sex workers, HIV prevalence is 18.8% and 28.7% respectively compared to 2.7% in the general adult population [12, 23]. To prevent epidemics expanding to the general population, HIV prevention efforts should focus on understanding the dynamics of HIV transmission, tracking the size and course of the epidemic and prioritizing and intensifying interventions in affected sub-populations.

In *generalized epidemic settings*, HIV prevalence is well established in pregnant women attending antenatal clinics, indicating that the presence of HIV among the general population is sufficient for sexual networking to drive the epidemic. Multiple partner relationships giving rise to sexual networks intensify HIV transmission and account for majority of infections. Importantly, the behaviors of most at risk populations through longer term multiple concurrent relationships sustain HIV transmission in the general population [42].

In countries such as Kenya (6.0%), Uganda (7.4%) and Tanzania (5.0%) [12], the adult HIV prevalence is in excess of 5% rendering the majority of sexually active people to be at an elevated risk of acquiring HIV. Thus, prevention efforts must focus on broad social movements that contribute to safer sex behaviors and extend to those in the general population with increased vulnerability to HIV, especially young people.

In *generalized, hyper endemic* epidemic settings HIV prevalence exceeds 15% in the adult population [42]. With more than 50% of women and girls living with HIV, risk factors for HIV acquisition are complex and diverse and driven by behaviors such as early sexual debut, high levels of longer term multiple concurrent sexual partnerships, gender based violence, intergenerational sex, inconsistent condom use with casual rather than with longer term partners, low acceptability of condom use in cohabiting couples and biological co factors such as low levels of male circumcision and the presence of STIs, including viral infections.

In such settings, high levels of HIV related stigma, gender based violence and sexual coercion fuel the spread of HIV in the general population, leading to excessively high prevalence [45, 46]. Countries such as Botswana (21.9%), Lesotho (22.9%), South Africa (19.1%), Swaziland (27.4%) and Zimbabwe (15.0%) have hyper endemic epidemics and similarly countries such as Malawi (10.3%), Mozambique (10.8%), Namibia (14.3%) and Zambia (12.5%) [12] have high HIV prevalence requiring exceptional effort and resources in the investment of communities to change sexual behaviors.

A unique feature of the generalized epidemic typology in this region is the occurrence of *concentrated sub epidemics* in “hidden” high risk populations such as men who have sex with men, people who inject drugs and sex workers. These groups are at an increased risk of infection, yet are less likely to access HIV prevention and treatment services because of the pervasive stigma and discrimination against these groups [38, 46]. A more recent concern has been the role of HIV super infection, which occurs when an infected individual is infected again, by another variant. Super infection leads to a spike in viral load and individuals can transmit either variant or a recombinant form to partners [47, 48].

Understanding HIV epidemic typologies has been central to the design of prevention programs, however a more in-depth and nuanced understanding of HIV transmission is needed to direct interventions. Recent efforts to reduce sexual transmission of HIV have made progress and strategies from recent evidence based interventions are promising and

should incrementally be tested and evaluated in populations at risk for HIV. To prevent the further spread of HIV, focus on combination strategies and reaching the majority of sex workers, their clients, MSM and other high risk individuals is key to altering epidemic trajectory [43].

## NEWER TOOLS TO TARGET HIV PREVENTION

"Knowing your epidemic" has been the basis and opportunity for countries to critically assess and match the prevention response to meet the priority needs [41, 42]. Whilst these have been useful as a national response and scaled up towards attaining universal access to prevention and treatment including care and support for all, these have failed to address social and economic factors and power in relationships. These relationships, together with physiological differences, determine to a great extent an individual's risk of infection and their ability to protect themselves. However, country level HIV data masks diverse, complex and heterogeneous epidemics at sub-national, regional and district level. Furthermore, as new HIV infections continue one or more sub-populations of virus emerge [47, 48] resulting in the spread of HIV viral variants.

The complexity and heterogeneity of local epidemics evolve with localized differences, highlighting the importance of "locations" and "populations" [49 - 51] as the overall country level HIV prevalence may mask the true complex mosaic nature of the epidemic in relation to key risk factors and populations. As evidenced by district level prevalence and geospatial mapping of HIV; South Africa, Nigeria, Mozambique, Burkina Faso and Malawi experience significant variability with "hotspots" clustered around truck stops, main transport routes, sex work and further complicated by migration and limited access to health care [49, 51 - 55].

