

Preventing HIV Infection in Women: A Global Health Imperative

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Women account for approximately one-half of all human immunodeficiency virus (HIV) infections worldwide. Sexual transmission is the dominant mode of HIV transmission to women, and there is a concomitant associated epidemic of transmission to infants. The majority of HIV infections in women are in sub-Saharan Africa, with a disproportionate burden in young women <25 years of age. Acquisition and prevention of HIV infection in women is complex and influenced by biological, behavioral, and structural factors. Efforts to reduce the incidence of HIV infection among women in sub-Saharan African could play a substantial role in altering global trajectories of HIV infection. Increasing access to sexual and reproductive health services, addressing gender-based violence and social instability, reducing poverty and the need to engage in sex for survival, and encouraging greater male responsibility are critical short-to-medium-term interventions. Efforts to find a microbicide and HIV vaccine need to be matched with efforts to deepen understanding of acquisition of HIV in the female genital tract to inform development of targeted molecules for prevention of HIV infection.

EPIDEMIOLOGY

In contrast to the first 2 decades of the human immunodeficiency virus (HIV) pandemic, currently, women comprise approximately one-half of all adults with HIV infection or AIDS worldwide [1]. Heterosexual transmission accounts for >80% of all new HIV infections in women. The majority of HIV-infected women live in sub-Saharan Africa, where there is a substantial associated concomitant epidemic of vertical transmission of HIV. Women acquire HIV infection at least 5–7 years earlier than do men. The prevalence of HIV infection is 3–7-fold higher among adolescent women than among adolescent men in sub-Saharan Africa (Figure 1). This age and sex differential in distribution of HIV infection is considered to be a key

driver of the generalized hyperendemic epidemics described in this region.

Some indication of the unfolding catastrophe for women can be gleaned from temporal trends in age-specific prevalence of HIV infection among pregnant women in South Africa [2]. Although peak prevalence of HIV infection is observed among women aged 20–24 years, the magnitude of that risk has grown 8–10-fold over 15 years. The devastation is revealed by the exponential increase over the past ~2 decades to approximately one-third of pregnant women having HIV infection, in comparison with the experience of birth cohorts of 1972 women aged 20–24 years in 1992, when HIV infection was rare in southern Africa [3].

Although the exact contribution of HIV infection and AIDS to maternal mortality rates is unknown, there is growing evidence that HIV infection and AIDS are becoming the leading causes of pregnancy-related death in some developing countries [4] and are also important causes of death in populations with a high prevalence of HIV infection [5]. Notwithstanding the estimated 8-fold higher transmission efficiency from men to women, compared with from women to men [6, 7], and the magnitude of the burden of HIV infection,

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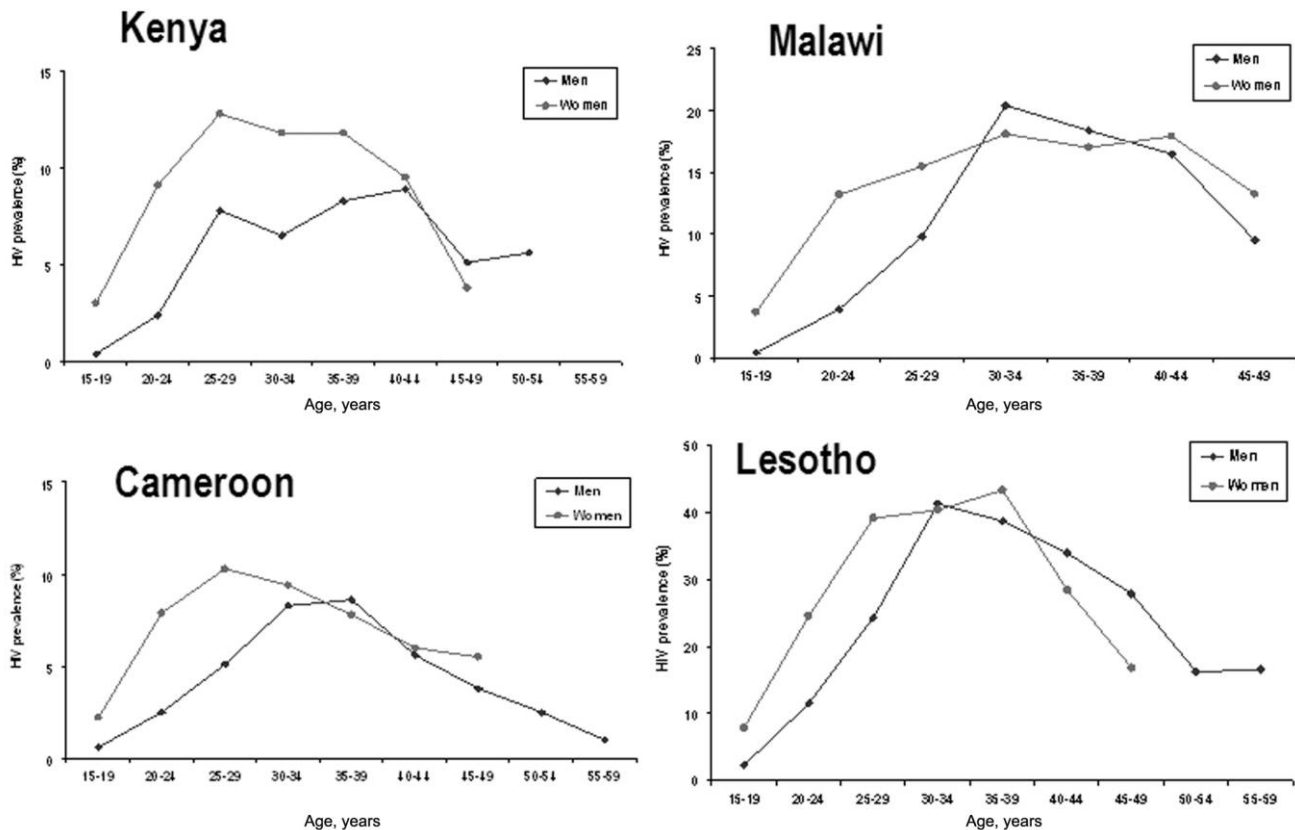


