

# One Choice Is No Choice: The need for female-controlled HIV prevention tools for women and girls worldwide

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In the third decade of the AIDS pandemic, and during a time in which sexually transmitted infections (STIs) are a serious public health concern, women have few prevention tools to choose from, and none that are under their direct control. Despite the fact that women are at greater risk than men of acquiring HIV and other STIs for a combination of biological, economic and socio-cultural reasons, no effective prevention methods that are entirely female-controlled yet exist. Most HIV/STI prevention messages follow the hierarchical “ABC” model: at best, “abstain,” if that is impossible, “be monogamous,” or as a last resort, “use condoms.” Since each of these options requires partner cooperation, success with the ABC strategy is unrealistic for many women. The absence of proven tools that are fully female-controlled constitutes an enormous

gap in the range of HIV prevention strategies. The burden of this gap falls upon the millions of women who do not have the power in their sexual relationships to insist on abstinence, fidelity, or condom use. Many of these women also lack the social and economic resources to leave partners who put their health at risk.

## **The Epidemiological Impact of Vulnerability**

Biologically, women are twice as likely as men to contract HIV from a single act of unprotected vaginal intercourse.<sup>1</sup> Multiple factors contribute to this susceptibility, including the fact that the female reproductive tract, including the vagina, cervix and upper genital tract, has larger exposed mucosal surfaces than the male reproduc-

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tive tract. The fact that semen (generally pH neutral) tends to contain higher concentration of HIV/STI pathogens than do vaginal secretions (which tend to have a lower pH) compounds women's vulnerability, as this mucosal surface may be exposed to a higher concentration of pathogens for a longer period of time than occurs in the urethra of the male after intercourse.

Women's physical vulnerability is further exacerbated by the fact that STI-infected women are less likely than STI-infected men to receive treatment for a variety of reasons, including the sex-specific manifestations of symptoms and differential access to treatment resources.<sup>2</sup> Even after infection, the potential consequences of STIs, including infertility, ectopic pregnancy and cervical cancer, are often more serious and permanent for women than for men.

Additionally, women and girls often have fewer economic opportunities than men and boys. Many women and girls are forced to rely on male partners for economic security. Whether in the context of marriage, long-term partnerships, or transactional sex, some women's lives include the exchange of sex for housing, child support, food, money, or other needed items. Moreover, disempowering gender norms, trans-generational coupling (typically involving older men and younger women or girls), and gender-based violence can further contribute to women's inability to negotiate safe sex, thereby increasing their vulnerability.

The epidemiological toll exacted by the confluence of these factors is chilling:<sup>3</sup>

- Women are the fastest-growing population acquiring HIV/AIDS,

and most become infected through heterosexual contact. Half of the 14,000 people infected with HIV every day are women. A woman is infected every 12 seconds.

- Almost two-thirds of all sub-Saharan Africans living with HIV/AIDS are women. Further, young women in sub-Saharan Africa are more than twice as likely as their male counterparts to have HIV.
- Worldwide, two-thirds of people under 24 living with HIV are women. In Botswana, young women's risk is so high that over half of all women in their late 20s are HIV-positive. Among teenagers in some African and Caribbean countries, girls are 5 times more likely to be HIV-positive than their male peers.
- New HIV/AIDS cases among American women have increased by 25% over in the last two years; new cases among European women by 30%. AIDS is the leading cause of death for African-American women between the ages of 25-34.

The escalating impact of HIV/AIDS on women and girls is closely related to the absence of HIV prevention tools that women can directly control. For decades, we have had no useful response for women who ask, "Isn't there something else I can use? I just can't get him to use a condom." The answer to this critically important question lies in the development of new prevention options that women and girls can use without necessarily having to negotiate with their partners.

*Taking condoms to be 95% HIV and STI effective, if a 50% HIV and STI effective microbicide is used in 50% of sex acts in which a condom is not used:*

Among couples initially using condoms X% of the time	Risk of infection	Comment
90%	Increases if condom use decreases slightly to 86% or less.	Among highly consistent condom users, even if condom consistency drops only slightly, overall risk of infection increases, because they already had very high levels of protection.
50%	Increase in risk only if condom use drops to 32% or less.	Among moderately consistent condom users, overall protection profile improves. Overall risk of infection will not increase unless condom use drops to less than a third of the time.
30%	Increase in risk only if condom use drops to below 5%.	Among those who rarely use condoms, protection is greatly improved by access to a microbicide. Overall risk of infection increases only if condom use nearly stops.
25% or less	Risk will not increase even if condom use falls to zero.	Even if condom use stops completely, risk will not increase.

