

Positive eople in India and Microbicides

Meeting Report
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Global Campaign for Microbicides (GCM)
PATH



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Representatives of the network of people living with HIV/AIDS in India.

Background

With approximately 2.5 million people living with HIV and an increasing number of new infections among women, India could benefit significantly from HIV prevention methods on the horizon, such as microbicides^[1]. Effective female-initiated HIV prevention choices are important for women who cannot always negotiate condoms with their male sex partners or who do not wish to use condoms (such as those who want to conceive).

Not only is India a key region for microbicides introduction, but it also participates in international multi-centre microbicides clinical trials and has sponsored its own development efforts. The country has a strong capacity for manufacturing as well as a network of influential NGOs that can be allies in accelerating access to microbicides both locally and globally. As HIV prevention needs and research efforts grow, civil society will be increasingly called upon to react to the expanding microbicides initiatives in India and will need information, resources and a platform for engagement on critical issues.

Microbicides (mɪˈkrɒʔbʔsɪd) are a range of substances that are currently being researched that may reduce transmission of sexually transmitted diseases (STIs) when applied either in the vagina or rectum.

In India, as well as the world over, women living with HIV/AIDS, have expressed the importance of investing in the development of female-initiated HIV prevention methods. Not only could candidate products reduce HIV transmission to HIV negative women, but they also have the potential to benefit HIV positive women by helping reduce their risk of infection with new or resistant strains of HIV and other STIs and by enhancing their sexual lives. Women living with HIV, however, may have different needs for, and responses to, various microbicides products. These factors must be considered *before* microbicides become widely available, because both women who know their HIV status will want to use them, as well as those who do not. The involvement of positive women in all stages of microbicides research and advocacy will, therefore, be crucial to successful development and eventual introduction, if microbicides are proven effective.

In India, people living with HIV have played a major role in spearheading a number of advocacy initiatives including access to anti-retroviral (ARV) treatment and community involvement in vaccine research. Microbicides research and advocacy will need their meaningful participation to shape an effective national and global strategy on microbicides development and access.

Purpose of the meeting

The National Working Group on Microbicides (NWG) is a multi-sectoral taskforce that is focused on examining and strengthening the policy environment for the development and introduction of microbicides in India. Formed in 2003 with the support of the Global Campaign for Microbicides (GCM) and PATH in India, it comprises scientists, policymakers and civil society representatives. During several consultations with key stakeholders in the past few years members of the NWG have identified the importance of involving the positive community in

developing an advocacy strategy. The community has in turn expressed strong interest in learning about microbicides research and has wanted to participate in microbicides advocacy.

In response to these requests, on 29 January 2007, the NWG, with support from GCM and PATH, convened a meeting on microbicides development and advocacy with representatives from several networks of people living with HIV/AIDS in India. Twenty-three representatives from 17 state-level networks were nominated by Positive Women's Network (PWN+) and Indian Network of Positive People (INP+) and attended the meeting. The meeting had the following broad objectives and outcomes:

Objectives

- Educate positive networks and in particular HIV positive women in India about microbicides research
- Build capacity of positive networks around the challenges, accessibility, availability and affordability of microbicides:
- Discuss the potential roles for positive networks to influence the national policy work around new technologies with a focus on microbicides.

Expected outcomes

- Increased knowledge-base among leaders of positive networks on microbicides research in India.
- Capacity-building needs identified to strengthen the involvement on positive networks in microbicides policy and advocacy work in India
- Key issues identified by positive networks around microbicides advocacy
- Next steps outlined

This report is a summary of the presentations, questions and next steps that were discussed at this meeting. The responses for many of the questions were compiled by the Global Campaign for Microbicides through personal communications with researchers working on microbicides and previous consultations with other networks of people living with HIV/AIDS around the world.

Introduction and welcome

The meeting commenced with an introduction and welcome from Tilly Sellers, Director HIV and Sexual Reproductive Health for PATH in India. Tilly expressed concerns that positive networks were not well-represented in microbicides work in India. The aim of the meeting was to update participants on the latest issues around microbicides research and development and assess potential ways in which positive networks could be more involved in microbicides advocacy. When the participants were asked about microbicides, only one person had been to meetings where microbicides had been discussed.

