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Preventing HIV Infection in Women

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Abstract

Although the number of new infections has declined recently, women still constitute almost half of the world's 34 million people with HIV infection, and HIV remains the leading cause of death among women of reproductive age. Prevention research has made considerable progress during the past few years in addressing the biological, behavioral and social factors that influence women's vulnerability to HIV infection. Nevertheless, substantial work still must be done in order to implement scientific advancements and to resolve the many questions that remain. This article highlights some of the recent advances and persistent gaps in HIV prevention research for women and outlines key research and policy priorities.

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Introduction

Although the number of new HIV infections has declined, as of 2011 women constituted almost half (49%) of the world's 34 million people with HIV infection.[1] Progress in reducing HIV transmission and acquisition among women is, to a great extent, the outcome of robust basic, biomedical, behavioral, and social research and the application of its findings. In this paper, we highlight key advances and gaps in these areas and point to priority areas for research and policy.

Among women, those aged 15 through 24 years are at highest risk of HIV infection,[2] which remains the leading cause of death among women of reproductive age.[3] Most women acquire HIV through sex with men. The distribution of HIV infection by sex varies considerably by region. In sub-Saharan Africa, women account for 59% of people with HIV, and women aged 15 to 24 years are eight times more likely than men of the same age to be infected.[2] In the Caribbean, young women are more than twice as likely to be infected as men. In Eastern Europe and Central Asia, where injecting drug use (IDU) and sex work are the primary drivers of the epidemic, about one-third of women with HIV acquired infection by injecting drugs, and an additional 50% likely acquired infection from partners who inject drugs.[2] Latin America's epidemic is predominantly concentrated among men who have sex with men (MSM) , but more than 20% of the region's MSM also report having sex with women.[2] In the United States marked racial/ethnic disparities in HIV infection rates persist. Although the estimated number of new HIV infections among Black women in the US fell by 21% between 2008 and 2010, Black women still accounted for 29% of all infections among Black adolescents and adults, with rates 20 times greater than those for US White women[4] and even higher incidence among some subsets of Black women.[5] We highlight below some of the core biological, behavioral, and social factors that individually and synergistically contribute to these HIV infection rates among women globally.

The female reproductive tract and risk for HIV infection

Research has begun to shed light on the complex interplay between the female reproductive tract, the immune system inflammatory response, and the vaginal microbiome; these interactions may either decrease or increase the tract's vulnerability to HIV infection. The mucosal immune system is unique in its need to balance the functional requirements of protecting the woman from infection while permitting survival of an allogeneic sperm and embryo.[6, 7], Sex hormones influence innate immunity in the tract by altering epithelial permeability, microbicide activity, and cytokine and chemokine secretion.[8] The presence of certain immune cells, however, enhances the tract's vulnerability to infection. Investigators recently identified a subset of cervical Th17 CD4+ cells with multiple HIV-enhancing factors, such as CCR5, alpha4beta7, CD69, and IFN-gamma that appear to increase susceptibility to HIV.[9]

Increasing evidence demonstrates the role of genital tract inflammation - whether due to infection, microscopic abrasions that result from sexual activity, douching, or other causes - in increasing women's susceptibility to HIV infection.[10] Seminal fluid introduced during intercourse produces an inflammatory response with induction of proinflammatory cytokines

and chemokines and recruitment of leukocytes. While these events presumably adapt the immune response to promote fertility, they could also affect response to HIV and other infections.[11] Research demonstrates the importance of the vaginal microbiome in maintaining the acidic environment that protects against HIV and suggests mechanisms by which lower genital tract infections can promote HIV acquisition among women.[12], [13]

Factors that affect risk of transmission to women

Estimates of the risk of heterosexual acquisition of HIV vary widely from as low as one transmission per 1000 contacts between uninfected and infected individuals to one transmission per three contacts.[14] Numerous factors, some of which are common in the population, likely increase women's risk and may contribute to the marked variation in these estimates of transmission. These factors include male partner characteristics, such as circumcision status and HIV viral load concentration; sexually transmitted infections (STIs), especially herpes; alterations of vaginal flora, such as bacterial vaginosis; and anal intercourse.[14] Other not yet fully defined factors, such as hormonal contraception[15] and reduced host susceptibility to HIV,[16] may also affect HIV acquisition risk. Common sexual network patterns, such as partners' participation in concurrent sexual partnerships[18] and dissortative sexual mixing by age,[17] increase individual women's risk of acquiring infection and also help spread HIV throughout the population.