Adapted from: Foss AM, Vickerman PT, Heise L, Watts CH. Shifts in condom use following microbicide introduction: should we be concerned? *AIDS* 2003;17:1227-37.

**Table 1: Impact of potential condom migration (due to the introduction of a microbicide) on individual risk of HIV infection, by frequency of condom use.**

## Developing New HIV/STI Prevention Methods for Women

At present, the female condom is the only available woman-initiated method for the prevention of HIV/STIs during intercourse. Female condoms are polyurethane barrier devices designed to protect the cervix, vagina and part of the vulva. Although female condoms are highly acceptable to some women and offer very effective protection from pregnancy and HIV/STIs, they are rather expensive, not widely available and typically require a partner's knowledge/cooperation for use. Nevertheless, the female condom remains an important option for many women, particularly for high-risk groups such as commercial sex workers.<sup>4</sup> Expanded distribution and use of the female condom should be pursued along with the develop-

ment of new prevention options.

Female-controlled prevention methods that can be used without a male partner's active participation, and possibly without his knowledge, are urgently needed. Acceptability research suggests that many women would likely discuss their interest in using such a method with their partners.<sup>5</sup> However, instead of interrupting sexual activity to put on a male condom or insert a female condom, a woman could potentially insert a female-controlled product well in advance of sex. She could also choose a neutral setting and time to discuss her interest in using the product with her partner, and that conversation could be a one-time event, occurring without the sense of urgency evoked by sexual arousal. All these contextual factors could contribute to the potential acceptability of this type of method to both partners.

Researchers are currently testing existing barrier methods (such as the dia-

phragm) and developing new products (such as microbicides) for HIV/STI prevention. These products may offer substantial protection, but they are not likely to be as effective as condoms at preventing HIV/STI transmission. Instead, they may have other characteristics that may make them appealing to potential users and to public health authorities. In the future, these technologies may provide more prevention options for women who are currently at-risk and unprotected.

### **Condom Use Patterns**

Data show that relatively few couples in long-term relationships use condoms consistently. In surveys conducted around the world, men and women appear to be fairly willing to use condoms with new or casual partners, but once a level of “trust” is established, consistent condom use wanes or ceases altogether.<sup>6</sup> Even sex workers who routinely use condoms with their paying clients may not use them with their boyfriends or husbands.<sup>7</sup> In Sub-Saharan African countries, the reported rate of condom use in primary partnerships is very low (always less than 5% except for South Africa where it has been documented at 7%). The reported rates of condom use in casual partnerships are higher, but still below 50%.<sup>8</sup>

Still, condom promotion programs have had an important impact on the HIV/AIDS epidemic in places like Thailand, leading many public health officials and policy makers to express concern about the introduction of new technologies that may tempt people to replace condoms with new, less effective methods, thus re-

ducing the overall level of protection in the population. The term “condom migration” or “condom replacement” describes regular condom users shifting away from condoms to another method. To explore the potential impact that the introduction of non-condom prevention tools might have on condom migration/replacement, researchers have looked to examples in the family planning field, as well as mathematical modeling.

Contraception research indicates that the overall number of protected sex acts tends to increase with the introduction of new methods.<sup>9</sup> One contraceptive study, for example, showed that the addition of a new contraceptive method to those available in an existing program increased the overall rate of contraceptive use by about 12% and decreased the crude birth rate by 5.3%. If this pattern extends to microbicide use, it is likely that women wouldn't stop using condoms (to the extent that they are able to now) but instead, would start using microbicides when condom use is impossible. Women who cannot or do not use condoms would also then have an option for HIV/STI prevention. In both groups the number of unprotected sex acts would go down, thus raising the overall level of protection.

