This Advocates' Brief has been developed by the Global Campaign for Microbicides in close collaboration with the other endorsing organisations. While it articulates the current concerns and positions of these organizations, it is also a work in progress. It is updated periodically to reflect new endorsers; the field's progress; and our collective, developing perspectives on these issues

Fact Sheet

HIV Positive Women and Microbicides

Microbicides have the potential to benefit HIV positive women by enhancing their sexual lives and helping reduce their risk of infection with new strains of HIV and other sexually transmitted infections (STIs). Access to effective, user-initiated HIV prevention tools is important for women who cannot always negotiate condom use with their male partner(s) or who do not wish to use condoms (for instance, those trying to conceive). On-going and targeted research is needed to ensure that promising microbicide candidates are safe, affordable, accessible, and responsive to the needs of HIV-positive women. Here are some of the critically important issues that the microbicides field raises for positive women:

Microbicides could benefit women with HIV, their partners and families.

Microbicides are being designed and tested which may (in the future) provide an HIV positive woman with some important benefits, including:

1. Lowering her risk of infection with other strains of HIV and, potentially, other STIs.
2. Enabling her to help protect her male partner(s) during sex if he is not using a condom; and
3. Helping her to protect an HIV negative partner(s) while leaving herself open to pregnancy, if she wishes to have children

1. Microbicides could help reduce a woman's risk of infection with new strains of HIV. Whether a microbicide could also help her reduce her risk of infection with other STIs as well will depend on how it works. Researchers are exploring diverse and increasingly sophisticated ways to block HIV. In future, some candidate microbicides might be broad spectrum (meaning they would work against other STIs as well as HIV).

   The current candidates in trials, however, are HIV specific and unlikely to reduce risk of other STIs. The candidate microbicides entering large scale effectiveness testing now are ARV-based microbicides. These may have a better chance of being effective than the previous candidates did because they target HIV very specifically. But this also means that they do not block other disease-causing pathogens or disable sperm. ARV-based microbicides also may not appropriate for use by women living with HIV, for reasons discussed in detail on page 2.

2. The microbicide trials currently underway are designed to answer the question of whether or not the test product works for primary prevention – that is, to help keep HIV negative people from becoming HIV positive. Once a product is proven to help protect HIV negative women, the next question will be whether it also works for secondary prevention – that is, to help prevent transmission of HIV from a positive person to a negative person. Research to determine whether a microbicides could protect the partner of an HIV positive person (that is, provide bi-directional protection) will require a separate and very different type of trial. If the first microbicides proven effective for primary prevention are *not* suitable for secondary prevention, then developing alternative products that do provide bi-directional protection will become all the more important. It is critical that search for non-ARV-based microbicides

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continues because HIV positive women need workable alternatives if ARV-based microbicides prove to be inappropriate for their use.

Microbicides are not expected to be as protective as condoms – but they will be far more protective than nothing when used by people who aren't using condoms. Ongoing male and female condom promotion efforts that emphasize the sexual and reproductive rights of women living with HIV are still essential, as is the rapid scale-up of existing prevention strategies and on-going, sustained sexual health education. Microbicides would simply complement these efforts by putting additional prevention options into the hands of those for whom condom use is currently difficult or impossible.

3. Women need to have access to both microbicides that can prevent prevent pregnancy and microbicides that do not interfere with getting pregnant. Since condoms prevent pregnancy, there is currently only one alternative available to HIV positive women wishing to become pregnant but also wishing to fully protect an HIV negative partner. This is alternative insemination – or inserting semen in the vagina with a device such as a tube (like a turkey baster) or a diaphragm, rather than during intercourse. A women who wants to reduce her negative partner's risk while attempting to become pregnant may also choose to have unprotected sex only right after ovulation (thus reducing the number of times her partner is exposed). Or she may reduce his risk by taking ARVs that may reduce the amount of HIV in her vaginal fluids (although by how much is still unclear). But alternative insemination remains the only method currently available for introducing sperm into the vagina without any risk of transmission to a male partner.