Figure 1. Age and sex distribution of HIV infection in Africa.

HIV acquisition among women is complex, multifactorial, and not well understood. The relative contributions of age, anatomy, concurrent sexual relationships, condom use, sex networks, poverty, education, economic autonomy, power imbalances between men and women, gender-based violence, access to sexual and reproductive health services, and political and sociocultural issues require elucidation.

BIOLOGY AND RISK OF HIV INFECTION

Age of sexual debut [8], viral load [9, 10], stage of infection [11], route of transmission [12], anatomy, epithelial integrity, and presence of curable sexually transmitted infections [6, 9, 11] are some biological factors associated with excess risk of HIV infection among women. The younger age of HIV acquisition in women than in men is associated with sex with older men who are more likely to be in concurrent relationships with multiple partners and more likely to have a higher viral load [13].

Although there is a growing body of knowledge on HIV acquisition through the genital tract, it is insufficient to fully understand the biological mechanisms responsible for driving the vulnerability in women. HIV infection occurs through cell-

associated and cell-free virus, and infection can occur through an intact epithelium; however, the mechanism of viral entry and passage across the mucosa remains incompletely understood.

Cervical explant studies showed that thickness of the mucosal layer could play a protective role from HIV invasion [14], and other studies have shown that any factor that undermines the thickness of this barrier increases the probability of HIV transmission across the mucosa. Progesterone-containing contraceptives have specifically been shown to lead to thinning of the epithelium, with subsequent increased incidence of simian immunodeficiency virus infection in macaques [15]. Epithelial thinning has also been demonstrated in humans [16, 17]; however, the subsequent translation into enhanced risk of HIV infection remains to be shown [18]. Because of the widespread use of progesterone-containing contraceptives in sub-Saharan Africa over intrauterine devices, implants, and/or sterilization [19], this gap in understanding requires urgent attention.

Studies investigating likely causes of breaches in the natural defense mechanisms in the female genital tract, such as breaks in the epithelial lining [20], douching [21], sexual intercourse [22], cervical ectopy with combined oral contraceptive use [23],

and cytological changes resulting from human papilloma virus infection [6, 20], have been inadequate and equivocal in explaining the excess burden of HIV infection among women and demand more attention. An estimated 340 million new cases per year of curable sexually transmitted infections occur worldwide in persons aged 15–49 years [24]; these infections could play a contributory role in HIV acquisition [25–27]. Although there was a promising 42% reduction in incidence rate of HIV infection in Tanzania [28] after treatment of sexually transmitted infections, these results were not reproduced in other randomized controlled trials in Uganda [29, 30] and Zimbabwe [31]. Notwithstanding the inconsistent findings from these randomized controlled trials, the significant sexual and reproductive health challenge posed by the high burden of curable sexually transmitted infections needs to be addressed in any efforts for prevention of HIV infection.