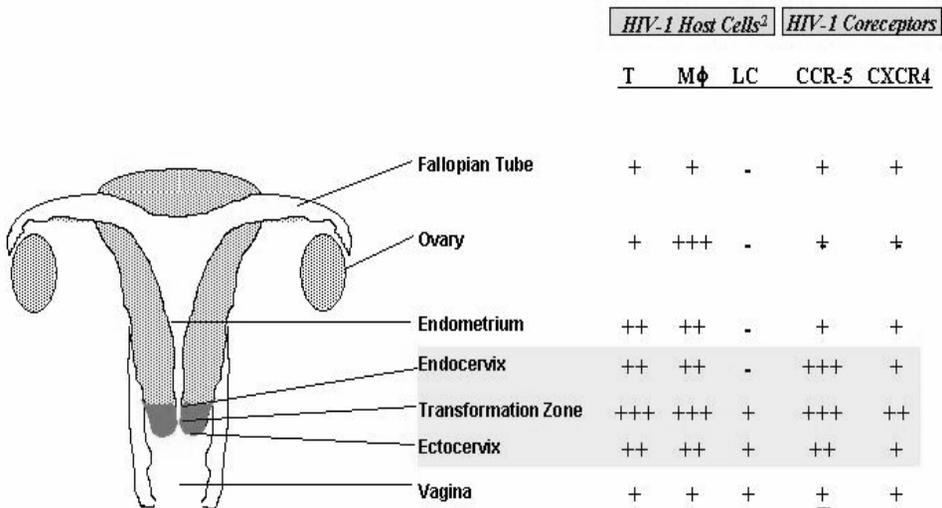
Some may argue that although this pattern may apply when women are choosing among a range of woman-controlled contraceptive methods, it is not predictive of the outcome when men have the opportunity to discontinue condom use in favor of relying on a less intrusive (but also less effective) method. To address this concern, researchers at the London School of Hygiene and Tropical Medicine constructed mathematical models to calculate

what level of condom migration could be tolerated following the introduction of a partially effective microbicide without increasing an individual's risk of HIV infection. As shown in Table 1, they found that it depended largely on the consistency with which condoms were already being used and with which the microbicide would be used in the absence of condoms.<sup>10</sup>

These findings suggest that even if some condom migration occurs, the vast majority of women are likely to be better protected overall when a partially effective microbicide (or other female-controlled HIV prevention product) is available. The

conclusions suggested by this mathematical modeling were supported by recent research on a female sex worker population, including women whose clients sometimes use condoms and women whose clients never use condoms. In this case, researchers found that the women would be able to reduce their risk of acquiring HIV by 17% if they used a 30-50% effective microbicide, or by approximately 28% if they used a 50-80% effective microbicide.<sup>11</sup> However, it is important to note that condom migration or replacement may be an issue among sex workers whose clients consistently use condoms and others who are

### HIV-1 INFECTABLE CELLS ARE CONCENTRATED IN THE CERVIX<sup>1</sup>



<sup>1</sup>Healthy women without evident genital tract infection

<sup>2</sup>T-CD4+ T lymphocytes, Mφ -Macrophages, LC-Langerhans Cells

□ Cervix

From: Anderson D. HIV Immunology. Oral presentation. Diaphragm Renaissance Meeting, September 2002; Seattle, Washington.

**Table 2: Concentration of HIV receptors in female genital tract**

able to achieve consistently high levels of condom use.

For the vast majority of people who do not use condoms consistently, the mathematical modeling research and experience in the field of family planning should help to assuage fears about condom migration/replacement and focus attention on the need for new prevention options to offer more and better protection for those who are at risk and unable to achieve consistent condom use.

