Female-Initiated HIV Prevention:
What will we learn from upcoming trials?

Anticipating the Results of the MIRA Diaphragm and Carraguard® Microbicide Trials

A publication of the AIDS Vaccine Advocacy Coalition (AVAC),
in collaboration with the African Microbicide Advocacy Group (AMAG)
and the Global Campaign for Microbicides (GCM)
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This brochure is designed to help HIV-prevention and women's health advocates understand the implications of findings from two studies of female-initiated HIV-prevention methods. One trial, known as MIRA, looks at whether protecting the cervix with a physical barrier such as the latex diaphragm reduces women's risk of HIV acquisition. The other trial examines a microbicide candidate called Carraguard®. There are many differences between the diaphragm and a microbicide like Carraguard. However, both methods are female-initiated, coitally-dependent (meaning that timing of use is related to when sex happens), and vaginally-inserted. This brochure gives information on the two methods and the ways that they were studied. It also explores the broader implications of potential trial results for other female-initiated methods.

This publication is part of AVAC's "Anticipating Results" series, which provides timely analysis of trials of AIDS vaccines and other new HIV-prevention options. AVAC is committed to working in partnership with other groups, and is proud to produce this publication in collaboration with the African Microbicides Advocacy Group (AMAG) and the Global Campaign for Microbicides (GCM). For other publications in this series, visit http://avac.org/publications.htm#series.

An informative moment in research on female-initiated HIV-prevention methods

From the earliest days of the AIDS epidemic, HIV-positive women and their allies demanded that public health officials recognize heterosexual women's vulnerability to HIV—then stereotypically viewed as a disease of homosexual men, injection drug users, Haitians, and hemophiliacs. These activists demanded broad structural changes to redress the ways that gender inequality fuels the epidemic. And from the earliest days of this struggle, they have also consistently demanded that attention and resources be devoted to identifying new HIV-prevention methods that women could use.

Today we are on the verge of learning the results from two efficacy trials of female-initiated HIV-prevention strategies. Right now, the female condom is the only biomedical HIV-prevention tool that women can opt to use themselves. It is hoped that these two trials will provide insight into how to develop other, more discreet tools, to expand women's options to prevent HIV.

These two studies look at two different experimental strategies. One study, known as Methods for Improving Reproductive Health in Africa, or MIRA, is evaluating the effect of the Ortho All-Flex® diaphragm used in combination with Replens® lubricant gel and with male condoms (intervention group) compared to male condoms alone (control group). This trial asks whether a barrier method that covers the cervix—which is thought to be particularly vulnerable to HIV infection—can provide additional protective benefit against HIV infection. Results from the MIRA study will be released in mid-July.

The other study is an efficacy trial of a microbicide candidate known as Carraguard®. The term microbicide refers to a class of experimental products designed to reduce a woman's risk of acquiring HIV and potentially other STIs when inserted in the vagina prior to sex. Although there are several microbicide candidates in efficacy trials at the moment, no proven microbicide exists to date. The Carraguard study will release its results in late 2007. Microbicides might also be used for protection during anal sex, but current efficacy trials are not examining this route of transmission *(see Box 5: What about anal sex?)*.

Good news will require coordinated and energetic advocacy.

Microbicides can be formulated and delivered in a variety of ways—as a gel, cream, or suppository, or pre-loaded into a sponge, vaginal ring, or cervical barrier that would slowly release the active ingredient over time. Like the other microbicides in large-scale trials today, Carraguard is formulated as a lubricating gel that is inserted into the vagina with a plastic applicator.

Today we are on the verge of learning the results from two efficacy trials.

Cervical barrier methods and the microbicides in efficacy trials today use different mechanisms to attempt to block HIV infection. However, they also have important similarities: both are female-initiated, vaginally-inserted, and effective only if in place before sexual intercourse occurs.

In addition, like all HIV-prevention approaches, both methods are expected to provide partial protection at best. Moreover, both of the studies discussed here may yield results that require careful interpretation and explanation by researchers, policy makers, and advocates at global, national, and grassroots levels.