Introduction:

The need for microbicides: *Dr. Amitrajit Saha*

The welcome was then followed by a brief overview of the need for microbicides, its role in HIV prevention and an overview of the mechanisms of action presented by Dr. Amitrajit Saha. Dr. Saha described how economic, social, cultural and biological factors all contribute to women's increased vulnerability to HIV/STI and speak to the need for female-initiated prevention methods. Crucially he noted that current prevention methods (including abstinence, fidelity, and condom use) require male consent. Women need alternatives that they can control – we can see this very clearly through the number of women with one lifetime partner who are infected in spite of their efforts to reduce risk by staying abstinent until marriage and being loyal to their partners.

He also mentioned that a microbicides could be produced in many forms, including gels, creams, suppositories, films, lubricants, or in the form of a sponge or a vaginal ring that slowly releases the active ingredient. They could prevent HIV and STIs by:

1. Killing or otherwise immobilizing pathogens.
2. Blocking infection by creating a barrier between the pathogen and the cells of the vagina or rectum; or
3. Preventing the infection from taking hold after it has entered the body.

Ideally, a microbicide would combine these mechanisms for additional effectiveness.

Presentation I:

Microbicides research and clinical trials: *Dr. Badri Saxena*

Microbicides research

Dr. Badri Saxena gave a detailed presentation on the various mechanisms of action of various microbicides and how microbicides are tested for safety and effectiveness. Candidate microbicides pass through a series of rigorous tests in the laboratory and in animals before they are allowed to be tested in human beings. Dr. Saxena described the three phases of human clinical trials:

1. Phase I trials determine whether the product is safe (does not cause immediate harm) if used by a small number of healthy low risk women over a few weeks.
2. Phase II trials also test for safety of the product, but over a longer time and with a larger number of women, some of whom may have higher risk factors.

3. Phase III trials enroll thousands of people in several sites. These trials measure effectiveness—that is, whether or not the microbicide actually works in the course of normal use to prevent HIV and/or STIs.

If the product appears to cause harm, research on that candidate is stopped and the product is dropped from consideration as a potential microbicide. Even when a clinical trial suggests that a drug is efficacious, there are many more steps that must be completed before it can be made available to consumers:

- Frequently, clinical trials need to be repeated to confirm their results or to test the finding in different populations.

At the time of this meeting Cellulose Sulfate (CS) was undergoing phase 3 clinical trials in Chennai and Bagalkot, India. At the end of January 2007, the Data Safety and Monitoring Boards (DSMB) of CONRAD met and based on a review of preliminary data, recommended that the Phase 3 trial of the candidate microbicide CS in Benin, India, Uganda and South Africa be discontinued. Early data suggest that CS may be contributing to an increased risk of HIV infection. Scientists are struggling to figure out exactly what this means given that 11 earlier safety trials had not revealed any safety concerns. Erring on the side of safety, the Family Health International DSMB recommended that the CS trial underway in Nigeria be closed as well, although review of the Nigerian data by that trial's DSMB found no evidence of increased risk.

For more information on the Cellulose Sulfate trial closure go to <http://www.global-campaign.org/cellulose-sulfate.htm>

- The drug must be reviewed and licensed for use by at least one drug regulatory agency.
- The product must be manufactured in large quantities, registered and introduced in different settings.

Even if a trial does not yield convincing results of effectiveness, it nonetheless increases knowledge. Each trial increases our knowledge and strengthens the field's ability to plan and mount successful trials in the future.

The research pipeline

Dr. Saxena went on to present a summary of lead microbicides in the pipeline globally (see Table 1) as well those being investigated in India.

Currently tenofovir/PMPA and praneem polyherbal vaginal tablets (an indigenous product of India) are in phase 2 clinical trials in India. There are several other candidate microbicides that are in pre-clinical trials in the country.

ARV-based microbicides and the implications for positive women

Dr. Saxena also discussed how some types of microbicides, that are currently being investigated, incorporate ARV drugs for vaginal application. These ARV-based microbicides could more directly target HIV and therefore have a higher potency against the virus. Researchers are also looking into delivering ARV-based microbicides through an intra-vaginal ring that could be worn for approximately three months and could therefore be longer acting.

There are a handful of drawbacks of ARV-based microbicides. First, they will not be effective against prevention of STIs. Secondly, it is possible that use of an ARV-based microbicide by an HIV positive woman could cause resistant strains of HIV to develop in her body. This

development could compromise her future treatment options. Some scientists think that resistance is unlikely to be an issue, basing their thoughts on *in vitro* (laboratory) studies which show that very low amounts of ARVs that are contained in these compounds and absorbed into the blood. But other scientists think that this could emerge as a serious issue if ARV-based microbicides are introduced in the real world and urge greater caution. If testing proves that drug resistance is a problem (which is still an open issue), this particular type of microbicide might only be appropriate for HIV negative women. In short, there is not yet consensus in the field on this issue.

