

The need for multipurpose prevention technologies in sub-Saharan Africa

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Women bear a disproportionate burden of the HIV epidemic in sub-Saharan Africa and account for about 60% of all adults living with HIV in that region. Young women, including adolescent girls, unable to negotiate mutual faithfulness and/or condom use with their male partners are particularly vulnerable. In addition to the high HIV burden, women in Africa also experience high rates of other sexually transmitted infections and unwanted pregnancies. The development of technologies that can

simultaneously meet these multiple sexual reproductive health needs would therefore be extremely beneficial in the African setting.

Keywords HIV, multipurpose prevention technologies, pregnancy prevention, prevention, sexually transmitted infections, women.

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HIV epidemic in Africa

Africa is the worst AIDS-affected region of the world, with eastern and southern Africa generally more severely affected than western and northern Africa (Figure 1). The HIV epidemic in Africa was identified in the early 1980s,¹ but probably originated several decades before this.²

While the emergence and magnitude of the HIV epidemic varies considerably between individual countries in Africa, the HIV-1 epidemic is now well established within the general population of sub-Saharan Africa where 5% of all adults are estimated to be living with HIV.³ Substantial progress has been made over the last decade in reducing the number of new HIV infections among adults and children and epidemiological trends indicate that most of the HIV epidemics in Africa are either stabilising or declining.³ However, these encouraging trends mask the continued spread of HIV in young women and sub-Saharan Africa still accounts for about 70% (25 million) of the 35.3 million people estimated to be infected with HIV globally in 2012.⁴ Countries like South Africa, Swaziland, Lesotho and Malawi continue to experience unprecedented high HIV prevalence and incidence rates.³

Access to anti-retroviral drugs to treat AIDS patients and reduce vertical transmission of HIV has resulted in a 24% decline in AIDS-related mortality since 2005 and almost

eliminated HIV infection in infants in some parts of the world. Despite these successes, the majority (70%) of AIDS-related deaths still occur in sub-Saharan Africa.³

Burden of HIV among young women

Women bear a disproportionate burden of the HIV epidemic in sub-Saharan Africa and account for approximately 60% of all infections in this region.⁵ HIV-infected women between the ages of 15 and 24 years represent 76% of the total cases in that age group.⁶ The rapid spread of HIV among adolescent girls and young women in South Africa has been described as explosive.⁷ National, annual, anonymous seroprevalence surveys in pregnant women using public sector healthcare facilities demonstrate that HIV prevalence has increased from 0.8% in 1990 to 30.2% in 2010.⁸ Although the national HIV prevalence appears to be stabilising in South Africa, these data conceal geographical variations as well as age and gender differences in HIV prevalence and incidence. HIV prevalence among pregnant women, aged 15–49 years, is lowest in the Western Cape Province (18.2%) and highest in the KwaZulu-Natal Province, reaching 37.4% in 2011.⁸ Five sub-districts within the KwaZulu-Natal Province have recorded HIV prevalence that exceeds 40%.⁸ Annual cross-sectional surveys of antenatal clinic attendees in one of these high-burden