This brochure is designed to help advocates understand these trials and what actions may need to be taken based on the trial results, because:

- Good news will require coordinated and energetic advocacy around next steps for possible product introduction such as operational research and pilot or introductory delivery programs.
- Indeterminate news will require careful explanation, interpretation, discussion and consensus building about possible next steps.
- A finding of no benefit will require HIV-prevention advocates everywhere to simultaneously communicate

Box 1: The key points

- The first efficacy trials of the microbicide candidate Carraguard and the Ortho All-Flex diaphragm (a cervical barrier method) were recently completed. Both of these trials tested new female-initiated HIV-prevention strategies. Results from the diaphragm study will be announced in July 2007; results from the Carraguard study are expected by the end of 2007.
- Advocates must prepare now for a variety of scenarios that could emerge from one or both of the trials, including clear evidence of benefit, indeterminate results, or no evidence of protective benefit.
- Any finding will bring challenges. Even clearly positive results will require careful planning and resource mobilization to ensure that products are licensed and delivered through effective programs along with proven HIV-prevention strategies.
- If neither product shows benefit, HIV-prevention advocates must vigorously advocate for continued research into female-initiated prevention strategies, including next-generation microbicides and new cervical barriers. Developing and testing new drugs and prevention tools is a long and challenging process. But expanding women's options and advancing women's control, autonomy and agency, is too important to abandon.
- Biomedical strategies alone will not solve the AIDS crisis in women. Development of new strategies should be accompanied by ongoing work to empower women and girls and to expand access and use to existing prevention methods.
- Regardless of outcome, these trials will have provided a wealth of information on women's preferences and how best to conduct clinical trials. These valuable lessons will be applied to future research into female-initiated HIV-prevention methods.

the results and emphasize the need for more well-designed studies on female-initiated methods, including additional user-dependent methods.

It is important to remember that a successful clinical trial is one which produces a scientifically accurate result. Even if it is not the result we had hoped for, if it is precise, it will help to answers questions that help the field move forward. At minimum, we will know what doesn't work, and perhaps be able to analyze the results to understand why.

No matter the outcome, we have a lot to learn—not only from the trial data, but from how the trials themselves were designed and conducted.

Why is a vaccine organization writing about other female-initiated methods?

AVAC was founded in 1995 to advocate for the ethical development and global delivery of vaccines against AIDS. Over a decade later, we are still committed to that cause. We are also well aware that other new prevention methods are needed as urgently and are likely to arrive sooner than a vaccine. And we think many of the issues we work on— accelerated research, community involvement and education, research ethics, global access, and policy analysis—are highly relevant to cervical barrier methods and microbicides. In the coming years, AVAC will continue to work in partnership with other advocates to advance ethical prevention research and ensure that the benefits are shared globally. We appreciate opportunity to collaborate with the African Microbicides Advocacy Group and the Global Campaign for Microbicides on this briefing paper, as well as our on-going partnership with them across the field of HIV-prevention research advocacy.

Defining female-initiated HIV prevention

A "female-initiated" method is one that a woman could use or receive *herself* to reduce her risk of becoming infected with HIV.[1] Behavioral change and partner negotiation skills can improve women's ability to negotiate use of the male condom with their partners—but the male condom still goes on the man's penis; it is not a method a woman can use herself without his cooperation.

Some female-initiated methods can be used by a woman without her partner's knowledge, which remains an important goal in giving women choices over protecting themselves without having to ask permission to do so. But in many situations, a woman's ability to consistently use a given intervention may be improved if she does not have to use it covertly and has the support of her sexual partner(s) in doing so. Indeed, social science research suggests that most women would tell their partners about their use of a microbicide, either because they are afraid of the consequences should their partners find out or because they want their partners to know.

Not all female-initiated methods require insertion by a woman into her vagina. Pre-exposure prophylaxis, AIDS vaccines, and treatment of herpes infection are potential prevention strategies that are not vaginally inserted but that a woman would, nevertheless, be able to use or receive without her partner's knowledge.[2]

There are many different types of female-initiated strategies currently being tested *(see Box 2: Experimental female-initiated HIV-prevention methods)*.

[1] The term "female-controlled" is sometimes used to refer to a subset of prevention options such as the diaphragm, cervical cap, or sponge, which a woman could potentially use without her partner's knowledge or consent. In this document, we use the term female-initiated to acknowledge the reality that in many situations a woman may want or need to discuss the strategy she is using with her sexual partners, while retaining the decision-making power over whether or not it is used.

[2] Traditionally, women's health advocates have also made an important distinction between user-initiated versus "provider dependent" methods. The provision of methods like an HIV vaccine or injectable contraceptive is controlled by health care providers and cannot be administered, reversed or discontinued at the discretion of the user.

Box 2: Experimental female-initiated HIV-prevention methods

Cervical barrier methods: Studies of cervical barriers as HIV-prevention methods aim to reduce women's risk of HIV infection by covering the cervix (the lower entrance of the uterus), which is thought to be highly vulnerable to HIV infection. The first device in this class to be tested for protection against HIV is the diaphragm, one of the oldest contraceptive methods. It is a dome-shaped cup which can be made out of silicone, rubber or latex. Other prospective cervical-barrier candidates for HIV-prevention are the cervical cap and the BufferGel Duet.

