

Microbicides in Obstetrics and Gynaecology

Empowering women in human immunodeficiency virus prevention

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Women comprise one-half of people infected with the human immunodeficiency virus in the world, and about 70% of them live in sub-Saharan Africa. Advancing, untreated HIV disease in women has resulted in substantial declines in fertility rates, life expectancy and infant mortality rates, and an increased burden of tuberculosis. Three decades into the pandemic, our knowledge of HIV acquisition in women remains sparse, as are options of what women can use to reduce their risk of acquiring HIV. Here, we describe the role of pre-HIV responses to venereal diseases and then discuss unwanted pregnancies, early perceptions of the HIV epidemic in setting prevention priorities, and the history of microbicide development. Opportunities to reduce HIV risk in women through sexual reproductive health services are highlighted. Women are key to turning the tide of the HIV pandemic. Microbicides provide an opportunity to ensure survival of women while addressing the power disparities that underpin women's vulnerability to HIV.

Human immunodeficiency virus and acquired immune deficiency syndrome in women

In contrast to the first 2 decades of the human immunodeficiency (HIV) pandemic, women now account for about one-half of all HIV infections globally. ¹ Most HIV infection in women is acquired sexually. An estimated 70% of all HIV-infected women live in sub-Saharan Africa, where women have about three-fold higher rates of HIV infection than do men. ² Women acquire HIV infection about 5–7 years earlier than men, and this age and sex disparity in HIV acquisition is a key driver of the epidemic in sub-Saharan Africa. ^{3 *4 5} In South Africa, HIV infection in 15–20-year-old women is three- to six-fold higher than their male peers, despite similar ages of sexual debut. ^{6 *7} The excess burden of HIV infection in women must result from a complex interplay of biological, social, cultural and political factors. ³

One outcome of HIV infection in women is a concomitant epidemic of HIV in infants that is acquired during pregnancy, intra-partum or post-partum in breastfed infants. ⁸ Advances in understanding the natural history of HIV infection in infants in the 1990s informed the development of targeted interventions to reduce transmission to infants through prophylactic use of anti-retroviral drugs, resulting in a substantial decline of HIV transmission to infants. ⁹ The gains made in almost eliminating HIV infection in infants should be applied to women; however, knowledge of HIV acquisition in women (including pregnant women) remains limited. ^{10 *11}

Life expectancy and fertility rates in women have reduced substantially owing to advancing HIV disease.¹² Increasing access to anti-retroviral treatment is starting to affect survival of women, but it is young women who continue to bear the brunt of the epidemic in sub-Saharan Africa and continue to contribute disproportionately to reversals in gains made on Millennium Development Goals MDG4, MDG5, MDG6 (infant mortality rates, maternal mortality rates, and tuberculosis cases) as a result of advancing HIV disease.^{10*11}

Preventing sexual transmission of human immunodeficiency disease

Although reducing sexual transmission of HIV has remained elusive for most of the first 25 years of the HIV pandemic, significant advances have been made since February 2010. Thus, prevention options have expanded from abstinence, mutual monogamy, use of male and female condoms, knowledge of HIV status, medical male circumcision, and treatment of sexually transmitted infections¹³ to the promise of a vaccine through the RV 144 trial findings, prophylactic use of anti-retroviral drugs, and treatment as prevention.^{*14 15} The implications of these advances, particularly in relation to use of anti-retroviral drugs for women, remain uncertain. Although CAPRISA 004,¹⁶ Partners PrEP,¹⁷ and the Botswana TDF2 trials¹⁸ reported a protective effect of prophylactic use of gel or oral formulation of tenofovir or oral truvada in women ranging from 39–72%, the FEMPrEP¹⁹ and VOICE trials²⁰ reported no effect of oral and gel formulations of tenofovir, respectively.

Despite advances in HIV prevention and the promise of the use of antiretroviral drugs for prevention, many gaps remain. The needs of women should be addressed, particularly in situations where abstinence is not an option and where faithful, mutually monogamous relationships or consistent use of male or female condoms are also not options. Why is it that 3 decades into the pandemic, we still do not have female-initiated HIV prevention methods? What can we learn from the past and how has the past shaped our responses to the HIV epidemic?

Lessons from sexual and reproductive health in the pre-human immunodeficiency era

Historically, sexually transmitted diseases (also referred to as venereal diseases) were seen as conditions in which women were the vectors and men the victims. Accordingly, prevention of venereal diseases often concentrated on men such as soldiers and sailors. The first controlled trial of the male condom randomly assigned condoms to sailors going on shore leave, and showed a protective effect against gonorrhea for men.²¹ In the HIV era, this trial has been cited as evidence for the effectiveness of the male condom with little consideration for women. Indeed a common assumption of HIV prevention efforts, including use of condoms, unfounded on any evidence, is that men will take responsibility and use condoms or adopt other prevention advances and thereby protect women. The current epidemic trajectories indicate otherwise.¹