Geospatial mapping is a novel approach that is being used to map HIV infections [51, 55] in order to understand geographic variation of the HIV epidemic, its drivers, and for increasing the efficiency of targeted interventions in high HIV burden, resource poor settings. Adding to this novel approach, phylogenetic analyses of HIV-1 viral sequences are increasingly being applied to map HIV transmission links. The transmission links are important to understand dyadic relationships, and to identify clusters or networks in communities. A combination of HIV phylogenetic analyses with the relevant socio demographic and behavioral data provide powerful knowledge on patterns and dynamics of HIV transmission networks across communities, which could guide HIV prevention and intervention strategies [56 - 58].

In the village of Mochudi, Botswana, a high proportion of Mochudi unique clusters were identified among sequences suggesting that the HIV epidemic in this community is dominated by locally circulating viral variants [56]. Meanwhile in Uganda, using locations of self reported sexual partners, approximately 39% of new viral transmissions occurred within stable household partnerships, and that among those infected by extra household sexual partners, 62% were infected by sexual partners from outside their community [50]. These data provide empirical evidence to understand the dynamic heterogeneity of HIV which to a significant degree is often masked at a country level [49].

Whilst there are ethical challenges in identifying who is infecting who and understanding sexual networks particularly in generalized epidemics, these data also highlight the importance of specific "locations" to understand the drivers of heterogeneity within a country, so that prevention and treatment efforts can be tailored and implemented within discreet and/or broader communities while targeting key populations and focusing on high transmission areas.

## HIV PREVENTION INTERVENTIONS

The HIV prevention field has evolved rapidly over the last five years. Numerous interventions to prevent HIV acquisition are available; however, these have not been implemented and utilized in relation to the magnitude of HIV burden. Comprehensive and effective public health strategies include programming for behavior change, condom use, HIV testing and knowledge of HIV status, harm reduction efforts for injecting substance use, medical male circumcision and provision of post exposure prophylaxis.

Whilst the combination of these HIV prevention packages has the potential to prevent more than 90% of HIV transmission during vaginal and anal sexual intercourse, their use is mainly influenced by relationship type and heavily influenced by the form of partnerships [59, 60]. For example condom use is generally highest in commercial sex work and lower and inconsistent in non commercial and regular partnerships [61]. Studies indicate that the majority of women are generally unable to negotiate consistent male or female condom use which is largely dependent on male partner co-operation.

Although increases in male condom distribution and use played a key role in declining HIV incidence during the period 2000-2008 [62], the major challenge has been sustaining consistent condom use [63] so men can protect

themselves and their partners. Similarly HIV counselling and testing (HCT) has been tested through several models [64 - 68] to enhance knowledge of HIV status, access HIV prevention and treatment programs and minimize stigma and discrimination in association with HIV Although these innovative approaches and expansion of services have been fundamental in promoting knowledge of HIV status to access treatment and promoting preventing onward transmission, knowledge of HIV status remains low.

Results from three randomized controlled trials (RCTs) and modelling data have paved the way for large scale roll-out of voluntary medical male circumcision (VMMC) as an important intervention by engaging men and reducing heterosexually acquired HIV [4 - 6, 69]. Translating VMMC for public health benefit requires wide spread coverage to over 80% with priority in the countries with high prevalence of HIV and low prevalence of VMMC.

Although the pace and uptake of VMMC is encouraging, VMMC prevalence varies with Ethiopia and Kenya reaching 57% and 63% respectively of the coverage target. In Lesotho, Malawi, Namibia, Rwanda and Zimbabwe where VMMC is stated to be a priority, coverage of adult VMMC is less than 10% [12]. These data suggest that for any benefit of VMMC to be realized, coverage must be scaled up. Improving surgical procedures and using novel approaches for recruitment for the safe delivery of high quality VMMC services would contribute to rapidly achieving targets for public health benefit [70 - 73].

Several RCTs of cervical barrier, diaphragm and non antiretroviral (ARV) based microbicides when applied vaginally have failed to show any significant benefit in preventing HIV acquisition [74 - 80]. However, recent breakthroughs have been testing of ARV based vaginal microbicides, oral pre-exposure prophylaxis (PrEP) and early ART initiation have transformed the HIV prevention agenda and provide hope in reducing the risk of acquiring HIV (Table **2**). The effectiveness of peri coital tenofovir gel in the CAPRISA 004 trial showed that women inserting one dose of gel vaginally within 12 hours before sex and a second dose as soon as possible within 12 hours after sex and not using more than two doses of gel in a 24 hours period, reduced the risk of HIV acquisition by 39% [81].