Microbicides: Microbicides are substances applied to the vaginal or rectal mucosa and are intended to reduce transmission of HIV and/or STIs when used during intercourse. A number of formulations are being developed to meet diverse user needs and preferences: cream; gel; suppository; pre-loaded diaphragm or cervical cap; or time-release sponge or vaginal ring. All of the products currently in late-stage clinical trials are gels.

Pre-exposure prophylaxis: Pre-exposure prophylaxis (PrEP) refers to an experimental HIV-prevention strategy that would use anti-retrovirals to protect HIV-negative people from HIV infection. In the strategy that is currently being tested, HIV-negative people would take a single drug, or a combination of drugs, orally, everyday, to potentially reduce their risk of HIV infection. These trials are ongoing.

AIDS vaccines: An AIDS vaccine has the potential to be a female-initiated prevention strategy. While no one knows exactly what characteristics an AIDS vaccine will have, immunizations might be offered at clinics or other service points that both women and men might be able to visit discreetly. Vaccine-related protection would not be coitally dependent.

For updated information on these trials, visit AVAC's prevention research timeline at http://www.avac.org/timeline-website/.

Understanding the Trials

For detailed summaries of the MIRA and Carraguard® study designs and objectives, go to www.avac.org/pdf/MIRA.pdf and www.avac.org/pdf/Carraguard.pdf, respectively.

Table 1 presents key similarities and differences between the MIRA and Carraguard trials.

Table 1: Key similarities and differences between the MIRA and Carraguard trials

Key similarities	Key differences
Both the diaphragm and Carraguard are female-initiated, coitally dependent, and vaginally inserted experimental methods for HIV prevention.	Mechanisms of action differ between Carraguard and the diaphragm plus gel.
Both products are expected to provide partial efficacy at best.	MIRA is an open-label, or unblinded study, meaning that participants and researchers knew who received the experimental product and who did not. The study is unblinded because there is no placebo to mimic the diaphragm.
Both trials were conducted in southern Africa, following extensive safety and acceptability evaluation in a range of settings in different parts of the world.[3][4][5][6]	Carraguard is a double-blind study, meaning that neither the researchers nor the participants in either arm knew whether they received the experimental product or the placebo gel.
Both trials provided participants with risk-reduction counseling, male condoms, HIV testing, and training on product use. Participants received diagnosis and treatment of STIs throughout the course of the study.	The diaphragm is already proven safe and effective as a contraceptive, and registered for use in some countries. While some family planning providers have at least some knowledge about the diaphragm, current access to and use of the diaphragm is still quite limited.
For study participants who became HIV-positive during the trials, sponsors facilitated care and support through existing services in the trial communities, including links with ARV programs.	Carrageenan, the active ingredient in Carraguard, is a food additive used as a thickener that has been designated as GRAS (generally recognized as safe) for ingestion by the US FDA. However, Carraguard has not yet been approved by the FDA for vaginal use, although it has undergone phase I and II safety studies.
Both trials have been periodically reviewed by independent data and safety monitoring boards, which found no evidence of overwhelming benefit or harm related to the product.	

[3] Coetzee N, Hoosen A, Blanchard K, de Kock A, Sebola M, Friedland B. "A randomized, placebo-controlled, double-blind expanded safety trial of Carraguard(tm) microbicide gel in South Africa: Signs and symptoms of genital irritation." Oral presentation, XIV International Conference onAIDS, Barcelona, Spain. July 2002.

[4] Coggins C, Blanchard K, Alvarez F, Brache V, Weisberg E, Kilmarx P. Preliminary safety and acceptability of a carrageenan gel for possible use as a vaginal microbicide. Sexually Transmitted Infections (2000), 76:480-483.

[5] Moench T, Chipato T, Padian N. Preventing disease by protecting the cervix: the unexplored promise of internal vaginal barrier devices. AIDS (2001), 15: 1595-1602.

[6] van der Straten, A, Kang MS, Posner SF, Kamba M, Chipato T, Padian N. Predictors of diaphragm use as a potential sexually transmitted disease/HIV prevention method in Zimbabwe. Sexually Transmitted Diseases (2005), 32(1): 64-71.

Understanding the possible outcomes from the current trials

As Figures 1 and 2 on pages 8 and 9 illustrate, there is a complex web of possible outcomes associated with each of these trials. The two most likely scenarios are:

1) No efficacy or indeterminate results

It is possible that one or both trials will show no statistically significant difference in rates of HIV infection in women between the experimental and control arms. This is always a possible outcome for prevention trials: if researchers knew before a trial started that an intervention provided a clear benefit, it would be unethical to deny this method to a group of participants.

