

## PREVENTION

# AN UPDATE ON FEMALE-CONTROLLED METHODS FOR HIV PREVENTION: FEMALE CONDOM, MICROBICIDES AND CERVICAL BARRIERS

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Worldwide, nearly 5 million new HIV infections occurred in 2005 with more than 3 million of these in sub-Saharan Africa. Despite declines in the HIV prevalence in some sub-Saharan African countries, many continue to be heavily affected.<sup>1</sup> In Zimbabwe data have shown a decrease in prevalence from 22.1% to 20.1% since 2003, yet there is no sign of a similar trend in South Africa, where the adult prevalence rate is 18.8%.<sup>2</sup> National-level prevalence rates, however, may not reveal the full impact of the epidemic on different populations. For example, 30.2% of pregnant women in South Africa attending public antenatal clinics in 2005 were HIV positive, with rates varying by province from 15.7% in the Western Cape to 39.1% in KwaZulu-Natal.<sup>3</sup> In addition, female youth aged 15 - 24 years were three times more likely to be infected than young men in the same age group.<sup>4</sup>

Women are increasingly bearing the burden of the epidemic. Of the 39 million people worldwide living with HIV/AIDS, half are women. UNAIDS estimates that of the new infections expected to occur between 2002 and 2010, 70% will be among women in the developing world.<sup>5</sup> Several factors account for women's higher risk of infection, including biological, socio-cultural and economic factors. For instance, the female reproductive tract is more susceptible to HIV infection than the male reproductive system, and young women are at highest risk of HIV infection due to an immature physiology. Further, sexual violence and gender inequalities frequently play a role in women's and girls' ability to practise safer sex.<sup>6</sup>

Current HIV prevention methods are male-initiated or require a male partner's co-operation, leaving women without sufficient means to protect themselves from infection. New female-controlled prevention methods are urgently needed to reduce women's and girls' risk of HIV infection. This article provides an update on currently available methods and others being tested and/or developed to provide women and girls with more HIV prevention options.

### AN EXISTING METHOD: THE FEMALE CONDOM

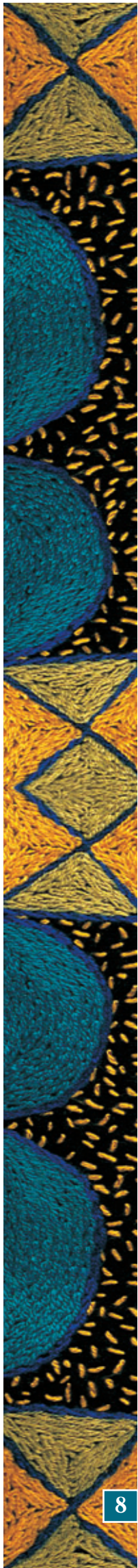
The female condom is the only female-initiated method (women instigate use but need co-operation of their partner) that is known to be safe and effective in reducing the risk of pregnancy and the transmission of sexually transmitted infections (STIs). The design of the female condom offers more protection to women than the male condom because the outer ring partially covers the external genitalia. Studies in a variety of countries and cultures show that, on average, 50 - 70% of male and female participants found the female condom to be acceptable.<sup>7</sup> An acceptability study in South Africa found that 30% of the female participants used the female condom at least once, and of these 86% said they would use it again and 95% said they would recommend it to friends.<sup>8</sup>

In terms of pregnancy prevention, the female condom is comparable to the male condom. Twenty-one per cent of women using the female condom will become pregnant in the

first year of use compared with 15% of male condom users.<sup>9</sup> With correct and consistent use, 5% of female condom users and 2% of male condom users will experience a pregnancy in the first year of use. More recent studies in China, Panama and Nigeria showed higher effectiveness rates of 94 - 98% for the female condom compared with 92 - 96% for the male condom.<sup>10</sup> Regarding prevention of STIs, a systematic review found that female condoms confer as much protection from