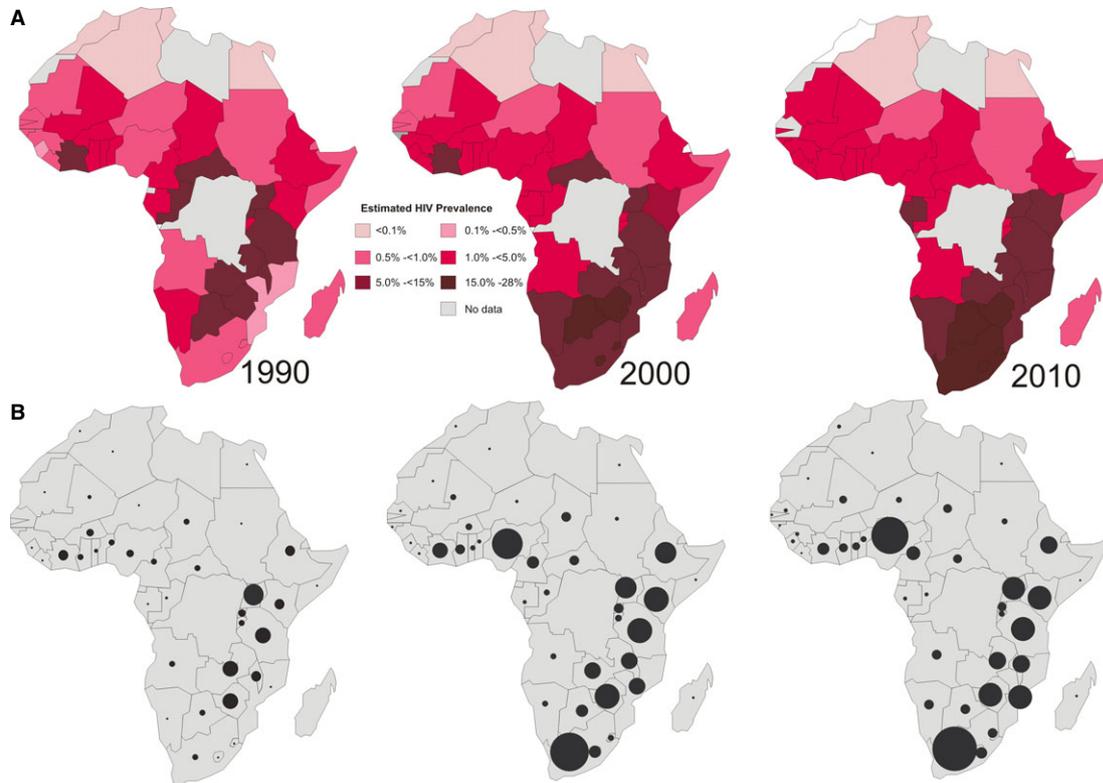


Figure 1. Trends in (A) HIV prevalence and (B) number of infections in Africa between 1990 and 2010. The size of the red circles represents the proportion of people infected. Source: Adapted from UNAIDS AIDSinfo www.unaids.org/en/

sub-districts demonstrate a disturbing rise of HIV infection among young women below the age of 20 years, increasing from 16.6% in 2006 to 20.8% in 2008.⁹ A survey conducted among high school students in this district shows that the HIV prevalence in girls was six-fold higher than in boys. An age-specific breakdown from this survey indicates that by age 18, 7.1% of girls are infected with HIV and by age 25 this increases to 24%⁹ (Table 1).

These exceptionally high HIV prevalence rates are being sustained by high HIV incidence rates among young women. Several cohort studies have been conducted in South Africa to measure HIV incidence.^{10–15} Results from one of these cohort studies conducted between 2002 and 2005 in preparation for a microbicide trial showed that the HIV incidence rate was 6.6 per 100 person-years. Factors that were associated most strongly with HIV seroconversion in this study included being below the age of 24 years, being single, and having an incident sexually transmitted infection (STI).¹⁴ Exceptionally high HIV incidence rates of 14.8 per 100 person-years (95% confidence interval [CI] 9.7–19.8) in women aged 18–35 years¹² and 17.2 per 100 person-years (95% CI 2.1–62.2) in urban women below the age of 20 years have been recorded in certain districts of KwaZulu-Natal.¹⁶ More recent data from the Centre of

Table 1. HIV prevalence in students in rural KwaZulu-Natal, South Africa.

Age group (years)	HIV prevalence in girls (95% CI) (n = 258)	HIV prevalence in boys (95% CI) (n = 230)
12–14	1.6 (0.1–9.8)	5.0 (0.4–18.2)
15–16	2.6 (0.5–10.1)	1.1 (0.1–7.0)
17–18	7.1 (2.7–16.6)	0 (0.2–7.3)
19–25	24.0 (13.5–36.5)	0 (0.2–11.2)

Adapted from Kharsany et al. (2012).⁹

AIDS Programme of Research in South Africa (CAPRISA) 004 tenofovir gel trial, completed in 2010, show that the HIV incidence rate remains high and was 9.1 per 100 person-years among 18- to 40-year-old women in the placebo gel arm.¹⁷

One of the key features of the HIV epidemic in sub-Saharan Africa is the age–sex disparity in infection where young women acquire HIV infection much earlier than their male peers. This age–sex disparity was first documented in South Africa in the early 1990s¹⁸ and more recent community-based surveys¹⁹ have demonstrated that

the same gender disparities remain but the difference in HIV prevalence between young women and men has been exacerbated. Throughout eastern and southern Africa, the prevalence of HIV in adolescent girls far exceeds that in teenage boys, and South Africa has one of the largest absolute ratios between girls and boys (Figure 2).