If there is a finding of no efficacy for either trial, or if there is an indeterminate result that *might* indicate some efficacy, questions may be raised about what these data actually mean. Lack of efficacy or an indeterminate result could happen in either of these two trials. Microbicides and the diaphragm plus gel must be used at each act of intercourse. Because of this "coital-dependence", lack of an effect in a trial could be either because the product did not work, or because it was not used. Or, there could be such high rates of successful condom use that it is impossible to measure the effect of the experimental intervention alone. This can be particularly true in an open-label trial such as MIRA where the control-group participants know they are not receiving the experimental product. For these complex reasons, scientists may have different ideas about what to infer from a trial that shows no effect.

From an advocate's perspective, there are some critical messages that must be supported if we find there are different interpretations of a trial showing limited or no effect. These include:

- **The failure to find a positive result in a single cervical barrier method or microbicide candidate does not mean that the entire class of products should be dismissed.** Other cervical barriers may prove effective; future microbicide candidates with multiple mechanisms (ARV and non-ARV containing compounds) should also be explored.
- **Social science research on sexual behavior, product acceptability and other issues is fundamental to trial design for user-dependent methods.** In trials of female-initiated, coitally-dependent methods, women are asked to report on their sexual behavior and rates of product use throughout the trial. Social scientific research on vaginal practices, sexual behavior, and adherence to product use informs the trial design and is critically important to the interpretation of studies that can gather this information systematically and accurately.
- **Future solutions may lie in innovative products and prevention combinations *and* in innovative trial designs.** A finding of no effect could be an indication that the trial design needed to be improved. It could also be an indication that the product needed to be improved. Alternative microbicide delivery systems such as vaginal rings or sponges, which might provide protection over an extended period of time, are being explored. Simply put: it is not an either-or decision. We need innovative strategies and innovative trial designs. Looking ahead, we need information on how to deliver and measure the efficacy of combinations like circumcision plus cervical barrier, vaccine plus pre-exposure prophylaxis, and so on.
- **Community involvement is critical.** This is true for all scenarios, but we are making the point here because the ability to design and conduct future trials, which test products that are relevant to women's lives, depends on the input, expertise and participation of women and their communities at the point at which trial results of no efficacy or indeterminate are being discussed.

2) Definitive evidence of partial efficacy

Like the rest of today's HIV-prevention trials, the MIRA and Carraguard® studies are designed to detect levels of partial efficacy or protective benefit. In other words, neither the diaphragm nor Carraguard nor any other experimental HIV-prevention strategy is expected to provide 100 percent protection against HIV infection. Instead, these strategies are being examined to see if they provide some benefit—a measurable, meaningful reduction in the risk of infection. Both the MIRA and the Carraguard studies were designed to detect at least a 33 percent difference in risk of infection between their control and experimental arms.

If either trial yields a result at the lower end of efficacy—around 33 percent—the method may likely

Figure 1:
Possible scenarios for MIRA trial outcomes

No Efficacy

Explore data and trial design to better understand the reasons for a finding of no or indeterminate effect, and gain insights for future research

Continue advocacy for and research on female-initiated prevention

Additional trials including studies in other populations; post-marketing studies and pilot projects to learn about best practices for delivery

New financial and human resources will be needed to support rollout, access, and effective delivery

Efficacy above 50%

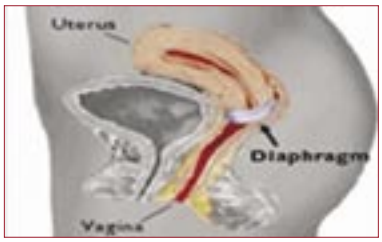
Women could consider using the diaphragm off-label until regulatory agencies dictate the type of confirmatory studies needed for a change in indication

Efficacy above 30%, below 50%

Consider testing diaphragm in combination with other effective strategies such as microbicides as they emerge