However, the effectiveness of daily or peri-coital vaginal application of tenofovir gel in the VOICE (Vaginal and Oral interventions to Curb the Epidemic) [82] and the Follow-on African Consortium for Tenofovir Studies (FACTS) 001 trial respectively failed to demonstrate a protective effect [83]. Similarly, the FEM PrEP trial tested a daily single oral dose of Truvada® which contain two ARV drugs: tenofovir disoproxilfumarate (TDF-300 mg) and emtricitabine (FTC-200 mg) also failed to demonstrate the effectiveness of truvada in preventing HIV acquisition [84]. Whilst these trials had no safety concerns, the major drawback was the lack of adherence and therefore the failure to demonstrate the effectiveness of the study products.

Nevertheless, PrEP in high risk populations are promising biomedical HIV prevention interventions. In the iPrEx (Pre-exposure Prophylaxis Initiative) trial in MSMs, a daily single oral dose of Truvada® demonstrated a 44% protection against HIV acquisition. The Centers for Disease Control(CDC) PrEP Study (CDC TDF2) which tested a daily single oral dose of Truvada® among heterosexual men and women in Botswana showed a 62.2% reduction in HIV acquisition [85]. In Uganda and Kenya, the protective effect of a single oral daily dose of TDFor Truvada® was 67% and 75% respectively among sero-discordant men and women [86]. The most promising results come from the testing of Truvada® as PrEP in the PROUD (Pragmatic Open-Label Randomised Trial of Pre-exposure Prophylaxis) [87] and IPERGAY [88] studies which tested daily and "on demand" dosing strategy respectively and both studies showed an 86% reduced risk of HIV [87, 88]. The MTN-020-ASPIRE Study tested a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine inserted monthly in women between the ages of 18 and 45 years in Malawi, South Africa, Uganda and Zimbabwe. HIV incidence was 27% lower in women in the dapivirine compared to the placebo group. In the modified analysis excluding data from two sites that had reduced rates of retention and adherence, HIV incidence in the dapivirine group was lower by 37%. In the post-hoc analysis, higher rates of protection were observed among women over the age of 21 years (56%) but not among those younger than 21 years (-27%) and this difference correlated with reduced adherence to study product [89]. The independent Data Safety Monitoring Board of IPM 027 (Ring-004) study, recommended the analysis of data prior to study completion. In this trial the dapivirine vaginal ring reduced the risk of HIV-1 infection by 30.7% relative to placebo in women 18 to 45 years of age from South Africa and Uganda with efficacy of 37.5% in women older than 21 years [90]. These results provide renewed hope for women initiated methods, whilst clinical trials on newer ARVs with alternate delivery mechanisms are currently underway and the role of potent broadly neutralizing monoclonal antibodies are being explored as newer HIV prevention interventions [24, 91].

These interventions would fill an important gap as HIV prevention options for young women and impact on new

HIV infections [24]. The major challenge of these promising interventions is that they are not yet licensed in sub-Saharan Africa for public sector use. Whilst vaginal microbicides and oral PrEP are urgently needed as behaviors are difficult to modify, effect and sustain, their effectiveness is largely dependent on risk perception, uptake of interventions and adherence to interventions [10], further complicated by genital inflammation with increased concentrations of HIV target cell recruiting chemokines and a genital inflammatory profile contributing to HIV acquisition [92].

Recent research has shown that providing ART early at higher CD4 cell counts as opposed to delaying treatment significantly reduces heterosexual transmission and prevent's 96% of transmissions [8]. These data are consistent with data from several cohort studies and with ecological studies which showed a >10% reduction in HIV incidence at a population level for every 10% increase in ART coverage of HIV positive individuals living in the same geographic area [13, 15, 96]. These findings provide compelling evidence to the importance of viral load as a key predictor of HIV transmission. Furthermore, adding VMMC, behaviour change communication, early ART and preexposure prophylaxis could achieve greater effect in reaching the goals of epidemic control.

More importantly, early ART has been supported through the contemporary WHO 2014 guidelines as an effective tool to reduce HIV transmission rates.