In contrast, the evolution of fertility control had women bearing the consequences of unplanned and often inconvenient pregnancies. Although the use of condoms, like withdrawal, was understood to be protective actions that men could take, if protection failed, men in some instances bore some of the blame and the consequences. With the development of hormonal

contraceptives, the responsibility shifted almost exclusively to women, and some argue resulted in men not using condoms. ²²

In the early days of the HIV epidemic, notwithstanding the infections reported in heterosexual men and women acquired through blood transfusions and or injecting drug use patterns, the fact that the first descriptions of the epidemic involved men having sex with men in the USA and in Europe made HIV appear to be a man's disease. ²³ For the first 2 decades of the HIV pandemic, HIV infection of women through heterosexual encounters was reported as either rare or not occurring in industrialised countries. This perception of the epidemic in the USA was critical in shaping research priorities and the provision of funding by the National Institutes for Health, the largest research funding body. The establishment in the USA of a large-scale, prospective study of 'at risk' men early in the epidemic is one example of this. In contrast, a comparable study among women in the USA had to wait more than a decade. ²⁴ Even now, it remains a problem that men do not encourage emphasis on the disease in women in more industrialised countries. ²⁵

In contrast, in Sub-Saharan Africa and the Caribbean, although HIV infection in women was a recognised priority, the focus of research efforts was on reducing infant transmission of HIV. Studies on reducing mother-to-child transmission of HIV started to flourish in the late 1980s and early 1990s in the USA and Africa, but research groups remained uninterested in pursuing research on HIV in women. ²⁶ Uninfected pregnant women were largely ignored, and the HIV-positive mothers a focus only in so far as they were pregnant and a vehicle to address the needs of the infants. A few sporadic reports were published of the stigma, fear, experience of violence and loss of security experienced by mothers who disclosed their HIV status learnt during HIV testing at a pre-natal visit. ^{27 28 29} Only more recently has attention started to focus on the health of the infected mother based on growing evidence that efforts to reduce HIV infection in infants or improve health outcomes in the infant is strongly influenced by the health of the mother. ^{10 *11} Male responsibility for pregnancy and HIV risk in these settings is only slowly starting to emerge.

Indeed, the separation between fertility control and venereal diseases ensured that service providers were also unprepared for their role in responding to the HIV epidemic. A good example of this is where family planning staff had been trained for years in providing contraceptive counselling to discourage use of condoms as an unreliable method of contraception. In the early days of the epidemic, clients requesting use of condoms in addition to more reliable forms of contraceptives were discouraged, as family-planning service providers had not made the connection with HIV until dual counselling for HIV prevention and fertility control became mainstream in the late 1990s. ³⁰

The history of microbicides

Before the HIV pandemic, women had not used male condoms themselves. Consequently, it became clear that, when they initiated condom use, it was met with suspicion and blame, and issues of love and trust were raised. ^{31 32 33} In this context, advising women to initiate male condom use in their relationships was absurd.

This impasse was first reported independently by several groups in the USA in the late 1980s,³¹³⁴^{*35} and led to numerous discussions convened by scientists, feminists, artists and political groups in the USA and from developing countries. The idea of creating a virucide was borne from these deliberations,³⁵ and was later more fully developed by Lori Heise and Chris Elias, at the Population Council and became known as a microbicide.³⁶ The presence of women from Africa in these deliberations was a sharp reminder of the urgent need and magnitude of the challenge for African women, and was an important impetus for the work initiated by the Global Campaign for Microbicides. The search for a microbicide became recognised as a movement for women and, at first, to a large extent by women.³⁶³⁷ The Global Campaign for Microbicides played a critical role in identifying potential obstacles to clinical testing of microbicides and developing consensus statements to address clinical trial ethics, scientific, investment and logistical challenges. At the same time, in Belgium, Marie Laga and Peter Piot were experimenting with a microbicide in the Congo.³⁶³⁷ In the UK, an early advocate was Alan Stone, at the Medical Research Council.

By the mid-1990s, the quest for a microbicide was taken up by Family Health International,³⁸³⁹ CONRAD,⁴⁰ The International Center for Research on Women, The National Institute for Allergy and Infectious Disease (Pro 2000[®], Buffer gel[®]), and The National Institute of Child Health and Human Development. The International Center for Research on Women under the leadership of Geeta Rao Gupta, with funding from The United States Agency for International Development, commissioned critical studies in several African countries to enhance understanding of vulnerability of women to HIV. These studies remain seminal contributions to understanding the social, political and economic factors that shape HIV risk in women in sub-Saharan Africa.⁴¹

Zena Stein's commentary in the *American Journal of Public Health* in the mid-1990s³⁵ is uniformly regarded as the pivotal catalyst to multiple parallel efforts for the quest for a microbicide, primarily funded by small biotechnology companies and the public sector.⁴² The increase in the number of clinical trials in the field with a vast array of products led to the establishment of Alliance for Microbicide Development in 1998 by Polly Harrison. The Alliance gathered together a wide range of players to co-ordinate and synergise efforts for the development of a microbicide.³⁷