Women and anal intercourse

A substantial proportion of women report anal intercourse, and it appears that the prevalence of heterosexual anal intercourse has increased in recent years.[19], [20] One-third of women in a national probability sample of US adults surveyed in 2002 and 2003 had ever had anal intercourse.[21] The proportion of women in Britain who reported anal sex during the preceding year rose from 6.5% in 1990 to 11.3% in 2000.[22] Surveys suggest significant prevalence of anal intercourse in other areas of the world as well; 18% of a sample of female sex workers (FSW) in India reported anal intercourse with a client.[23] Although the increased reporting of anal intercourse may be due in part to decreased reluctance to report previously stigmatized behavior, some studies also suggest that increased access to pornography through the internet may be a contributing factor, [24], [25], [23] an observation that attests to the importance of new communication methods in influencing behaviors that affect health outcomes.[26]

Anal intercourse not only increases efficiency of HIV transmission,[14] but participation in heterosexual anal sex has been consistently associated with other risk characteristics, such as multiple and concurrent partnerships, drug or alcohol use during sex, and buying or selling sex.[27], [28] A result of the under-recognition of the prevalence of anal intercourse is that HIV prevention research and interventions for women have tended to focus almost exclusively on vaginal intercourse. Women are less likely to report condom use during anal intercourse than during vaginal intercourse[24], [25] and some women erroneously perceive that transmission risk is lower for anal than for vaginal sex.[23]

Changing patterns in drug trafficking

While sexual activity remains the primary route of HIV transmission among women globally, in many settings, drug use—particularly injecting drug use (IDU)—is a substantial contributor.[29] Therefore, the dynamic patterns of drug use and drug trade are relevant to global HIV prevention efforts for women as well as men. The prevalence of IDU is high in North America, China, Southeast Asia, Russia, Eastern and Central Europe, and Central Asia, and IDU has long been a force in the HIV epidemic in these regions.[30]

Considerably less is known, however, about the prevalence of IDU in Africa, [30] which has emerged as a hub in cocaine and heroin trafficking as these drugs are shipped from and to destinations outside this continent.[31], [32] Drug trafficking can introduce drugs to residents of regions where use was previously unknown. IDU is now established in Kenya, Tanzania, Nigeria, Mauritius, and S. Africa. [30], [29] In Mauritius, for example, IDU accounted for 73% of HIV cases in 2010, and HIV prevalence among IDUs was 47%.[33] In a sample of female sex workers in that country, 40% reported ever having injected drugs, with respective HIV and HCV prevalence among these women of 28.9% and 43.8%, respectively.[33] IDU often results in participation in commercial sex to finance a drug habit, and conversely, sex work may lead to IDU. Thus, drug use and risky sex emerge as synergistic modes of HIV acquisition for women. Moreover, anecdotal reports note exceptionally unsafe practices, such as blood sharing,[34] which exacerbate the already increased risks faced by women who inject drugs.[35] There is therefore considerable concern about the potential for IDU to fuel HIV transmission among women and men in regions of the world where IDU had not previously been a major problem.

Sexual Violence

History of trauma, especially sexual abuse, is another significant risk factor for HIV infection among women.[36], [37] Gender-based violence inside and outside the context of intimate partner relationships is a common experience for women worldwide and increases their risk for HIV acquisition through several biological, behavioral, and social mechanisms: by causing genital injury as a result of forced intercourse with an infected partner; by limiting women's ability to negotiate safer sexual behaviors; and by creating a pattern of sexual risk taking among women who experienced abuse during childhood or adolescence. [38] War and conflict situations especially heighten women's risk of experiencing sexual violence, including rape.[39] The intersection between sexual violence, anogenital injury, and HIV infection may be a critical factor in HIV's disproportionate impact on women and girls in some regions of the world with generalized epidemics. [40] Researchers have therefore recently called for a multidisciplinary focus on three key areas: sexual violence perpetrated against adolescent women, sexual violence in conflict-affected areas, and effects of such violence on the HIV epidemic.[40]

Interventions for preventing HIV infection among women

Using antiretrovirals for HIV prevention

Research has demonstrated that administering effective anti-retroviral therapy to HIV-infected individuals can reduce sexual HIV transmission within sero-discordant partnerships by 96%.[41] This finding suggests that widespread implementation of diagnosis and treatment of HIV-infected individuals ("treatment as prevention") is likely to be a highly effective means of preventing HIV infection among both men and women. But treatment for prevention has yet to be fully implemented in any country. Moreover, because women remain at risk for acquiring HIV from partners who are unaware of their infection, or who lack access to or do not wish to take anti-retroviral therapy, there remains a need for effective strategies that uninfected women can use to protect themselves from HIV acquisition.