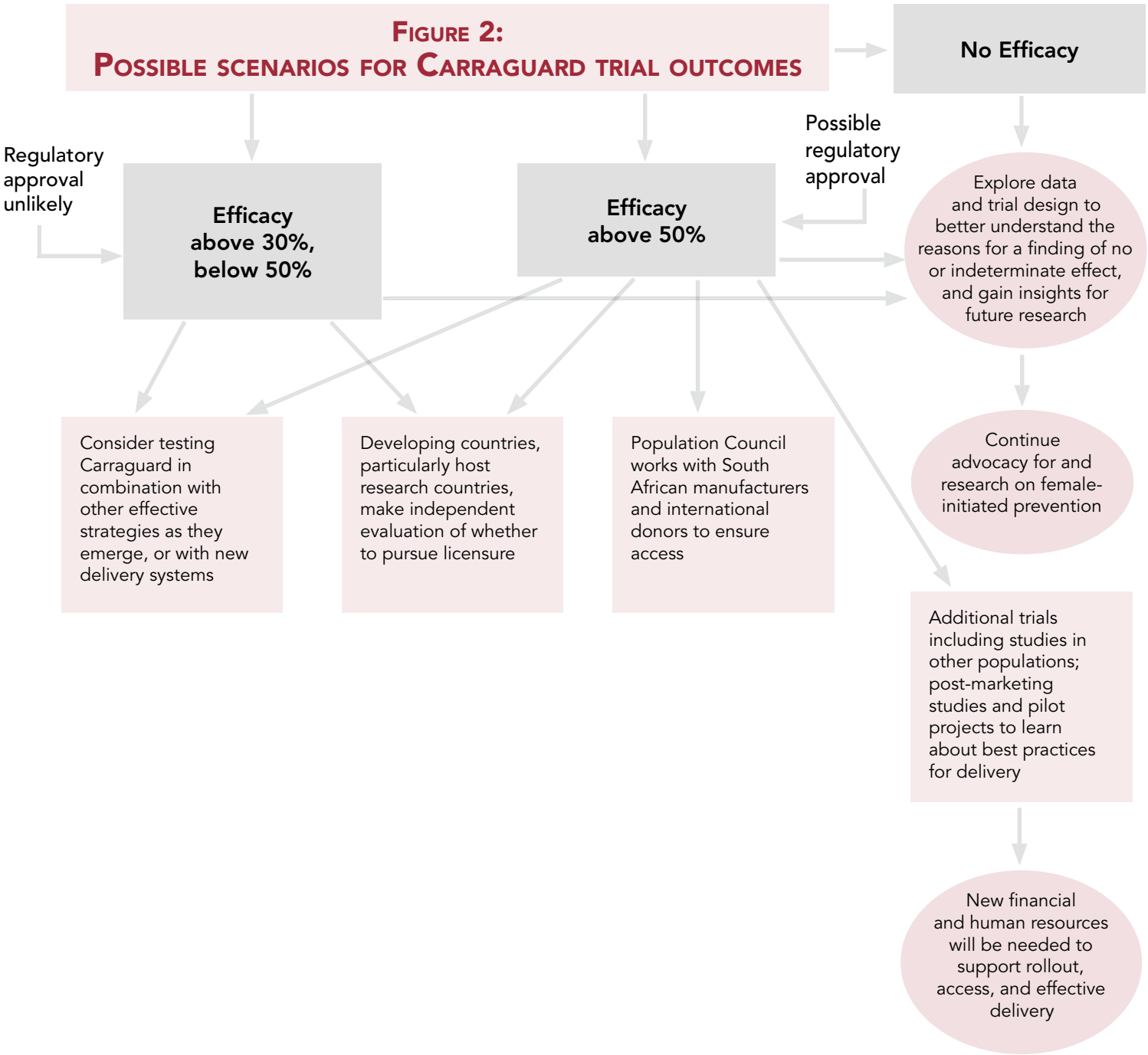
WHO/UNAIDS develop recommendations/ guidelines for developing countries

Developing countries, particularly host research countries, make independent evaluation of whether to add diaphragm for HIV prevention to existing programs



Inserted diaphragm

Figure 2:
Possible scenarios for Carraguard trial outcomes



be tested in combination with additional experimental strategies to see if this improves the overall efficacy. So, for example, Carraguard might be tested in combination with another active ingredient—or with the diaphragm. Alternatively, the Population Council is already testing a second generation product that combines a potent anti-retroviral drug with Carraguard to potentially enhance its efficacy.

If either trial yields a result of moderate efficacy—around 50 percent—it is possible that the intervention will be taken forward, as is, for introduction as an HIV-prevention strategy. Here, a number of variables will help determine whether and how quickly a microbicide or diaphragm will become available in different settings:

- The degree to which regulators and policy makers are convinced that introducing a product of the designated efficacy could help reduce HIV transmission in their setting.
- The capacity of local regulatory agencies to review and approve registration of these new product classes.
- The ability to scale up manufacturing of Carraguard and/or the diaphragm to meet expanding need.
- The need, with regard to microbicides, to collect additional data to establish the products safety and efficacy for use among pregnant women and younger adolescents.
- The degree of demand for and acceptability of the intervention in various settings and communities.
- The extent to which HIV service provision and family planning service provision have been successfully integrated.
- The availability of resources for developing pilot programs and best practices.

No matter what the efficacy level, there will be a need for additional research.

What else needs to happen?