   A non-contraceptive, bi-directional microbicide would give HIV positive women who want to have children another option for safer pregnancy. Contraceptive, bi-directional microbicides, on the other hand, would give women who do not wish to become pregnant another way to avoid an unwanted pregnancy while also possibly reducing their partners' risk of HIV exposure. They would also offer a much-needed alternative to women choosing not to use hormonal birth control methods like pills or patches. The candidates furthest advanced in trials right now are all non-contraceptive. But it is possible, if one of them proves effective, that a contraception component could be added to it for women who want a contraceptive version.

Candidate microbicides must be tested to assess safety and appropriateness for HIV positive women

Women living with HIV are likely to have different needs for, and responses to, various microbicide products than HIV negative women. We must understand these factors *before* microbicides become widely available; both because positive women will be using them, and because many women may not know their HIV status before using a microbicide. Thus, candidate microbicides must go through early trials to assess their safety for HIV positive, as well as HIV negative, women. These preliminary safety trials must be followed by trials that generate long-term use data among women living with HIV so that researchers can adequately assess the long-term impact of such products. These early safety trials must be followed by more trials which generate data on the long-term use of microbicides by HIV positive women.

If an ARV-based microbicide is proven to be both safe and effective for HIV negative women, it may still not be appropriate for use by HIV-positive women. There is a chance that it could cause the development of drug resistant virus in her body, which might compromise her future treatment options. Scientists have not yet determined whether the small amount of ARV contained in these

candidate products is likely to cause resistance but, if it does, this particular type of microbicide might only be appropriate for HIV negative women[1].

Drug resistance is not the only potential safety concern that positive women have raised in connection with microbicides. Another concern expressed is that the early safety trials on two candidate microbicides (Savvy and Cellulose Sulfate) were apparently insufficient to predict the potential for harm that was later suggested in efficacy trials. This raises questions about whether the methods currently used to evaluate the safety of microbicide candidates are adequate. Researchers are now debating the strengths and limitations of the methods that have been used to date and how they can be improved. This general concern is compounded for positive women by the fact that very little background data are available so far on the natural vaginal ecology of HIV positive women and how various factors – including pregnancy, use of candidate microbicides, use of hormonal contraceptives, etc. – may affect HIV positive women.

Research is underway to address these questions and some progress is evident. The way in which researchers think about measuring safety has changed enormously in the last five years. Colposcopy (using a microscope during exam to examine the vaginal lining), for example, used to be a primary tool used to see whether damage to the vaginal lining was occurring. Now researchers agree that colposcopy does not look deeply enough into the cell layers and better methods are being developed.

Among the other methods of assessing safety that are currently under consideration is looking for biomarkers of suggested harm. When the body is damaged and its immune system is activated, the natural balance of the vagina changes. Looking for **biomarkers**, or substances that increase or decrease when an injury occurs, may be another way of checking to see if the product is causing damage in the vagina. The difficulty with this approach is that scientists do not yet know exactly which, if any, biomarkers accurately indicate whether a candidate microbicide is safe or not[2].

Larger early human safety trials are needed to help scientists better identify the signals that may indicate safety concerns. Scientists also need to learn more about how positive women's bodies work. One research team in New York City, for example, has observed that the protective proteins contained in vaginal fluids appear to be *more protective* in the bodies of HIV negative women than in positive women. The research to determine why this is the case – and what it really means for positive women – is ongoing. But this is one of the few funded investigations into an area that may well affect how positive women's bodies respond to microbicides.

Research on bi-directional protection must occur on products proven effective for primary prevention

When an effectiveness trial turns up a microbicide that works for primary prevention, focus will then switch to looking at whether it also works for secondary prevention. The clinical trials to test this will look very different from the primary prevention trials – and will be more complicated and expensive to conduct. Instead of enrolling HIV negative women, the secondary prevention trials will have to enroll **sero-discordant** couples (where one partner is HIV positive and one is HIV negative) in which the woman is HIV positive and the man is negative. Their goal will be to see whether men become infected over the course of the trial.