*The female condom.*



STIs as male condoms.<sup>11</sup> In addition, laboratory studies have demonstrated that the female condom blocks the passage of microorganisms, including HIV.<sup>12</sup>

Currently, the only female condom that is approved by the US Food and Drug Administration and procured by large donor agencies is the FC Female Condom<sup>®</sup> produced by the Female Health Company; two other female condom brands are marketed outside the USA. The most common complaints about the female condom – aesthetics, difficulty with insertion and noise – typically fade with repeated use. Nevertheless, several new condoms are being developed that address these concerns and may also be less expensive. The World Health Organization announced in August that the second generation FC2 Female Condom, made of nitrile, a latex derivative, had met international standards for dual protection against pregnancy and STI/HIV infection and will be cheaper to produce.<sup>13</sup>

Since the female condom entered the market in 1992, more than 100 million have been distributed in more than 90 countries.<sup>14</sup> Since the female condom was introduced into the country in 1998 through a national pilot programme, South Africa has become the second-largest distributor of female condoms globally (following Brazil) with procurement of female condoms growing from 1.3 million in 2002 to 2.4 million in 2005.<sup>15</sup> A forthcoming study reports that if 53.7 million female condoms were distributed in South Africa, 32 000 HIV infections would be prevented, which would translate into cost savings of between \$5.3 and \$35.7 million.<sup>16</sup>

There also have been several recent efforts to scale up female condom programmes. In September 2005, a global consultation was held in the USA to develop a plan of action for garnering international support for the female condom. Also in 2005, the United Nations Population Fund launched the Global Female Condom Initiative, which aims to scale up female condom programming in at least 23 countries. Finally, the recently launched Prevention Now! Campaign is working to promote universal access to female condoms and other existing STI/HIV prevention options.

### PROMISING NEW METHODS UNDER DEVELOPMENT: MICROBICIDES

Microbicides are substances designed to reduce transmission of HIV and/or other STIs when applied vaginally and will probably come in a variety of forms including gels, creams, films, suppositories and vaginal rings. Although not yet available, microbicides are a promising female-controlled method that have been under development for the past 15 years. Microbicides could work by:

- Boosting the body's natural defenses against infection (vaginal defense enhancer)
- Damaging the surface membranes of pathogens rendering them ineffective (surfactant)
- Binding to a pathogen or healthy cell to prevent

attachment by an infectious agent (entry and fusion inhibitor), and/or

- Incorporating antiretrovirals which could work by preventing viruses from replicating in a cell (replication inhibitors).

Currently there are 12 candidate microbicides in clinical evaluation with 4 in large advanced studies (Table I).<sup>17</sup> The earliest results are expected in 2008. South Africa serves as a clinical research site for all 4 of the microbicide candidates currently in late-stage trials for HIV prevention.<sup>18</sup>

TABLE I. MICROBICIDES IN ADVANCED CLINICAL TRIALS\*

Mechanism of action	Candidate product	Developer	Phase
Vaginal defense enhancers	BufferGel <sup>®</sup>	ReProtect, Inc.	Phase 2/2B
Entry/fusion	Carraguard <sup>®</sup>	Population Council	Phase 3
	Cellulose sulfate gel (CS)	CONRAD	Phase 3
	PRO 2000	Indevus Pharmaceuticals, Inc.	Phase 3

\*Adapted from the Alliance for Microbicide Development.

Because of their different modes of action, some microbicides are designed to reduce the risk of pregnancy and STIs, including HIV, while others aim only to prevent infection, enabling women who want to conceive to protect themselves from disease.