### **Cervical Barriers**

Cervical barriers, including diaphragms and cervical caps, are among the oldest known contraceptives. A century ago, diaphragms and cervical caps were popular contraceptives in many European countries, and during the 1920's and 30s, the diaphragm was the most frequently prescribed contraceptive in the United States.<sup>12</sup> Today cervical barriers are approved for contraceptive use around the world. However, distribution is limited and rates of use are low compared to other contraceptive methods.<sup>13</sup>

Diaphragms and cervical caps are soft latex or silicone cups that fit at the upper end of the female genital tract, covering the cervix. Cervical barriers are safe, often reusable, and have very few side effects. Used correctly and consistently, they are an effective means of pregnancy prevention. The diaphragm is 84-94% effective when used with spermicide.<sup>14</sup>

New research suggests that covering the cervix (with a diaphragm or cervical cap) may offer dual protection: preventing pregnancy while simultaneously protect-

ing against HIV/STIs.<sup>15</sup> Compared to the squamous epithelium of the vaginal walls, which is more than thirty cell layers thick, the columnar epithelium of the cervix is only a single cell layer thick. The cervix is the preferential site of infection for many STIs, including bacterial pathogens such as chlamydia and gonorrhea and viruses such as the human papilloma virus (HPV).<sup>16</sup> Researchers recently demonstrated a concentration of HIV receptor and co-receptor sites in the cervix, as well as in parts of the uterine lining and fallopian tubes (see Table 2).<sup>17</sup> Covering the cervix could also protect these vulnerable areas in the upper genital tract.

Given this new evidence on the potential role of the cervix in HIV infection, the diaphragm is currently being tested for its ability to reduce transmission of HIV/STIs. The Methods for Improving Reproductive Health in Africa (MIRA) trial is a randomized, controlled trial currently underway in South Africa and Zimbabwe that aims to measure effectiveness of the diaphragm used with Replens<sup>®</sup> lubricant gel for HIV prevention among women. All participants receive condoms, safer sex counseling and STI treatment, and half of the participants also receive a diaphragm, gel and counseling on how to use the method. Results from this study are expected in 2007. Other studies in Zimbabwe, Madagascar, Kenya and the Dominican Republic are investigating diaphragm use for the prevention of STIs (principally chlamydia and gonorrhea) and acceptability of the diaphragm for HIV/STI prevention.

In recent years, new cervical barrier methods have become available, and others are currently under development. The FemCap<sup>™</sup> is a silicone cervical cap with a

removal strap that was recently approved by the FDA for use as a contraceptive. Lea's Shield is a one-size-fits-all silicone cap with a removal strap and a valve for the passage of cervical secretions and menstrual blood. Currently being developed by the Program for Appropriate Technology in Health (PATH), the SILCS diaphragm will be a one-size-fits-all diaphragm with an arched rim and small finger cup for easy removal. The BufferGel Duet, being developed by ReProtect, Inc., is a one-size-fits-all disposable cup pre-loaded with BufferGel, a candidate contraceptive microbicide. This method is called a cervico-vaginal device (CVD), to emphasize that it is intended to protect both the cervix and the vagina. As interest grows and as research results on HIV/STI prevention become available, more methods may emerge to provide women with increased options for dual protection.

## **Microbicides**

Microbicides may soon provide another option for female-controlled HIV/STI prevention. The word "microbicide" refers to a range of different products currently under development that share one common characteristic: the ability to prevent the sexual transmission of HIV/STIs when applied topically. A microbicide could be formulated in many different ways, including as a gel, cream, suppository, or film. They could also be loaded into a vaginal sponge or ring, thus introducing the possibility of a time-released microbicide that could be released over a longer period of time. Some microbicides are being designed to prevent pregnancy, while others will be non-con-

traceptive.

A non-contraceptive microbicide would provide important new options for women. Since condoms prevent conception, women currently have to choose between childbearing and HIV prevention. This is an untenable dilemma for many women, particularly those living in societies in which status and/or security is attained through motherhood. A microbicide capable of substantially reducing HIV risk without preventing pregnancy could offer women the chance to protect themselves from disease without impeding their childbearing goals.

HIV (and other STI pathogens) infects the body in multiple ways, and an effective microbicide will help to prevent infection using various mechanisms of action. Most microbicides under development act in one or more of the following ways:<sup>18</sup>

- Killing or inactivating pathogens or viruses by breaking down their surface membranes.
- Creating physical barriers, in the form of gels or creams, between pathogens and vulnerable cells in the vaginal and cervical epithelium.
- Strengthening the body's normal defenses by supplementing or enhancing naturally occurring defense mechanisms, such as the vagina's natural acidity.
- Inhibiting viral entry by interrupting the binding of the HIV virus to matching receptors on the target cell's membrane, or by introducing other molecules that will bind with the receptors in advance, thus blocking the sites and

preventing HIV attachment.