The cervix is thought to be an efficient primary site for viral transmission. The negative findings from the recently completed Methods for Improving Reproductive Health in Africa (MIRA) trial, which tested the efficacy of diaphragms for prevention of HIV infection, have been a setback in testing this hypothesis [32]. More-recent studies suggest that HIV is transmitted more efficiently across the uterine lining than across the ectocervix [33, 34] and that multiple mechanisms of transmission are used in the female reproductive tract [33, 34].

A deeper understanding of the female genital tract and mucosal immunity is key to guiding the development of strategic and targeted products most suitable for combating HIV infection in women. Two critical gaps in preventing HIV infection in women relate to (1) our understanding of what underlies transmission efficiency from men to women, compared with from women to men, and (2) the viral-host events that occur immediately before and after exposure to HIV. Specifically, it is necessary to understand (1) the sequence of events required to establish mucosal infection, (2) the role of mucosal immunity in preventing HIV infection, (3) characteristics of protective mucosal immune responses, (4) the role of innate immunity during early HIV infection, and (5) the interface between innate and adaptive immunity to HIV infection [35].

BEHAVIOR AND RISK OF HIV INFECTION

Abstinence, monogamy, male and female condoms, voluntary counseling and HIV testing, and medical male circumcision are widely promulgated as the cornerstones of efforts for prevention of HIV infection. However, partnership characteristics, patterns of sexual networking, and the age differences between partners impact on the relevance and adequacy of these factors for HIV prevention in women.

Abstinence. Abstinence is a strategy for prevention of HIV infection that is promoted for adolescents, especially adolescent women. In practice, abstinence often entails either delaying

sexual initiation for a limited period or practicing secondary abstinence (ie, a prolonged period without sexual activity for persons who have previously been sexually active) [36, 37]. Evidence for the success of this approach remains sparse, despite the widespread implementation of abstinence messages, particularly through life-skills education in schools and faith-based interventions aimed at reduction of risk of HIV infection. In settings where the epidemic is generalized and the probability of infection is high because of high disease burden, postponement of sexual initiation in women simply delays the age of infection, but does not reduce rates of infection [38, 39]. Promotion of abstinence in young women is a key intervention (1) to enable young women to complete school and increase their economic opportunities; (2) to enable more-informed decision-making about when, with whom, and how to have sex; and (3) for acquisition of the skills to communicate desires about preventing HIV infection and unwanted pregnancies and about other issues to protect women's rights as autonomous beings and to life.

Monogamy. The practice of intergenerational sexual coupling between young women and older men, a common pattern of sexual networking in sub-Saharan Africa [40, 41], has been shown to increase the risk of HIV infection among women almost 7-fold when the age difference is 5–7 years [13, 42]. The reason for this is that older male partners are most likely to already be HIV infected or may engage in concurrent or multiple partnership patterns that increase their own and their partners' risk of HIV infection. Such sexual partnering is an important contributing factor to the 24.5% prevalence of HIV infection among young adult women [39].

Young persons with multiple or concurrent sex partners also have an increased risk of HIV infection [43], although sex and other factors strongly influence this association [39, 44]. Concurrent relationships are more common in sub-Saharan Africa than are 1-time casual encounters, and the average duration of relationships is relatively long, resulting in tightly linked, overlapping sexual networks [45]. This link between age difference and concurrent relationships and risk of HIV infection appears to be restricted to younger women and older men. Young men report concurrent relationships ~3 times more frequently than do young women (23% vs 8.8%); however, the prevalence of HIV infection among young men remains lower than that among young women [46, 47]. Interventions targeted at reducing risk of HIV infection among women require more-targeted efforts directed at boys and young men. Greater male responsibility for actions and for risk of HIV infection is critical for men and their sex partner(s). The risk of HIV infection associated with concurrent partner relationships and/or sexual relationships that involve frequent partner changes needs to be more directly addressed.

Condoms. Numerous studies conducted over the past de-

cade have demonstrated the steady increase in acceptability and use of male condoms by young persons [36, 48], particularly in settings where consistent messages are promoted and support for continued use is provided through access to free condoms [39, 49]. Of significance, very high levels of consistent condom use are required to reduce incidence rates of HIV infection. A review of studies on risk of HIV infection [50] estimated that only ~20% of adolescents use male condoms consistently. Although 70% of young persons reported having ever used a condom, ~50% reported use of a condom at their last coital encounter [39, 51–53].