Pre-exposure prophylaxis (PrEP) for HIV uninfected individuals is one such potential strategy. Five studies that included women have reported the results of trials using topical or oral tenofovir with or without emtricitabine to prevent HIV acquisition; three demonstrated efficacy,[42], [43], [44] and two did not.[45], [46] The US Food and Drug Administration approved tenofovir/emtricitabine for use as oral pre-exposure prophylaxis (PrEP) in July 2012.[47] These PrEP efficacy trials were conducted in countries where HIV incidence is high. A number of questions remain about women's use of PrEP, not only because of conflicting efficacy results, but also because in many countries lower HIV incidence in the general population may decrease the risk/benefit ratio of long-term systemic drug use to prevent infection. For example, some studies have shown changes in bone mineral density associated with tenofovir use[48], [43] and higher rates of adverse effects.[43], [45] Moreover, exposure to tenofovir/emtricitabine and its active metabolites varies widely in different mucosal tissues, with substantially lower concentrations of the active metabolites in vaginal and cervical tissue than in the rectum,[49] suggesting that tenofovir/emtricitabine use will be less forgiving of lapses in adherence for women exposed to HIV through vaginal intercourse than for individuals whose risk of HIV infection is primarily through anal intercourse.

Despite documentation of variable adherence,[45], [46] PrEP's acceptability has generally been high when studied among trial participants, such as female sex workers in Kenya[50] and women in Uganda, South Africa, and the US.[51] Other studies of hypothetical use among people not participating in trials have reported willingness to use oral PrEP among young urban African American men and women,[52] although a substantial proportion (40%) of male and female emergency room patients in two New York City hospitals indicated that they were unlikely to use it.[53] Among female sex workers in China, willingness to use PrEP correlated with interpersonal factors, such as level of trust in physicians.[54]

Focus groups among men and women in the US revealed that interest in PrEP will likely depend on its effectiveness, cost, and ease of access. [55], [52] However, the best way to market PrEP to women is unclear and is likely to vary *between* countries - and among women at risk *within* countries. Preferences for vaginal gel versus tablets for PrEP, for

example, varied somewhat among clinical trial participants by region, with US women preferring tablets, while African women were divided in their preference for gel or tablets.[51] The study's authors note that a potential advantage of a gel over a pill or condom is that the increased lubrication afforded by the gel may allow its promotion as a sexual health benefit that improves sex and partner satisfaction rather than simply as a disease prevention device that may raise questions of infidelity.[51] Further research is needed to better define the efficacy of PrEP in women, identify new drugs for PrEP, and enhance adherence to this intervention.

Female condoms

The excitement and enthusiasm about recent biomedical advances for HIV prevention may have diverted attention from other existing methods of prevention, such as the female condom.[56] Widespread use of this method has been limited due to its cost, clinicians' and patients' lack of awareness of the existence of the product and how to obtain it, and aesthetic concerns that decreased acceptability among some users.[56], [57] Nevertheless, the female condom is acceptable to some women at high risk of HIV acquisition and affords several advantages.[57], [54] It is free of systemic side effects, protects women from STIs at least to a similar extent as male condoms,[56] prevents pregnancy,[58] and requires less male cooperation than the male condom. In 2005, a second generation nitrile version of the female condom was released whose mass production is cheaper than the original polyurethane model. Studies in Brazil, South Africa, and Washington, DC suggest that expanded distribution would be cost effective in preventing HIV infection in those settings.[59], [60]