Need for additional research

No matter what the efficacy level, there will be a need for additional research. If there is no efficacy, then there is a need to continue funding a full spectrum of prevention trials of other female-initiated methods. If there is low to moderate efficacy, there will be a need for additional trials that aim to improve on the existing strategy, for example, by using the diaphragm or microbicide in combination with another method or by developing an improved version of the product. And if there is sufficient efficacy to warrant wide introduction, there is a need for operational research to figure out how best to introduce and implement the new intervention as part of a package of proven prevention services and strategies. *Why is this?*

- **Because efficacy in a clinical trial setting does not equal effectiveness in the "real world."** A clinical trial by its very nature is a "controlled" environment. The results seen during a trial may either overestimate or underestimate the effect of a microbicide or diaphragm on risk of HIV infection when made available outside of the trial. For example, women in general might be more motivated to consistently use a strategy with proven efficacy than the participants in a trial—who are told repeatedly that the strategy is not proven as reliable protection. Conversely, women in general might be less able and willing to use a strategy consistently without all of the counseling and support provided within the trial setting.
- **Because the products will be less than 100 percent effective.** A finding of partial efficacy for a new female-initiated prevention strategy would raise questions for regulators, policy makers, providers, funders, advocates and community groups. These questions include:
  - How much efficacy is enough to warrant the complexity, cost and uncertainty of introducing a new product?
  - How much efficacy would women want in order to feel comfortable using the new strategy?
  - Where would women best be able to access these products and information?

- How can the product be introduced in a way that doesn't lead people to switch from more effective prevention methods—where such methods are currently being used?
- How do these methods fit together within the range of other current and potential HIV-prevention methods?

There is strong evidence that a partially-protective microbicide or vaccine could have a significant impact on new HIV infections at both an individual and a community level, but it will take hard work and significant resources to realize these benefits.

Need for information to guide decision-making

Today the burden of HIV lies in the developing world. Decision makers at the community, national and regional level in resource-poor settings have a critical role to play in guiding research on and introduction of new prevention technology. In order to play this role, however, stakeholders at all levels need information about how a new strategy might affect a particular epidemic.

There is strong evidence that a partially-protective microbicide or vaccine could have a significant impact.

Epidemiologists and other experts have modeled the impact of partially-effective HIV-prevention strategies on different kinds of epidemics, including ones that are "generalized" (HIV is found throughout the population) or "concentrated" (rates of HIV infection are highest and concentrated in specific communities or geographical areas). They have found that even a moderately effective microbicide or vaccine could have a significant impact.

These models do not completely predict the impact of new interventions in the real world. But they are important tools for developing country stakeholders to use to weigh the benefits, costs, risks, and potential impact of new prevention strategies. It will also require in-country advocacy to amplify the views and voices of the most affected communities' need and concerns with respect to partially-effective options.

Box 3:
Women's bodies & vulnerability to HIV

There are biological reasons why women may be particularly vulnerable to HIV. The cervix—the narrow lower entrance of the uterus—is considered highly susceptible to HIV. In contrast to the thicker multi-layer lining of the vagina, the cervical epithelium—the outer layer of the tissue—is made up of only a single layer of delicate cells. These cells have high concentrations of a surface molecule called CD4, which HIV uses to enter cells, making them potential targets for early infection. Although it has not been proven, scientists believe that the cervix may be more vulnerable to HIV transmission than other parts of the genital tract although the other parts can also become infected with HIV.

The cervix has also been shown to be the most common entryway for STIs, including gonorrhea, Chlamydia, and human papillomavirus (HPV). Moreover, cervical contractions help facilitate the movement of fluids, including any infectious agents, up into the uterus, fallopian tubes, and ovaries, which may also be important sites of HIV transmission.[7] Accordingly, it is thought that blocking the cervix would reduce HIV transmission.

Need for continuing advocacy for additional female-initiated prevention methods

Whatever trial results emerge, they will not spell the end of AIDS in women. There is a need for continued advocacy to support female-initiated prevention research and programs that look across the spectrum of strategies: from biomedical approaches (PrEP, microbicides, vaccines, etc.) to behavioral interventions, to services and support in combating structural issues including gender-based violence, poverty, and entrenched gender norms. These strategies must be tailored to women of different ages and life situations: adolescents, married women, pregnant women, sex workers, etc.

[7] Moench TR, Chipato T, Padian NS. Preventing disease by protecting the cervix; the unexplored promise of internal vaginal barrier devices. AIDS (2001), 15:1595-1602.

Box 4: Trial design challenges

Both the MIRA and Carraguard® trials have helped focus attention on some of the challenges in female-initiated prevention research. These challenges can affect the data that are gathered from a study.

Challenge 1) Measuring adherence
Both the microbicide and diaphragm are user-dependent. This means that the effectiveness of the product depends on correct and consistent use by the woman every time she has sex. Injectable contraceptives and vaccines are examples of non-user-dependent interventions. The woman receives a shot and does not have to do anything else for the intervention to have its effect.