Researchers cannot just enroll men to answer this question because it will be their female partners, the HIV positive women, who will be inserting the candidate products vaginally. In any clinical

[1] *For more information on how scientific efforts to evaluate safety in microbicide trials is evolving, see "Evaluating the Safety of Vaginal Microbicides: The Fundamentals" a report posted on the Global Campaign's website at www.global-campaign.org.*

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trial, all participants (women and men) must be well informed about all aspects of the trial and clearly understand the risk and benefits associated with it before agreeing to participate in any way. It would be unfair to the women, in this case, if researchers just gave test products to men and asked them to get their partners to use it. All trial participants must receive all the available information about the trial and the test product directly -- not through a partner or another intermediary – and have every opportunity to ask questions, consider all aspects and make their own decision about whether or not to enroll in the trial. This is the meaning of informed consent.

Since these two trial designs are very different from each other, it is not possible to answer both questions (whether the product protects both women and men) in the same trial. Funders will only support secondary prevention research on products that succeed in primary prevention trials. This does not mean that finding out whether HIV-positive women can use microbicides to protect their partners is not a high priority. It just means that the questions must be asked and answered in order.

While waiting for a product that works for primary prevention, the field can and should prepare itself for secondary prevention trials by investing more money in gathering vital background data on vaginal immunology, ecology, viral shedding, and the mechanisms by which HIV transmission from women to men occurs.

Microbicide trials must protect the confidentiality and health of all participants and promote access to care for those who seroconvert

Clinical trial staff take specific measures to protect women's confidentiality and to counteract any public perception that women excluded from clinical trials are presumably HIV positive. Care is taken, for example, to assure that community members and involved community groups understand clearly that a women might not participate in a trial even after being screened for enrolment because she has other health problems; wants to become pregnant in the near future; does not have time for the many clinic visits or simply decides that she is not interested in participating.

Although HIV positive people are enrolled in small-scale safety trials, the large-scale effectiveness trials have to enrol exclusively HIV negative women in order to find out if the candidate product works for primary prevention. But large-scale microbicide trials do touch the lives of HIV positive women in two ways:

1. Testing during screening may be the way a woman finds out that she is HIV positive
2. A woman may seroconvert during the trial because, even though she is provided with free condoms and risk reduction counseling, she may still be unable to protect herself.

Regardless of when they test positive, *all* women need post-test counselling and psychosocial support on living with HIV; including sexual health, dealing with issues around disclosure, screening for tuberculosis (TB), access to male and female condoms, referrals to appropriate care providers and a range of other services.

All women enrolled in microbicides trials, whether positive or negative, need to receive sexual health services. These should include:

- laboratory screening and treatment (if needed) for STIs;
- cervical screening (Pap tests) for participants if some publicly supported cervical cancer prevention services exist in the trial location, including diagnosis and treatment for dysplasia. In countries where no public cervical screening and treatment services exist, investigators should advocate for, and support initiation of, needed services. Clinical trials can improve access to services by offering to train public sector providers in screening colposcopy, including appropriate low-tech approaches such as visual inspection of the cervix with acetic acid wash (VIA) where they are approved;
- contraceptive and sexual health counseling by appropriately trained staff and provision of safe, appropriate contraception to women who want it.

With regard to HIV care, researchers have a stronger ethical obligation to provide care for women who actively participate in the study (and seroconvert during the trial) than those who are screened for study participation but are not enrolled. Currently, women who are HIV-positive at screening are offered extra post-test counselling and referred to HIV/ART programs and other support services. Most trial sites monitor whether women follow through on these referrals or not. At some sites, trial staff help women schedule appointments and/or accompany them (if they wish it) to make sure they get connected to the medical and psychosocial support they need. And some go beyond this to provide other psychosocial, medical and nutritional services.

Most women who seroconvert during the trial have immediate and serious counselling needs. They may or may not see themselves as having immediate physical health care needs. There is currently a debate in the medical community about how soon after seroconversion people should start on ARV treatment. Women should be informed of all their treatment options and the potential immediate and long-term benefits and disadvantages of starting ARV treatment quickly rather than waiting until a later point. Regardless of the woman's decision, clinical trial sponsors and researchers have a responsibility to ensure that women who seroconvert during a microbicide trial have the psychosocial and clinical support they need when they test positive, and that they have access to comprehensive HIV care including ARVs when appropriate, even if it is long after the trial has ended.