Among women, partnership type strongly influences condom use, with condoms generally viewed as less acceptable or desirable in long-term partnerships based on love and trust [54–56], but more acceptable in casual relationships. Various obstacles to condom use include negative beliefs about and attitudes toward condoms that are often grounded in traditional sex constructions [46, 57]. Some studies have found that young persons may also associate condom use with promiscuity and sexually transmitted infections, including HIV infection and AIDS [58–60]. Furthermore, peer pressure or stigma about condom use inhibits actual use [61–63]. Despite comparable efficacy rates between male and female condoms [64] and high acceptability levels [65], limited access to female condoms and substantially higher costs have limited uptake and use of female condoms and, thus, an opportunity to reduce the prevalence of HIV infection among women through a women-initiated method.

Counseling and testing. Voluntary counseling and testing has been shown to be efficacious in reducing risky sexual behavior [66] and is cost-effective as a prevention intervention [67]. Knowledge of HIV status is an important gateway to access of prevention or treatment services, including reducing vertical transmission of HIV in generalized epidemic settings. However, large numbers of individuals do not know their HIV status, especially in sub-Saharan Africa [68]. Despite recognition of the risk of HIV infection, fear of stigma and discrimination and/or experience of violence remain major obstacles to HIV testing, particularly for women, for whom there have been low voluntary counseling and testing uptake rates in prevention of mother-to-child transmission programs in sub-Saharan Africa [69]. Because the primary users of antenatal services in sub-Saharan Africa are young women aged <30 years, transformation of delivery of prevention of mother-to-child transmission programs with greater emphasis on couple counseling, prevention of unwanted pregnancies, maintenance of HIV-uninfected status in mothers, early initiation of antiretroviral therapy for HIV-infected mothers, and assurance of safe infant feeding practices could make a substantial difference to current maternal and infant mortality rates and life expectancy patterns among women in these settings.

Medical male circumcision. Three independent randomized controlled trials conducted in Africa have consistently demonstrated a 50%–60% protective effect of medical male circumcision [70–72]. Mathematical modeling has demonstrated the substantial prevention impact of medical male circumcision in generalized HIV epidemics with low rates of male circumcision [73]. Of significance, reducing the number of HIV-infected male individuals is likely to reduce the risk of HIV infection among young women in these settings, where marriage is rare, concurrent relationships are common, condom use is low, and sexual coupling with young women is the norm. However, despite compelling scientific evidence, most countries in sub-Saharan Africa have been slow in developing national policies on circumcision or programmatically providing access to medical male circumcision. This provides another missed opportunity for reducing risk of HIV infection among young women and for implementing a highly efficacious intervention for prevention of HIV infection.

Microbicides. Use of microbicides, first proposed almost 2 decades ago, represents a strategy for prevention of HIV infection that women can initiate. Currently, there are >50 candidate microbicide products in preclinical development, and 11 products are being tested in 21 ongoing trials. An additional 16 clinical trials are planned [74]. PRO 2000 Gel (Endo Pharmaceutical Services) and tenofovir gel are in the most advanced stages of effectiveness testing. Thus far, only PRO 2000 Gel has demonstrated a moderate reduction in the incidence of HIV infection [75]. Although promising, further evidence of the effectiveness of the PRO 2000 Gel is still required. VivaGel (Starpharm) and dapivirine are likely to enter last-phase efficacy trials in the near future, and research has started on combination microbicides with multiple active ingredients and/or that target different points of viral entry. Despite numerous scientific, ethical, and methodological challenges, microbicides provide real potential to influence the course of the HIV epidemic, are likely to be available and accessible sooner than will HIV vaccines, and will fill an important gap for women-initiated prevention methods. Such investments and research for an efficacious microbicide needs to continue to be a priority in the global agenda for prevention of HIV infection.

STRUCTURAL FACTORS AND RISK OF HIV INFECTION: SEX, POVERTY, POWER, AND MIGRATION

There has been slow but growing recognition and appreciation of the critical importance of how structural factors influence risk of HIV infection, particularly the role of sex and how it impacts HIV acquisition in women, affects access to services and social support when persons are infected or affected by HIV infection or AIDS, and single-handedly compounds the effects of biological and behavioral risk. Because of the social

and economic constraints that limit women's access to resources in many developing countries, sex becomes a commodity to ensure survival. In such a context, the definition of sex work is complex, because there are many transactions that it can encompass, such as serial monogamous relationships; sporadic or occasional exchange of sex for transportation, school uniforms and fees, food, and accommodation; and the more conventionally identified formal occupation as a sex worker [76–78].