**Table 2. Randomised clinical trial evidence for preventing sexual transmission of HIV (adapted from [93]).**

| Randomised Clinical Trials | Effect size (95%CI) | Reference |
|---|---|---|
| ***Vaginal Microbicide*** | | |
| **CAPRISA 004 - peri-coital tenofovir gel**<br>(Women in South Africa) | 39% (6; 60) | [81] |
| **MTN003/VOICE - daily tenofovir gel**<br>(Women in South Africa, Uganda, Zimbabwe) | 15% (-21; 40) | [82] |
| **FACTS 001- peri-coital tenofovir gel**<br>(Women in South Africa) | 0% (-40; 30) | [83] |
| **MTN-020-ASPIRE -monthly vaginal ring containing dapivirine**<br>(Women in Malawi, South Africa, Uganda, and Zimbabwe) | 27% (1; 46) | [89] |
| **IPM 027/Ring Study monthly vaginal ring containing dapivirine**<br>(Women in South Africa and Uganda) | 30.7% (0.90-51.5) | [90] |
| ***Oral Pre-exposure prophylaxis*** | | |
| **IPERGAY - on demand emtricitabine and tenofovir***<br>(Men who have sex with men in France) | 86% (39; 99) | [88] |
| **PROUD - daily emtricitabine and tenofovir**<br>(Men who have sex with men in United Kingdom) | 86% (62; 96) | [87] |
| **Partners PrEP - daily emtricitabine and tenofovir**<br>(HIV serodiscordant couples in Kenya, Uganda) | 75% (55; 87) | [86] |
| **Partners PrEP - daily tenofovir**<br>(HIV serodiscordant couples in Kenya, Uganda) | 67% (44; 81) | [86] |
| **TDF2 - daily emtricitabine and tenofovir**<br>(Heterosexuals men and women in Botswana) | 62% (22; 84) | [85] |
| **iPrEx - daily emtricitabine and tenofovir**<br>(Men who have sex with men in America's, Thailand, South Africa) | 44% (15; 63) | [94] |
| **FEMPrEP - daily emtricitabine and tenofovir**<br>(Women in Kenya, South Africa, Tanzania) | 6% (-52; 41) | [84] |
| **MTN003/VOICE - daily emtricitabine and tenofovir**<br>(Women in South Africa, Uganda, Zimbabwe) | 4% (-49; 27) | [82] |
| **MTN003/VOICE - daily tenofovir**<br>(Women in South Africa, Uganda, Zimbabwe) | -49% (-129; 3) | [82] |
| ***Other*** | | |
| **HPTN 052- Antiretroviral therapy as prevention**<br>(HIV serodiscordant couples in Africa, Asia, America) | 96% (73; 99) | [8] |
| **Medical Male circumcision**<br>(Men in South Africa, Kenya, Uganda) | 61% (34; 77)<br>60% (32; 77)<br>51% (16; 72) | [4 - 6] |
| **STD treatment**<br>(Men and women in Mwanza, Tanzania) | 42% (21; 58) | [95] |

*emtricitabine and tenofovir - Truvada®

Although high coverage of early or universal ART with VMMC, behaviour change communication and pre-exposure prophylaxis could achieve greater effect to reach the goal of epidemic control and virtually eliminate HIV

transmission [9, 11], population-based RCTs are currently ongoing to determine the effectiveness of these regimens in reducing the HIV incidence [97].

## ACHIEVING UNIVERSAL ACCESS TO ANTIRETROVIRAL THERAPY PROGRAMS

Effective ART first introduced in 1996, led to dramatic reductions in morbidity and mortality [20]. There has been a parallel increase in the number of pregnant women receiving ART for the prevention of mother to child transmission of HIV and significantly more women and children are receiving ART [98]. In sub-Saharan Africa, AIDS related deaths overall have declined by 39% in the period 2005 to 2013 with dramatic declines in Rwanda (76%), Eritrea (67%), Ethiopia (63%), Kenya (60%), Botswana (58%), Burkina Faso (58%), Zimbabwe (57%), Malawi (51%), South Africa (48%) and Tanzania (44%) attributable to the rapid increase in the number of people on ART.

Most countries have progressed with scaling-up ART provision and with a commitment to increase the numbers over the next several years. In South Africa alone over 2.0 of the 6.4 million HIV positive individuals are on ART, making it one of the largest programs in the world [99, 100]. Similarly Botswana, Namibia and Rwanda have made remarkable progress with more than 80% coverage of eligible individuals on ART based on WHO 2010 guidelines, whilst several other countries like Zambia and Swaziland are steadily increasing ART initiation.

Approximately 75% of all people receiving ART live in sub-Saharan Africa, yet many more are in need of and are eligible for ART; and as such promising results from the INSIGHT START trial [3] of initiating ART in the early asymptomatic stage at CD4 cell counts of >500 and the TEMPRANO ANRS trial [1] of early ART and including isoniazid preventive therapy offer significant benefits in further reducing AIDS related severe illness including death.