HIV positive women have important roles to play in microbicides research and advocacy

Participating in safety trials is just one role that HIV positive women can play in microbicides research at this time. Positive women also play vital roles when they work with researchers, sponsors and other community members to:

- assess the acceptability and usefulness (or lack thereof) of a trial to a specific community and advise the researchers and trial sponsors accordingly before the trial is started;
- craft accurate and appropriate messages for the community about trials;
- develop informed consent processes that enable participants to fully understand trial-related information;
- help researchers learn about when, where and how people will access care in a given community – and adjust the trial's care provision plans accordingly;
- guide the planning of services that will support women who seroconvert during the trial while protecting their confidentiality at every step;
- pinpoint problems and concerns arising during trial implementation;
- negotiate for the development of solutions acceptable to the broader community; and
- if the product is effective, develop strategies for safe and reasonable product introduction and join in deliberations on "next steps" (including efforts to transition the product into secondary prevention research).

Community voices, including the voices of positive women, must be amplified and integrated into trial design and implementation if the field is to progress as efficiently and effectively as possible.

Furthermore, positive women have an essential role to play in advocacy – demanding not only resources for the field but also highlighting the unique expertise and experiences HIV-positive people bring to HIV prevention and asserting their right to be involved in decisions about when, where, how and under what circumstances microbicide trials are conducted.

What is the advocacy message?

HIV-positive women are some of the most vocal advocates for microbicides, as well as for expanded research on all aspects of HIV positive women's reproductive health. Together, we can advocate forcefully for the development of woman-initiated interventions, such as microbicides, that promote sexual and reproductive health and rights. To be effective, prevention strategies must be responsive to and compatible with the practical realities HIV-positive people contend with in trying to protect themselves and others. We recognize that many women need methods that enable them to promote their sexual health and that of their sexual partners.

Some areas in which our advocacy is urgently needed now include:

1. Making sure that all candidate microbicides are tested for safety among positive women and men before being allowed to advance to large-scale effectiveness trials. Large-scale efficacy trials enrolling HIV negative women must also enroll enough HIV positive women to yield valid safety data.
2. Insisting that the microbicides field invest and engage now in gathering essential information on vaginal immunology, ecology, viral shedding and the mechanisms by which HIV transmission from women to men occurs.
3. Calling on the field to commit to secondary prevention trials that assess the potential bi-directional effectiveness of any non-ARV-based candidate microbicides shown to work for primary prevention. Also urging research institutions and funders to continue to pursue the search for non-ARV based candidates, thus providing an alternative for HIV positive women in the event that ARV-based microbicides prove to be inappropriate for their use.
4. Advocating to increase the involvement of HIV positive women, along with other civil society and community representatives, across the entire arc of research, development and product introduction. Calling for improved and expanded communication channels between HIV positive women and microbicide trial researchers, sponsors and developers. Demanding recognitions of the fact that positive women, especially those living in the communities in which trials are taking place, have key roles to play in trial development and implementation.
5. Insisting that HIV positive women must be included in Community Advisory Boards (CABs), national research planning bodies and donor proposal review processes and other decision-making venues. Requiring each clinical trial site to explicitly define the health care services that it will provide to trial participants and negotiate the package of prevention services that will be provided to participants with relevant community and civil society stakeholders. It must also specify how access to this care will be ensured and provided.
6. Calling on trial sponsors and researchers to link with local sexual and reproductive health care services; build their capacity; and contribute to their development; and, thus, improve these services in appropriate and sustainable ways. In addition to using trial-related resources to train and build capacity; trial staff and sponsors must also use their influence to advocate for accessible, non-stigmatizing services that will benefit women in the community (whether trial participants or not) beyond the life of the trial.
7. Demanding that all microbicide trials are designed to fully protect participant confidentiality and privacy; that the sexual and reproductive health needs of all participants are met; and that women who seroconvert during the trial have access to comprehensive HIV care, including ARVs when necessary. Women who seroconvert while participating in ARV-based microbicide trials must receive resistance monitoring to determine whether or not they develop a drug resistant virus as a result of their trial participation. If they do, they must be assured access to second-line therapies (ARVs that are effective against drug-resistant viruses), as needed.