- Inhibiting viral replication by utilizing technology from the field of anti-retroviral drug development to suppress replication of HIV once it has entered a cell in the vagina or rectum, thus preventing systemic infection.

Microbicides could potentially be used in a variety of ways for HIV prevention, including use in combination with condoms or cervical barrier methods, as a mouth rinse for protection during oral sex, and rectally for protection during anal sex. Most importantly, they will offer a usable form of primary protection to those unable or unwilling either to use condoms consistently or to rely on abstinence or monogamy as their primary risk reduction strategies.

Scientists are currently testing dozens of potential products for safety and to see whether they can reduce transmission of HIV/STIs. Five candidate microbicides have completed the safety testing phase and are now in large-scale efficacy trials to determine whether they can substantially reduce the risk of HIV transmission. Prior to 2000, scientists had hoped that nonoxynol-9 (N9), an over-the-counter spermicide, would prove effective for HIV/STI prevention. A large multi-national study among sex workers, however, showed that N9 did not reduce the risk of HIV infection.<sup>19</sup> Only when testing indicates solid evidence of both safety and effectiveness is a product presented for evaluation by regulatory agencies and, if approved, made publicly available.

Microbicide advocates calculate that a total of \$140 million was spent globally on microbicide research, development and

advocacy in 2004. This amount is not adequate to move the product pipeline forward efficiently, and under-funding is slowing the progress of microbicide development. Correcting this underinvestment, they estimate, requires a doubling of research funding, a 50% increase in product development funding and 60% increase in advocacy funding per year between now and 2010.<sup>20</sup> Like contraceptives and treatments for diseases associated with poverty, microbicides are currently positioned as a classic public health good, a product that yields a social or public health benefit but fails to attract significant private sector investment.

Since microbicide development is funded almost exclusively by federal and philanthropic grants, the speed with which this research progresses depends substantially upon the level of political will and public demand that can be mobilized to increase investment on the part of governments and private foundations. A pharmaco-economic study by the Rockefeller Foundation indicates that first generation microbicide products are likely to create enough of a market to attract private investment. Market forces, once engaged, are then likely to drive the development and refinement of second and third generation microbicides, which are hoped to have efficacy rates as high as 80-90%.<sup>21</sup> Therefore, governmental investment will not be required indefinitely. Rather, increased public investment in microbicides development is needed in the short-term to propel forward the innovative research that will provide new public health interventions capable of saving millions of lives in the near future.

## Effectiveness and Prevention Messages

Microbicides and cervical barriers are unlikely to be as effective as condoms in preventing HIV/STI transmission. Whereas condoms prevent exposure of vaginal and cervical mucosal tissues to semen,<sup>22</sup> cervical barriers reduce but do not entirely prevent exposure, and microbicides work by killing or disabling pathogens after they enter the body.

“Partial efficacy” is the term used to describe a method that reduces, but does not eliminate, the risk of infection. Although neither cervical barriers nor microbicides will be 100% protective when used alone, they may potentially offer a highly effective method of dual protection when used together.

Given the probable partial efficacy of these new prevention products, it is vital that public health messages continue to encourage people to use condoms whenever possible. This can best be accomplished by adopting a “risk reduction” or “hierarchical” messaging approach.<sup>23</sup> The ABC approach is one such hierarchical model, and it should remain an important component of public health messaging, supplemented by messaging about new prevention methods that can be used together with condoms for extra protection or added pleasure.

The option of using non-condom methods, such as cervical barrier methods and/or microbicides once effectiveness is demonstrated, also needs to be added to the risk reduction hierarchy if we are to address the needs of people unable or unwilling to use the more highly effective options. They

will provide far more protection than using nothing, which is currently the only option for many women now who cannot insist on condoms, monogamy, or abstinence.

The provision of a partially effective method that women can use consistently also, arguably, provides more protection than a more highly effective method that is only used occasionally. The condom left in the drawer, obviously, has an effectiveness rate of zero. It is important to balance the technical efficacy rates of various methods against their acceptability and “real life” usage rates before drawing conclusions about which HIV prevention options provide the highest rates of protection in a given population or for any particular individual.