A very good product can be ineffective if it is used improperly or not at all. Trial sponsors, staff, and volunteers have invested a lot of effort into different approaches to measuring adherence in MIRA, Carraguard, and many other prevention trials. In both studies presented in this brochure, participants were interviewed about product use. The Carraguard study also tracked the number of applicators returned that had been used, employing the dye stain technique to determine whether a given applicator had been vaginally inserted.

Whatever the trial outcomes, MIRA and Carraguard researchers are performing additional data analyses to learn more about whether and how the method was used—with specific partners, at specific times, etc. This qualitative data will help researchers identify the barriers-to-use and factors that increase adherence and accuracy in self-reporting. This may help guide future trial design and better screen for highly adherent participants. The data may also underscore the need for sustained-delivery products such as the sponge or vaginal ring with a slow releasing agent.

Challenge 2) Pregnancy during the trial
Trials of experimental HIV prevention candidates like microbicides or vaccines ask women volunteers not to get pregnant for the duration of the study. This is because the impact of the candidates on fetal development is not known. Instead, women volunteers are asked to use reliable methods of birth control, and are generally offered family planning on site. This information is reviewed at each study visit.

However, many microbicide trials have found that women volunteers do get pregnant at higher-than-expected rates. These women discontinue use of the experimental product and are usually followed through pregnancy outcome to gather information on any potential effects the experimental product might have. Higher-than-expected rates of pregnancy can complicate analysis of trial data, because trial designers plan for a certain number of women to finish the study. When pregnant women leave the study, the total number of participants drops; this can reduce the statistical power of the data analysis.

Solutions to this include providing contraceptives on site and conducting expanded reproductive toxicity tests (in animals) on experimental candidates so that women participants might be able to remain in the trial and continue using the product during pregnancy.

What does it all mean?

Only one thing is certain about the data from these first efficacy trials of novel female-initiated prevention methods: these findings will be the beginning, not the end, of the search for methods women can use to protect themselves against HIV.

Advocates have an important role in untangling the significance of findings, whether they are positive, negative, or indeterminate. Here are some core messages:

Regardless of their outcomes, the trials provide important information. Together, the MIRA and Carraguard® trials enrolled over 11,000 women and followed them up to two years, demonstrating that trials of this size are feasible. Participants were provided with medical care and treatment, family planning options, and safer sex education and counseling. As a result, we know better how to conduct research including how to reach, recruit, and retain women. Both products seem to be safe for vaginal use based on the interim safety data reviewed throughout the trials, and checks and balances are in place to ensure the safety of participants. We will also learn important lessons about how women decide on using products under different circumstances.

The trials and the products can be a foundation for work on next-generation candidates. The trials will provide important lessons for the broader HIV-prevention research field. And if the products themselves show signs of efficacy, they may be important elements of future joint strategies, such as combination microbicides, or diaphragm plus microbicide combinations.

Partially-effective products can be powerful tools. Neither the diaphragm nor Carraguard is expected to be 100 percent protective against HIV infection. Neither will be a substitute for proven prevention strategies. However, more products will provide women with more options. And, like the female condom that expands the range of options for women, new, even partially-effective products can have a significant effect on reducing individual risk and on rates of infection.

Community involvement is critical. Strong representation from the community and an active community advisory board and/or other community engagement processes produces a high level of understanding and communication among researchers, participants, and the broader community.

The priority is to expand the package of proven prevention options. There will not be one single solution to the AIDS epidemic. Each new intervention must be made available in the context of a package of proven options including male and female condoms and behavior change counseling. This is true for male circumcision today, and it will be true for an effective cervical barrier, microbicide, or vaccine if and when one is identified.

Biomedical solutions are not enough. Cervical barriers, microbicides, and other female-initiated prevention options could potentially increase women's control and autonomy in protecting themselves from HIV infection. But these biomedical tools cannot be sufficient to counteract the social, economic, and political factors that compromise women's lives around the world. Although new biomedical strategies are essential, so, too, are systematic, structural approaches to reducing gender-based violence, women's poverty, disenfranchisement, and the many other factors that affect the overall status of women.

Box 5: What about anal sex?

The major focus of the microbicide field today is identifying products that can protect women against HIV infection during vaginal sex. However, it is also possible that a microbicide candidate could be developed for rectal use to protect against HIV infection during anal sex between men or between men and women. There are significant differences between the rectum and the vagina, so an answer about vaginal use will not provide data on anal sex. Groups are advocating for studies on the safety of vaginal microbicides when used in the rectum, so they can be appropriately labeled. A similar issue has already emerged around male circumcision, which has a proven protective benefit for HIV-negative men having vaginal sex with women; but there are no clinical trial data related to anal sex, whether heterosexual or among men who have sex with men.

Advocates are emphasizing the need for research on microbicides for anal sex. One group in this area is the International Rectal Microbicide Working Group. For more information, visit www.irmwg.org/.