It is estimated that the first microbicides will be 50 - 60% effective in preventing HIV – much lower than the approximate 90% effectiveness rate of male condoms.<sup>19</sup> However, microbicides offer an important alternative in those situations when male condom use is impossible. For example, if only 20% of people at risk of HIV use a microbicide that is 60% effective in protecting against HIV transmission, 2.5 million infections could be averted over 3 years.<sup>20</sup>

More than 60 studies have been conducted in developed and developing countries to determine the characteristics of an acceptable microbicide. Interest in microbicides is higher in areas where women perceive their HIV risk to be greater. In addition, these studies indicate the need for a variety of products to meet the range of demands of a diverse consumer population. In South Africa, qualitative research revealed support for microbicides stemming from respondents' concerns around the HIV epidemic, rape, sexual coercion and unplanned consensual sex.<sup>21</sup>

Microbicides have garnered much greater attention in the past few years. After the record-level attendance for the Microbicides 2006 conference in Cape Town, South Africa, microbicides again took centre stage at the recent XVI International AIDS Conference in Toronto, Canada. Bill Gates opened the conference by stating, 'We need to put the power to prevent HIV in the hands of women.'

Greater attention and advocacy has increased funding for microbicide research and development with annual global investment rising from US \$65 million in 2000 to US \$163 million committed for 2005.<sup>17</sup> Public-private partnerships have played a critical role in advancing microbicide research. Commercial investment has been sorely lacking, while funding from national level sources is increasing. Experts agree that despite increased investment a global funding shortfall remains and that US \$280 million is needed on an annual basis.

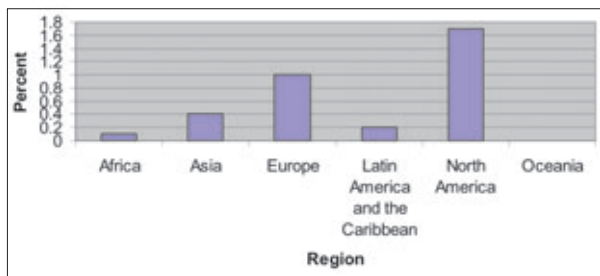
### NEW POTENTIAL OF OLD METHODS: CERVICAL BARRIERS

For thousands of years women have used various forms of cervical barriers for reproductive health purposes. For example, the contraceptive diaphragm was developed in the late 19th century and by 1930 was the most frequently prescribed contraceptive method in the USA. Diaphragms and cervical caps were also popular contraceptives in the early 1900s in Europe, including Holland, Germany, England and France.<sup>22</sup>



*The diaphragm.*

Cervical barrier methods when used with spermicide have proven contraceptive benefits. However, internationally few women rely on cervical barrier methods for contraception. According to the United Nations Population Division, only 0.5% of women (married or in partnerships currently using contraception) aged 15 - 49 years use vaginal barrier methods, including the diaphragm, cervical cap and spermicidal foams, jelly, cream and sponges (see Fig. 1 for worldwide use).



*Fig. 1. Percentage of women\* using vaginal barrier methods† worldwide, United Nations Population Division 2003. (\*Married or in-union women of reproductive age currently using contraception. †Diaphragm, cervical cap, spermicidal foams, jelly, cream and sponges.)*

Historically, cervical barrier use has been limited in much of Africa partly owing to the lack of providers trained to counsel clients on use and to fit vaginal devices. Providers may also shy away from offering cervical barriers because of the need to clean and sterilise devices used for fitting.<sup>23</sup> Misperceptions about cervical barriers and lack of knowledge about these products as well as provider bias towards other methods may limit support for use of cervical barriers. Some providers in a three-country study perceived appropriate candidates for the diaphragm to be educated and 'open-minded' women; however, attitudes toward the diaphragm changed following provider training.<sup>24</sup> Newer, more effective pregnancy prevention methods, such as hormonal contraception, have also led to a decline in interest in cervical barriers in Africa and other parts of the world.