What makes young women more vulnerable to HIV?

Several factors contribute to the increased vulnerability of young women to acquiring HIV in sub-Saharan Africa.

Biologically, women appear to be more susceptible to acquiring HIV than men. According to the US Centers for Disease Control and Prevention, the risk of HIV infection is 1 per 2000 contacts for the male partner compared with 1 per 1000 contacts for the female partner in penile–vaginal sex.²⁰ Hence, on average, women are twice as likely to become infected as men after a single sexual encounter (Table 2). Although the biological mechanisms that make women more vulnerable than men in acquiring HIV are not fully understood, inflammation in the female genital tract is

emerging as an important risk factor for acquiring HIV.²¹ In the CAPRISA 004 trial, women with genital inflammation had an almost three-fold higher risk of HIV acquisition.²¹

The risk of acquiring HIV also increases with repeated exposure, co-infection with ulcerative STIs,^{22–24} genital immaturity, receptive anal sex, circumcision status of male sexual partner,²⁵ stage of HIV infection^{23,26} and the susceptibility of the exposed individual.

While young women and girls are possibly more biologically prone to infection, this can only partially explain the large gender differences in HIV prevalence. Discrimination against women and girls in terms of access to education, employment, health care, land and inheritance is common in many low- and middle-income countries.²⁷ Many women, particularly those from impoverished backgrounds, form relationships with men for financial and social security.²⁸ Data from several African countries have shown that young women who have sexual partners who are 5–10 years older than them are at an increased risk for acquiring HIV.^{29–32}

In addition to the intergenerational sexual coupling patterns, early sexual debut and sexual violence also impact on the vulnerability of young women in acquiring HIV infection

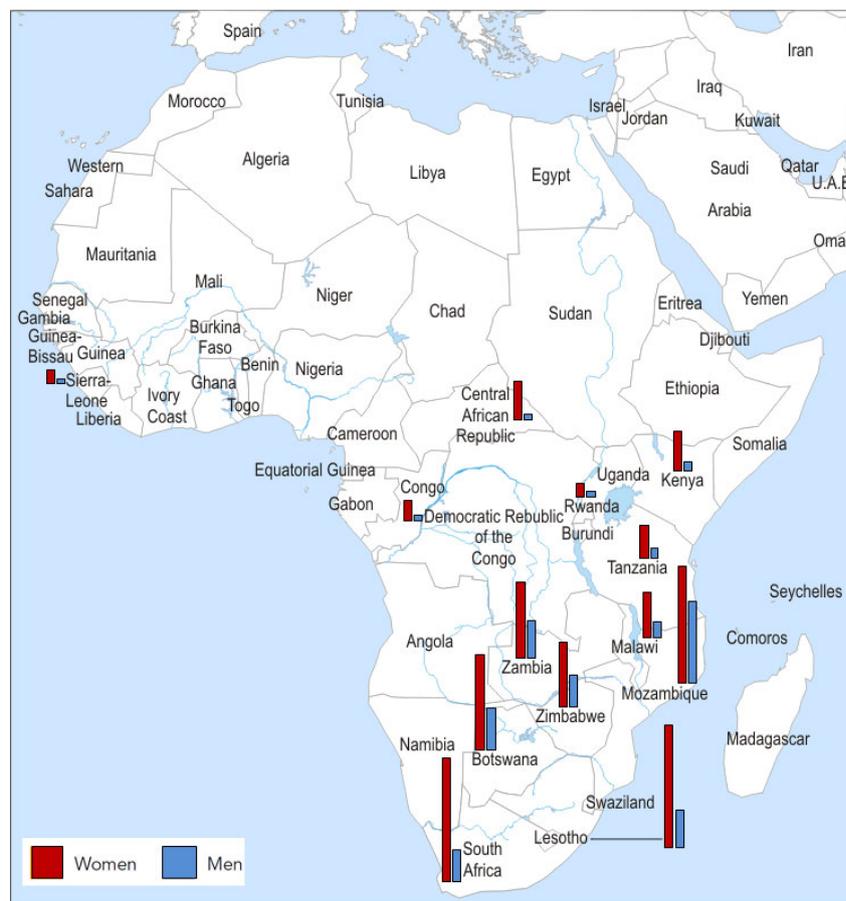


Figure 2. HIV prevalence (%) among people aged 15–24 years, by sex in selected African countries, 2008–11.⁵

Table 2. Estimated per-act probability of acquiring HIV from an infected source, by exposure act.