Notwithstanding the success of the region as a whole in scaling up ART, this masks significant in country variability with some countries *e.g.* Botswana, South Africa, Zambia, Zimbabwe and Malawi are providing better treatment access compared to countries such as Nigeria and Central Africa Republic where less than 25% of the adult population have access to treatment [12]. The variability in treatment access remains a challenge and may potentially reverse the gains made thus far. The major milestones of ART provision aiming for maximum coverage through early or universal ART is rapidly advancing in many countries [101]. However, some countries have not met their targets highlighting the complex challenges of patient populations that remain under-served and undermining the parallel prevention efforts. It is hoped that strengthening of health systems, reducing costs, improving and simplifying treatment are more likely to improve adherence to drug regimens with better chances for long term survival. New ART formulations can also help address some of the current challenges including funding constraints.

## HIV PREVENTION CONTINUUM

Current models and measures of HIV care include testing and diagnosis, linkage and enrolment into care, initiation of ART, retention in care and achieving viral suppression at HIV RNA <1000 copies /ml [102]. This approach has been successful for individual benefit in reducing morbidity and mortality. However, the HPTN 052 trial which showed a 96% reduction in the number of linked HIV transmissions due to early ART initiation illustrates the importance of this strategy to achieve viral suppression and onward transmission [8].

Whilst a few individuals with HIV are aware of their infection, the majority have never tested to know if they are infected. Comprehensive HIV testing programs with either community centered or innovative approaches which include self-testing would improve knowledge of HIV status. Furthermore, of the many individuals with HIV, less than half receive adequate and ongoing treatment and less than a quarter of those on ART successfully maintain viral suppression. Therefore undiagnosed HIV infection and inadequate viral suppression remain significant factors fueling the epidemic and threatening epidemic control in sub-Saharan Africa.

The WHO recommendation of 2014 to offer treatment at CD4 cell count of 500 cells/mm$^3$ or less provides almost universal access to ART which, if implemented, could potentially be cost effective as many lives would be saved. It provides hope for controlling the virus at the individual level decreasing mortality and importantly and at the public health level decreasing HIV transmission. Thus, populations that are currently underserved would benefit from large scale HIV testing, knowledge of HIV status, expediting early access to and adherence to treatment, mitigate stigma and discrimination and realization of prevention benefits from early treatment initiation [97, 103 - 107].

## KEY POINTS

Sub-Saharan Africa bears the highest burden of HIV infection globally. Notwithstanding success in a growing

number of countries with stabilized epidemics and or reductions in new HIV infections, the continued high burden of new HIV infections in South Africa, Swaziland, Lesotho, Zimbabwe, Botswana, Mozambique, Namibia and Zambia contribute to new infections globally.

It is imperative that innovative models of delivery, together with information and education on HCT, male and female condoms and VMMC are expanded to maximize on the coverage of these existing cost effective interventions. The rapid scale-up of targeted primary prevention and testing and treatment services for high risk individuals such MSMs, PWID and sex workers are needed to prevent further transmission.

A geospatial prioritization with targeted HIV prevention services within and between countries could reduce the burden of HIV in sub-Saharan Africa and impact on the global burden of HIV. A better understanding of structural, biological and behavioral factors, including the chains of transmission by applying molecular methods and phylogenetic analysis of HIV-1 sequences could improve the efficient targeting of HIV prevention efforts.

A group that has not yet benefitted from these global and regional HIV trends is young women. Adolescent girls and young women acquire HIV infection 5-7 years before men. This age-sex difference in HIV acquisition is a major driver of new HIV infections despite unprecedentedly high HIV prevalence. There remains a knowledge gap in women initiated prevention technologies and interventions for this critical group of young women. The potential for ARV based vaginal microbicides, PrEP and passive immunity offer hope for young women but are several years away. It is therefore crucial that clinical trials include adolescent women towards an AIDS-free generation.

Sub-Saharan Africa contributes disproportionately to the number of HIV/AIDS deaths. ART guidelines have been changing to increase coverage of those infected but, despite large numbers on treatment, death rates remain high. A large number of people remain unaware of their HIV status and therefore fail to be adequately linked to care and treatment programs. Prevention benefits of treatment will require large numbers of men to be tested and initiated on treatment - men who are not typical users of health services and less likely to initiate treatment.

Notwithstanding gaps in our efforts, the confluence of science and knowledge of the HIV epidemic marks one of the most optimistic moments in our response. What we do collectively will define what impact we make on epidemic control even as we continue our quest for a vaccine and cure for eradicating and ending the HIV epidemic.

## CONFLICTS OF INTEREST

The authors confirm that this article content has no conflict of interest.

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