Structural interventions

Structural interventions for HIV prevention have received increasing attention in recent years – in part because of the increasing recognition that interventions that change social determinants of health have potential for the greatest population impact.[61] These interventions typically attempt to change the environment in which people engage in health-related behaviors- often by enacting policy or legislation, empowering communities and groups, enabling environmental changes; shifting harmful social norms; or catalyzing social and political change.[62], [63] Earlier structural interventions that employed community mobilization strategies and government policy initiatives have been associated with increased condom use and decreased STI rates.[64], [65], [66] More recently, investigators in India used community mobilization strategies to reduce violence, harassment, stigma, and discrimination against sex workers to reduce this population's vulnerability to HIV and other STIs.[67] A randomized controlled trial of cash payment for adolescent girls in Malawi for staying in school demonstrated decreased prevalence of HIV and HSV-2 infections.[68] The intervention's effect appeared to operate partly by shifting participants from older partners to younger partners with whom they had less frequent sexual activity.[68] The ongoing HIV Prevention Trials Network Study 068 is evaluating the effects on HIV incidence among young women in South Africa of a cash transfer that is conditional on school attendance. Finally, the Affordable Care Act, enacted in the United States in 2010, is a structural intervention that could markedly decrease the currently large number of women and men in

the US whose lack of health insurance hinders their access to HIV prevention and treatment interventions.

Outstanding questions

While significant progress has been made in understanding and addressing the biological, behavioral, and social factors that affect HIV infection among women, numerous research questions persist and cry out for attention; these include the need to:

1. Develop safe, effective, acceptable, affordable methods women can use to prevent their acquisition of HIV. These methods should require minimal adherence, be controlled by the woman, and not require a partner's cooperation.
2. Resolve the persistent questions concerning the effect of hormonal contraception – especially depot medroxyprogesterone acetate - on women's risk of acquiring and transmitting HIV.[15], [69], [70], [71]
3. Determine how best to employ rapidly changing new media and other communication technologies for prevention tasks, such as increasing medication adherence and marketing prevention products and services to women and providers. [72],[73], [74],[75],[76]
4. Identify and implement interventions that eliminate stigma and discrimination. Societies have made little headway in combating stigma, despite the longstanding recognition that stigma undermines HIV prevention efforts, and considerable gaps remain in the HIV-related stigma literature. Prevention studies should include research to define, measure, and eliminate stigma toward those living with and those at increased risk for HIV infection, such as sex workers and homosexual and bisexual men.[77]
5. Identify and work to change laws, policies, and other structural arrangements that increase women's vulnerability to HIV infection, such as inheritance laws and property rights violations, and educational, occupational, and income factors that drive women into sex work for economic survival.[78], [79]

In addition, a key and pressing research question is how to determine the efficacy of interventions in settings where the HIV incidence among women is low. In many settings where HIV incidence is low, new infections are still occurring, underscoring the need for effective prevention interventions; this situation makes the conduct of clinical trials with HIV incidence outcomes difficult because the low incidence requires prohibitively large sample sizes. One potential approach is to assume that biological efficacy does not vary by country and to restrict studies in lower incidence countries to determination of safety of new interventions or the conduct of implementation studies in order to refine uptake, acceptability and adherence in these settings, issues that are likely to be influenced by context and culture. Thus, it is not always reasonable to assume that a biomedical intervention that requires adherence will have the same efficacy in one cultural setting that it has in another. This situation is particularly important for women in industrialized countries, such as the US, where a marked racial disparity exists in HIV infection rates in women in

the context of overall low HIV incidence and demands the conduct of further intervention studies.

Conclusions

While the recent decline in HIV incidence in some settings is encouraging, important biomedical, behavioral, and social science questions remain concerning how best to prevent HIV infection among women globally. Women need safe, effective, acceptable, accessible and affordable methods whose use they can control themselves without requiring a partner's cooperation. Ideally, new methods should require infrequent dosing and have minimal adherence requirements. Like contraception, women need a variety of HIV prevention methods that can be used with different partners and/or at different stages of their lives. Some methods should prevent both HIV infection and pregnancy, while others should prevent HIV infection without affecting ability to conceive.

Research has yielded substantial progress in preventing HIV infection among women. Further gains will require pursuing and resolving remaining research questions and fully implementing the many advances that have been made. In order to achieve the goal of an “AIDS-free generation,” researchers, clinicians, public health practitioners and advocacy groups must convince the public, funders, and policy makers that continued support for HIV prevention research and implementation of effective high impact prevention programs for women is critical.

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