Type of exposure	Risk per 10 000 exposures
Sexual	
Receptive anal intercourse	50
Receptive penile–vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile–vaginal intercourse	5
Receptive oral intercourse	Low
Insertive oral intercourse	Low
Parenteral	
Blood transfusion with infected blood	9000
Needle-sharing during injection drug use	67
Percutaneous (needle-stick)	30

Adapted from Centers for Diseases Control and Prevention²⁰

in sub-Saharan Africa. On average, young people begin having sex in their teenage years and generally do not use condoms consistently. Studies from South Africa have shown that the likelihood of early sexual debut increases when the first sexual partners are older or if the sex is coerced.³³ A younger age of first sexual intercourse is associated with subsequent sexual risk-taking behaviour, such as having multiple partners,³⁴ and an increased risk of acquiring STIs including HIV infection.^{29,35} Teenage girls who acquire HIV often drop out of school, which further perpetuates the vulnerability of young women as they transition to adulthood due to the limited economic options available or accessible to those who do not complete high school.

Women who have been subjected to intimate partner violence have also been shown to be at an increased risk for acquiring HIV³⁶ and often adopt behaviours that place them at an increased risk for acquiring HIV.⁵ Violence, the fear of violence and stigma and discrimination also discourage women from disclosing their HIV status.

Desperate economic circumstances also force some women to engage in commercial sex for survival, which places them at risk of contracting HIV and transmitting the virus to others. According to the World Health Organization, prevalence of HIV among sex workers in sub-Saharan Africa is estimated to be 37%. The proportion of HIV prevalence in the general female adult population that is attributable to sex work has been estimated through modelling to be 15% in 2011.³⁷

High burden of STIs

Sexually transmitted infections are a major global public health problem, resulting in acute illness, severe medical complications, infertility, long-term disability and death in

millions of women each year.³⁸ The burden of these STIs is particularly severe in sub-Saharan Africa and especially in young women. The World Health Organization estimates that 110 million new cases of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Treponema pallidum* (syphilis) and *Trichomonas vaginalis* occurred in the African region in 2005.³⁸

The presence of STIs, particularly those that cause genital ulceration or inflammation, has been shown to play an important role in the transmission of HIV by increasing the infectiousness of HIV-infected individuals and the susceptibility of HIV-uninfected individuals.^{39–42} Herpes simplex virus type 2 (HSV-2) for example, which is a lifelong and incurable infection that can cause recurrent and painful genital sores, has been shown to be associated with a 2.8-fold and 3.4-fold increased risk of HIV acquisition in men and women, respectively, after adjustment for sexual behaviour.⁴³ An estimated 536 million (16.5%) sexually active adults between the ages of 15 and 49 years were infected with HSV-2 in 2003.⁴⁴ The burden of HSV-2 infection is highest in sub-Saharan Africa where up to 80% of sexually active women and up to 50% of sexually active men are estimated to be infected.^{44–46}

Human papillomaviruses (HPV), which include a highly diverse group of obligate mucosal pathogens capable of infecting and replicating in the genital epithelium, may also increase the risk of acquiring HIV.⁴⁷ A systematic review of the association between HPV infection and HIV demonstrated that the risk of HIV infection doubled in the presence of HPV.⁴⁸ In addition to the HIV risk, certain high-risk HPV types have been shown to cause cervical cancer.⁴⁹ An effective vaccine against HPV has recently become available and could potentially reduce the risk of both HIV and cervical cancer.

Given the strong association between the presence of STIs and the increased risk of acquiring HIV, the treatment of curable STIs would seem like a logical HIV prevention tool. Unfortunately, only one trial, which was conducted in Tanzania, has demonstrated a significant reduction in HIV incidence rates following the treatment of STIs.⁵⁰ Nevertheless, the significant sexual and reproductive health (SRH) challenge posed by the high burden of curable STIs warrants the scaling up of known STI treatments, irrespective of their impact on HIV.