What you can do

Today there are more HIV-prevention strategies in the pipeline than ever before. Some, like the diaphragm, are for use by women only. Others, like male circumcision, are targeted solely at men. But in the real world, uptake of new interventions and support for ongoing research depends on *everyone*: men, women, adolescents, and families.

In the real world, uptake of new interventions and support for ongoing research depends on everyone.

- Educate yourself about the spectrum of prevention research going on today. Find out what is happening in your area. *(see Box 6: Resources)*
- Support the only female-initiated HIV-prevention method currently available: the female condom.
- Advocate for the implementation of new strategies like male circumcision or the HPV vaccine—programs that deliver these interventions today could be excellent starting points for delivering new interventions tomorrow.
- Participate in trials or community advisory mechanisms.
- Continue to follow the Carraguard, MIRA and other HIV-prevention trials for their outcomes, get involved in understanding and disseminating the information, and advocate for the development of sensible, evidence-based policies and planning to assure wide-spread availability and affordability of new interventions once they are proven both safe and effective.
- Sustain the global commitment to a comprehensive prevention response, including research in new HIV-prevention approaches for the long run: there are no simple answers or immediate solutions.

Box 6: Resources

For more information on microbicides:

- African Microbicides Advocacy Group, www.global-campaign.org/amag.htm
- Alliance for Microbicide Development, www.microbicide.org
- Family Health International, www.fhi.org
- Global Campaign for Microbicides, www.globalcampaign.org
- HIV Prevention Trials Network (HPTN), www.hptn.org
- Ibis Reproductive Health, www.ibisreproductivehealth.org
- International Partnership for Microbicides, www.ipm-microbicides.org
- Microbicides Development Programme, www.mdp.mrc.ac.uk
- Microbicide Trials Network (MTN), www.mtnstopshiv.org
- Population Council, www.popcouncil.org

For more information on cervical barriers:

- Cervical Barrier Advancement Society, www.cervicalbarriers.org
- FemCap, Inc., www.femcap.com
- The Female Health Foundation, www.femalehealth.com
- Ibis Reproductive Health, www.ibisreproductivehealth.org
- PATH, www.path.org
- Reproductive Health Technologies Project, www.rhtp.org
- Women's Global Health Imperative, www.wghi.org

For more information on vaccines and other prevention research trials:

- AIDS Vaccine Advocacy Coalition's Prevention Research Timeline, www.avac.org/timeline-website/

The AIDS Vaccine Advocacy Coalition (AVAC)

Founded in 1995, the AIDS Vaccine Advocacy Coalition (AVAC) is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and global delivery of vaccines against HIV/AIDS.

This special report and AVAC's continuous policy analysis, advocacy, education, and outreach work are made possible by the dedicated labor of AVAC advocates and support from the Bill & Melinda Gates Foundation, the Blum-Kovler Foundation, Broadway Cares/Equity Fights AIDS, the Ford Foundation, the International AIDS Vaccine Initiative, UNAIDS, the Until There's a Cure Foundation, the WHO-UNAIDS HIV Vaccine Initiative, and many generous individuals who have become AVAC Members.

AVAC is an IRS-certified 501(c)(3) tax-exempt organization, and donations are tax deductible.

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www.aidsvaccineclearinghouse.org

The African Microbicides Advocacy Group (AMAG)

The African Microbicides Advocacy Group (AMAG) was launched in 2004 as a coalition of microbicide and other new prevention technology advocates from organisations and institutions based and/or working in Africa. Its main objectives are to foster the creation and implementation of an African-driven agenda for microbicides research, development, advocacy and sustainable access; and to strengthen the capacity of national or community groups for advocacy work. The AMAG network is comprised of over 450 members—researchers, community advocates, policy-makers and media —from 30 countries across and beyond Africa.

African Microbicides Advocacy Group

For more information, please contact the African Microbicides Advocacy Group (AMAG):

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Fax: +233-21-256270
E-mail: **amag_info@yahoo.com**
Web: **www.global-campaign.org/amag.htm**

The Global Campaign for Microbicides

The Global Campaign for Microbicides (GCM) is a broad-based, international effort that uses advocacy, policy analysis, and social science research to accelerate microbicide product development, facilitate widespread access and use, and protect the interests and rights of trial participants and future end-users, especially women. Founded in 1998, the Global Campaign now has 55 active partners and over 285 organizations worldwide that have endorsed its mission. The Secretariat of the Campaign is housed at PATH, an international, non-profit health organization, with offices around the world. Campaign staff are now working from Washington DC, Brussels, Nairobi, Ottawa and New Delhi.

Global Campaign FOR Microbicides

For more information, please contact the Global Campaign for Microbicides:

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