The XIIIth International AIDS Society conference hosted in Durban in 2000 was a historic moment in the development of microbicides, as it was the first international AIDS conference to have a plenary talk on microbicides. In this meeting, the disappointing findings of the Col-1492 trial results were reported⁴³; however, the positive news was the Gates Foundation announcement of \$20 million to CONRAD for microbicide development, marking the first substantial investment in microbicide development and acknowledgement of the urgent need for preventative options for women.⁴⁴ Shortly thereafter, the Rockefeller Foundation commissioned a report on the development of a microbicide by the Boston Consulting group,⁴⁵ which culminated in the establishment of the International Partnership on Microbicides and, independently, the National Institutes for Health funded Microbicides Trial Network (MTN) in the mid-2000s. The creation of IPM and MTN, together with the experience garnered in the previous decade through the conduct of the pre-clinical and clinical studies, resulted in generating a momentum and scientific focus initiated almost 2 decades earlier by persistent

endeavours by scientists, non-governmental organisations, donors, advocates and tens of thousands of volunteers participating in the research.

At the Microbicides 2006 meeting hosted in Cape Town, the potential role of microbicides among men who have sex with men was highlighted. It is anticipated that this convergence of needs for a rectal and vaginal microbicide will benefit men and women, and increase efforts in finding an effective microbicide. ⁴⁶

The release of the positive results of 1% tenofovir gel at the International AIDS Society conference in Vienna ¹⁶ signalled the first light at the end of the tunnel, but much remains to be done before we have a safe and efficacious product that can be used by men and women.

Barrier methods for women

In contrast to microbicides, the testing of barrier methods for HIV prevention in women has not attracted much interest among advocates for women, funders, or scientists. Female condoms ^{47 48} are available, and data from Brazil show that the introduction of the female condom there led to an increase in protected sex acts either by the male or female condom. ⁴⁸ In part, costs have been a barrier as well as the fact that it is not a covert method as a microbicide is. Over the years, lower cost versions have emerged, but access and uptake remain as barriers.

The negative result from the Methods for Improving Reproductive Health in Africa trial ¹³ testing a diaphragm halted further studies of other barriers, such as cervical caps. More recently, attention has been turning to combining diaphragms with anti-retroviral agents.

Bridging the gap between efficacy and effectiveness

History has taught us that a huge gap exists between proof of concept and implementation and scale-up. Notwithstanding challenges of licensure and manufacturing, a large and well-established bibliography elaborates how this gap can be closed. In the HIV era, important lessons have been learned in the context of preventing mother-to-child transmission of HIV programmes, introduction of female condoms, anti-retroviral treatment provision and, more recently, on scaling up medical male circumcision. ^{49 50 51} Each time a new programme has been introduced, healthcare workers require adequate training and support to ensure its successful introduction. Where healthcare workers receive adequate training, attention to strengthening of healthcare delivery infrastructure, good financial investments, good supply chains, ongoing support to staff, and adequate health information systems for monitoring and evaluation, success and good coverage tend to occur. Making better use of these opportunities will enhance our responses to the epidemic and increase male involvement and responsibility; more importantly, it will empower and enable women with currently available resources, ^{*11 *52} even as we continue efforts to advance the development of more specific female-initiated technologies.

Conclusion

Much remains to be done to enhance options for women to reduce their HIV risk. Through working in partnership across countries, disciplines and communities, we know much more than

we did through knowledge sharing and support systems, respecting the possibilities and choices for girls and women, and listening to their voices. There is room for hope at last in defeating this virus and its effect on women.

Women are key and central to the development of communities given their multiple roles socially, economically and politically. In settings where their status is low and economic opportunities are limited, power differentials are vast and HIV risk is high. The health and status of women is key to transforming societies. Currently in sub-Saharan Africa, HIV is cutting a devastating swathe, with young women being the worst affected. Although technological advances are critical to turning the tide of HIV in women, the root cause of their vulnerability (i.e. vast disparities between men and women in relation to social, political and economic power) remains to be addressed.

Conflict of interest

None declared.

Practice points

- Make use of opportunities, especially in high HIV-burden settings, to screen women for HIV.
- Ensure adequate screening and counselling support for treatment of sexually transmitted infection, appropriate fertility control methods, and HIV risk-reduction support.
- Ensure HIV-positive women have appropriate care and access to treatment that includes regular Pap smears and appropriate fertility-control options.
- Monitor advances in pre-exposure prophylaxis and microbicide field, and prepare for integration into existing health services.

Research Agenda

- Continue efforts to find an effective microbicide or other technologies for use by women.
- Explore options of combining microbicides with barrier methods.
- Make use of opportunities during prenatal and antenatal services to enhance HIV prevention through knowledge of HIV testing and appropriate triaging to treatment or prevention services, including prevention of unwanted pregnancies.

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