## Acceptability and Access

If new prevention products are proven effective, they must also be acceptable and available to the people who need them most in order to have an impact on the HIV/AIDS epidemic.

The body of knowledge regarding acceptability is growing, and includes clinical trial data gathered by asking trial participants about their opinions of the test product, as well as studies designed solely to examine acceptability issues. In general, acceptability studies have underscored the urgent need for, and interest in, female-controlled HIV prevention methods.<sup>24</sup> A supportive policy environment and a sustained financial commitment from governments, foundations and manufacturers are required to ensure that product supply meets this anticipated demand.

Microbicide acceptability research indi-

cates that women want both contraceptive and non-contraceptive products. Formulation preference studies suggest that no single formulation or delivery device will meet the needs and preferences of all women.<sup>25</sup> Some women prefer a gel applied with an applicator; others may opt for a film, suppository, or sponge. Research indicates that perceived safety and effectiveness are more important than most product attributes in determining a woman's willingness to use a microbicide.<sup>26</sup> Ultimately, a variety of products with a range of qualities, including formulation, packaging and indications, are necessary to meet the needs of a wide range of users.<sup>27</sup>

Studies indicate that women in a variety of socioeconomic and cultural settings find cervical barriers acceptable for family planning.<sup>28</sup> Research on acceptability of the diaphragm as a contraceptive method has been conducted in the United States, Columbia, Turkey, the Philippines, Brazil and India. Recent research has investigated the acceptability of the diaphragm as an HIV/STI prevention method. In Zimbabwe, for example, the UZ-UCSF Collaborative Programme in Women's Health conducted a study of diaphragm acceptability among sexually active urban women who were inconsistent condom users. After six months of participation in the study, 92% were very comfortable inserting and removing a diaphragm. This study concluded that, if proven effective against HIV/STIs, the diaphragm used alone or in combination with a microbicide could provide an acceptable alternative to male condoms in at-risk Zimbabwean women.<sup>29</sup> Ongoing and future acceptability studies and social science components of efficacy studies will continue to inform this issue.

If new prevention technologies are to have an impact on the HIV/AIDS epidemic, they must be made both acceptable and accessible to at-risk women and girls who are currently unable to use effective prevention methods. Careful attention to access, as well as acceptability, is critical because experience demonstrates that new health technologies rarely become widely available in developing countries until more than a decade after approval in the US or Europe.<sup>30</sup> As the burden of the HIV/AIDS and STI epidemics falls most heavily on populations with limited access to medical care and health technologies, adequately addressing issues of cost, supply, regulatory approval and social and political environment will be vital to the success of new prevention interventions.

### **Potential Impact**

The potential global impact of a safe and effective female-controlled HIV prevention product is enormous, especially in populations with low levels of condom use. A study conducted by the London School of Hygiene and Tropical Medicine showed that if a 60% effective product was offered to 73 lower income countries, and was used by 20% of people reached by current health care services in just 50% of unprotected sex acts, then 2.5 million HIV infections among men, women and children could be averted in three years.<sup>31</sup> These are not ambitious assumptions. Despite the limitations of products and public health systems, development of these important technologies could have an incredible public health impact.

Speaking to microbicide researchers and

advocates at an international conference in 2004, Stephen Lewis, UN Special Envoy on HIV/AIDS in Africa, spoke of circumstances he has encountered: "I move from country to country, from hinterland to rural hinterland, from project to project, and everywhere I go the lives of women are compromised." In closing, he said, "I ask only that you see microbicides, not merely as one of the great scientific pursuits of the age, but as a significant emancipation for women whose cultural and social and economic inheritance have put them so gravely at risk. Never have so many died for so little reason. You have a chance to alter the course of that history. Can there be any task more noble?"<sup>32</sup>

For over two decades now, women confronted with a raging pandemic have had no tools beyond condoms with which to protect themselves. The need among women and girls worldwide for prevention methods that they can directly control could not be more obvious, nor could the potential public health impact that such options may offer be more exciting. 

## Acknowledgements

A portion of this work is supported by a grant from the University of California, San Francisco with funds from the Bill and Melinda Gates Foundation.

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