High rates of unintended pregnancies

Besides a high STI burden, women in low- and middle-income countries also experience high rates of unintended pregnancies. According to the Guttmacher Institute, of the 208 million pregnancies that occurred in 2008, about 86 million (41%) were unintended.⁵¹ About half (41 million) of these unintended pregnancies were terminated, often under unsafe conditions in non-health facility settings and especially in settings where termination of

pregnancy is not legal.⁵¹ These nonspontaneous terminations of pregnancy, the majority of which occur in low- and middle-income countries, contribute to an estimated 70 000 maternal deaths and lead to serious complications that require medical treatment in a further 8 million women per year.⁵² About half of all maternal deaths each year occur in young African women.⁵³ Maternal deaths in sub-Saharan Africa are being exacerbated by the HIV epidemic, making the strengthening of HIV services for pregnant women an urgent priority.^{54,55}

Prevention of HIV, STIs and pregnancy

HIV prevention options for women

Despite the greater vulnerability of women, the options available for reducing their risk of acquiring HIV infection are limited.

Since the beginning of the epidemic the most widely advocated HIV prevention methods have been the 'ABCCC' campaigns promoting Abstinence, Be faithful, Condomise, Counselling and testing and later, Circumcision. However, because of gender power imbalances, women are often unable to successfully negotiate condom use with their male partners, insist on mutual monogamy, or convince their partners to have an HIV test.^{27,33,36,56} Furthermore, medical male circumcision primarily benefits the male partner and does not seem to directly reduce the HIV-acquisition risk in women.⁵⁷

Since 2010, however, there have been a series of trials demonstrating the efficacy of anti-retrovirals, as treatment⁵⁸ or oral/topical prophylaxis,^{17,59–61} in reducing the risk of sexually transmitted HIV infections. These new findings have reinvigorated the HIV prevention field and the challenge now is to translate the clinical trial evidence into practice and public health impact.

Treatment as prevention has been shown to reduce HIV transmission in discordant couples by 96%.⁵⁸ However, for a woman to benefit from this prevention strategy she would need to rely on her HIV-positive discordant male partner to know his HIV status, to agree to be initiated on anti-retroviral therapy even if he does not have AIDS and to adhere to lifelong anti-retroviral therapy so that she can benefit by being protected from acquiring HIV infection. Given the reluctance of male partners to use the already available prevention interventions, it is unlikely that they will agree to early treatment initiation to benefit their partners.

In contrast, oral and topical anti-retrovirals, used as pre-exposure prophylaxis, enable women to directly control their own risk of acquiring HIV. Results from the Partners PrEP⁶⁰ and Botswana TDF2⁶¹ studies have demonstrated that oral pre-exposure prophylaxis (PrEP) is effective in preventing HIV in women. However, two additional studies, the VOICE trial⁶² and the FemPrEP,⁶³ showed no pro-

TECTIVE effect, primarily because of low levels of adherence in those trials. These findings suggest that oral prophylaxis is effective when used but may not be suitable in all populations and regions. Despite the potential impact of PrEP, so far only the US Food and Drug Administration (FDA) has officially approved Truvada[®] (Gilead Sciences Inc., Foster City, CA, USA) as an HIV prevention option, and guidelines have been developed for its use by the US Centers for Disease Control and Prevention.^{64,65} Since Truvada[®] has not been approved by medicine regulators in any other countries, country-specific individual patient guidelines and programmatic public health guidelines on the implementation of PrEP have not been developed.