Several acceptability studies have been conducted in a range of developing countries including Egypt,<sup>25</sup> Turkey,<sup>26,24</sup> Colombia,<sup>24</sup> the Philippines,<sup>24</sup> Brazil,<sup>27</sup> Zimbabwe<sup>28</sup> and India.<sup>29</sup> These studies show that diaphragms are generally well accepted, particularly if women receive counselling from providers and support from their partners. In India, researchers reported that even in the absence of privacy or a bathroom at home, women were capable of using the diaphragm successfully.<sup>29</sup> Findings from a recent study conducted in Johannesburg, South Africa, showed that 78% of participants were willing to try microbicides while 60% and 56%, respectively, were willing to use the diaphragm and the female condom.<sup>30</sup>

Although the diaphragm was previously available in South Africa, it is not currently available in either the private or the public health care sector. Despite this lack of availability, 16.4% of all women surveyed in the 1998 Demographic and Health Survey had knowledge of the diaphragm as a contraceptive method and 0.8% of women had ever used the method. Among women currently using contraception, unsurprisingly, none reported use of the diaphragm.<sup>31</sup>

Although not yet proven, cervical barriers may also provide some protection against HIV and STIs. Prior observational studies indicate that women who used a diaphragm with spermicide had a reduced risk of acquiring STIs and associated long-term sequelae.<sup>32</sup> All of the studies compared diaphragm users with non-users, and all used some type of multivariate analysis to control for known co-factors or confounders such as socioeconomic status or age. Because these studies were not designed to test the efficacy of the diaphragm, and because they are all observational studies and therefore subject to biases, their results must be considered as suggestive rather than definitive. Clinical trials are currently underway to investigate whether the diaphragm may reduce STI/HIV transmission.

Indeed, there is biological plausibility that the diaphragm may also decrease risk of HIV acquisition. Several characteristics of the cervix may mean it is more vulnerable to STIs/HIV than other areas of the female reproductive tract. First, recent evidence suggests that the cervix has a high concentration of

HIV-susceptible cells, resulting in a heightened vulnerability to HIV infection.<sup>33</sup> Second, compared with the thicker cell lining of the vagina, the cervix is more fragile, covered only by a single layer of cells. It is therefore biologically more susceptible to trauma, and therefore STI/HIV infection, than the vagina. Third, research shows that the cervix is the preferential infection site for many STIs, including gonorrhoea, chlamydia, and human papillomavirus (HPV),<sup>34,35</sup> and the presence of STIs increases HIV transmission risk and vice versa.<sup>36</sup> Finally, the cervix is the entryway to the upper genital tract, which may also be an important site for HIV infection.

Demonstrating the increased activity and interest in cervical barrier methods, the Microbicides 2006 conference featured nearly 30 presentations reporting on research aiming to determine the safety and acceptability of diaphragms and other cervical barriers as potential STI/HIV prevention methods. For example, one study among US women found that two candidate microbicides, Acidform™ and BufferGel® were safe when used with a diaphragm. In addition, researchers at the University of California, San Francisco and University of Zimbabwe found that Cellulose Sulfate gel, another potential microbicide, when used with the diaphragm was shown to be safe. Another research trial demonstrated that the BufferGel Duet™, a cervical barrier that is combined with the candidate microbicide BufferGel®, was easy to insert and remove, validating the idea that a cervical barrier can be prepackaged with a microbicide. One of the most exciting pieces of news were the results presented by the University of Pennsylvania showing that BufferGel™ used with the diaphragm is as effective as the diaphragm used with nonoxynol-9 (N-9) spermicide for contraception. Having an N-9 alternative is a significant advance, because N-9 is not recommended for women at high risk of HIV.

For more information on research and issues related to cervical barriers, visit the Cervical Barrier Advancement Society (CBAS) website at [www.cervicalbarriers.org](http://www.cervicalbarriers.org).

## CONCLUSION

Although female-controlled HIV prevention methods cannot address the root causes of women's vulnerabilities, they will provide women with more alternatives to protect themselves from infection. No one method will be right for every woman or girl, but reproductive health and rights are advanced by putting the tools of prevention in women's hands. Because health care providers are at the forefront in the fight against HIV, they play a key role in educating clients about available options, such as the female condom, staying informed about the development of new promising methods such as microbicides and cervical barriers, and supporting women in their method choice.

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