In settings where marriage is rare, women enter into a series of monogamous relationships to ensure their survival and their children's survival [79]. Often, these women have a child to ensure continued financial support from the father, and in the course of a lifetime, may have several children with different biological fathers. Because these women are preoccupied with survival and have limited access to information and health services, the risk of infection and options to reduce risk are not immediate priorities for them.

Poverty and lack of economic opportunities are more pronounced in rural and geographically isolated areas and influence both men and women to migrate in search of employment and income [80]. In settings where men and women are away from home for prolonged periods or seasonally, conjugal stability and social cohesion are disrupted; this increases the risk of HIV and other sexually transmitted infections [81], because the individuals are likely to establish new sexual networks that present a greater risk of HIV acquisition. After these individuals return home, gender role expectations and dominant ideologies about marriage and procreation make it unlikely that they will use methods for prevention of HIV infection, such as male condoms [77].

The intersection of sex with age is an important determinant in the distribution of power in any society, with younger members of society typically having less power than older members and younger women having less power than younger boys. Gender-based violence is perhaps the grossest manifestation of the power imbalance between men and women [82]. In the context of the HIV pandemic, it renders young women even more vulnerable to HIV infection and further limits their ability to protect themselves. The overall power imbalances between men and women, at both societal- and individual-relationship levels, have their roots in adolescence [77, 83].

Notwithstanding context-specific differences, there is consistency in role differences between men and women, particularly in access to resources and in decision-making authority, that create and sustain an unequal balance of power. Typically, men are expected to generate income through economic activities outside the home, and women are expected to be responsible for maintaining the home through child nurturing and rearing. Almost uniformly across the world, women have less access to and control of productive resources outside the

home. Evidence for this imbalance in power includes the gender gaps in literacy levels, employment patterns, access to credit, land ownership, and school enrollment rates. This imbalance in access to and control of productive resources translates into an unequal balance in sexual relations in favor of men.

Although at a global level, the economic divisions between developed countries and developing countries have increased substantially in the past decade, the challenges in terms of unemployment, wage gaps, literacy levels, and occupational segregation are greatest for poor, indigenous women. In South Africa, an important factor contributing to the high prevalence of HIV infection among women is the widespread circular migration of men who work in the cities, where they have “town wives,” while maintaining their spouses and children in rural areas [84]. These circumstances place young women in rural areas in a uniquely vulnerable situation for acquiring HIV. In a rural survey, the prevalence of HIV infection among women who saw their partners <10 days per month was 15%, compared with 0% among women who saw their partners more frequently. The prevalence of HIV infection among mobile couples is 2–3-times higher than that among more stable couples [85].

Of significance, these structural factors render both men and women vulnerable to HIV infection. An exclusive focus on behavioral and biological factors to reduce the prevalence of HIV infection will have little impact. There is increasing evidence of the positive impact of conditional cash transfers on catalyzing adherence in substance use programs, antismoking efforts, weight reduction, school attendance, and human development outcomes [86–88] and of the importantly intrinsically sustained impact of benefits. Thus far, the impact of providing financial incentives for reducing risk of HIV infection remains to be established. Government efforts for prevention of HIV infection need to be matched by the private sector, in which the nature of occupation fosters conjugal instability, such as mining and trucking industries, to creating conditions that reduce the risk of HIV infection. New economic initiatives need to be cognizant of potential sources of labor in deciding location. Short-term gains from a more urban and central location may be off-set by medium-to-long-term goals resulting from premature deaths and expertise due to AIDS.

CONCLUSIONS

This article highlighted the complexity of HIV acquisition in women, as well as the biological, behavioral, and structural challenges in reducing this risk. Our failure to curb the HIV pandemic is a reflection on our failure to reduce the prevalence of HIV infection among young women, especially in sub-Saharan Africa. HIV infection and AIDS are making a substantial impact on reducing life expectancy among women and increasing maternal and infant mortality rates, especially in sub-Saharan Africa, thus undermining the region's efforts to meet

the Millennium Development Goals. Despite the many challenges associated with reducing the prevalence of HIV infection among women, there are numerous opportunities to effectively act on now, even as efforts continue for longer-term solutions for prevention of HIV infection.

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