Given that women bear a disproportionate burden of HIV, prevention options that they can use and control remain an important goal. The use of microbicides is one of the most promising female-controlled HIV prevention options in development. The candidate product in the most advanced stage of testing is tenofovir gel, which was shown in the CAPRISA 004 trial to reduce the risk of HIV by 39% and of HSV-2 by 51% in women,¹⁷ making it a multipurpose prevention technology (MPT). It was widely anticipated that the VOICE (Vaginal and Oral Interventions to Control the Epidemic) trial, which examined the safety and effectiveness of 1% tenofovir gel and two oral anti-retroviral agents (tenofovir and Truvada[®] [a combination of tenofovir and emtricitabine] taken daily to reduce the risk of HIV acquisition in women), would confirm these results. Unfortunately, when the results were announced in 2013 they showed that none of the interventions provided protection against HIV. The lack of protective effect observed in the VOICE trial⁶² is largely a consequence of suboptimal adherence; where only 23% of women assigned to the tenofovir gel arm had had detectable drug levels.⁶² Another phase 3 trial, FACTS 001,⁶⁶ is currently underway to confirm the findings from the CAPRISA 004 trial. If successful, the FACTS 001 trial could provide the data needed for regulatory approval of tenofovir gel and pave the way for the introduction of the first microbicide.

Contraception

In contrast to limited prevention options for HIV, a multitude of safe and effective options are already available to prevent unwanted pregnancies. Despite the wide range of available products, many unplanned pregnancies continue to occur each year. Many of the undesired pregnancies could be avoided if the unmet need for contraception, estimated to be 25% in sub-Saharan Africa, was met.⁶⁷ However, the inability to access contraception is not the only reason for high rates of unintended pregnancies. Even in the high-income countries like the USA, where access to contraceptives is good, almost half of all pregnancies are

unintended at the time of conception.⁶⁸ Many individuals and couples simply struggle with consistent, correct and effective use of contraception.

Experience has shown that many men and women have a negative attitude towards condoms, which represents a significant barrier to their effective use. In the context of HIV prevention, risk perception also impacts on willingness to use condoms; individuals who do not perceive themselves to be at risk appear less likely to wear condoms.^{69–71} Furthermore, in relationships where effective forms of contraception like the oral pill or injectables are being used, the use of condoms will be less likely. Likewise, in relationships where pregnancy is desired, or where subordination of women limits their ability to negotiate safer sex practices, condom use will be low.⁷² Female condoms also face additional challenges of higher cost, lower availability and low acceptability, although new products being developed and marketed strive to ameliorate some of these challenges.

Multipurpose prevention technologies

Although STIs and unintended pregnancies are distinct sexual and reproductive health problems, they are inextricably linked. Women who are at risk for unintended pregnancies are also those who are at risk of acquiring STIs, and vice versa. Given the high rates of both STIs and unwanted pregnancies and the strong association between HIV and maternal mortality in Africa, the development of technologies that can simultaneously address these SRH needs would be extremely beneficial.

The MPTs often referred to as ‘combination’ or ‘dual’ technologies, are innovative products currently under development that are configured for at least two SRH prevention indications. The products are intended to simultaneously prevent unintended pregnancy, and STIs, including HIV, and/or reproductive tract infections.⁷³ Multipurpose prevention technologies in development include combinations of devices and drugs, combinations of drugs or vaccines, and other novel approaches.⁷⁴ Barrier devices like male and female condoms and diaphragms are already available and address multiple SRH needs. A multitude of new MPT candidates are also in development and focus on the development or improvement of physical barriers, chemical barriers, and physical/chemical barrier combinations. By targeting multiple SRH needs simultaneously, MPTs potentially offer a cost-effective approach to addressing an important public health need, which could result in social and economic benefits to women and their families worldwide. Multipurpose prevention technologies also include programmatic combinations of existing technologies that individually meet multiple SRH needs as part of an integrated service.

Conclusion

Young women in the reproductive age group in sub-Saharan Africa bear a disproportionate burden of HIV infection, unwanted pregnancies and STIs, which are reversing gains made in Millennium Development goals 4, 5 and 6. Keeping young women in this region uninfected with HIV and free of STIs and unwanted pregnancies will have enormous individual and population-level health and development benefits. Yet, investment in technologies and programmes to address their needs remains limited. There is an urgent need for technologies including MPTs to meet the SRH needs of women in sub-Saharan Africa. In addition to the individual benefits of preventing HIV and or pregnancy or STIs, the enhancement of HIV acquisition in the presence of STIs makes prevention of both STIs and HIV particularly important for the synergistic benefits of MPTs. However, as with the development of the individual technologies, the development of MPTs remains challenging.

Disclosure of interests

The authors have no conflicts of interest.

Contribution to authorship

All authors contributed equally to the manuscript.

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