With the exception of ARV-based microbicides, it is imperative that scientists investigate all candidate microbicides – even those intended to protect HIV negative women – for whether and under what conditions the product might cause harm among positive women and men. Products should be evaluated for this type of safety before being allowed to advance to large-scale effectiveness trials. Generally, comprehensive safety assessments address a variety of questions:

- Does the product harm the vaginal lining (epithelium) or create an inflammatory response that may facilitate HIV or other STI transmission?
- Does it affect the natural vaginal environment that helps to keep the vagina healthy?
- Does the product penetrate the vaginal epithelium?
- Is it absorbed into the blood stream? If so, to what degree?
- Are there any negative effects of using the product on other body functions?

To date all four of the leading candidate microbicides have been tested for safety in HIV positive women (see Table 1).

Participation of HIV-positive women in effectiveness trials for microbicides

Dr. Saxena also discussed how in addition to gathering data about how safe microbicides will be for use by women living with HIV, we also need to give high priority to the question of whether they will protect the partners of HIV positive women.

Since male to female transmission is much more likely to occur than female to male transmission, enrolling HIV negative women is the fastest way of determining “proof of concept” – i.e. showing whether the basic concept of a microbicide is feasible. These efficacy trials won’t show exactly how good the potential microbicide is at preventing male to female transmission – only whether the women who use it experience fewer sero-conversions than those who are provided with condoms and the inactive product (placebo).

If one of these trials demonstrates that the test product does help prevent male to female transmission, then it will be time to look at the opposite question – whether it can also prevent transmission from HIV positive women to their male partners. But a clinical trial to test this concept will look very different from these first trials. Instead of enrolling HIV negative women, these “next question” trials will have to enroll sero-discordant couples in which the woman is HIV positive and the man is negative. The goal of this trial will be to see whether, significantly fewer men, among those whose partners used candidate microbicides, contract HIV than would ordinarily be expected, over the course of the trial when compared to those couples using the placebo product.

Researchers can’t 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 into their vaginas. These women will need to be well informed about all aspects of the trial before giving their consent to use the test product. It would be unfair to the women if researchers just gave test products to men

and asked them to get their partners to use it. It is essential that the women, themselves, receive all the available information about the trial and the test product and give their informed consent before using it.

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. But this doesn't mean that finding out whether HIV-positive women can use microbicides to protect their partners isn't a high priority. It just means that the questions must be asked and answered in a logical order. While waiting for the initial proof of concept to be established, the field can and should prepare itself to answer the second question by investing more money in gathering vital background data on vaginal immunology, ecology, viral shedding, the mechanisms by which HIV transmission from women to men occurs.

Effectiveness and timing of microbicides availability

Dr. Saxena concluded by noting that the first generation of microbicides is likely to reduce risk of transmission by no more than 40 to 60 percent. But even a partially effective microbicide can provide substantial protection from HIV, especially if used consistently. Even a 60% HIV/STI efficacious microbicide could avert 2.5 million HIV infections over 3 years, if introduced into 73 low-income nations, according to modeling done by the London School of Hygiene and Tropical Medicine.

If one of the candidates that are currently in advanced clinical trials proves to be effective, a microbicide could be ready for distribution in a handful of countries by the end of 2010.^[2] If the current set of products does not prove effective, the time horizon will be longer (although there are several second-generation leads already in human testing). The microbicide community is working hard to accelerate development and ensure that products get to those who need them as quickly as possible.

Presentation II:

Ethics and community involvement: *Anandi Yuvaraj*

Long time HIV/AIDS advocate, Anandi Yuvaraj highlighted the key issues around ethics and community involvement in microbicides research. She noted that HIV prevention research poses new challenges to investigators and advocates including:

- The epidemic's disproportionate impact on vulnerable communities
 - The nature of prevention research, which enrolls uninfected ("healthy") volunteers, and therefore differs from research aimed at treating a disease or condition currently experienced by the trial participants
 - Dependence on public and donor resources, so that large scale trials are often funded by wealthy countries while conducted in poorer, highly affected ones.
 - Stigma and discrimination experienced by individuals and communities affected by HIV and AIDS
 - The legacy of past exploitative research practices and lingering social injustices
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Advocates for microbicides (and other HIV prevention research) can address these challenges by resolving thorny ethical dilemmas through broad-based, participatory dialogue and debate, and by promoting meaningful partnerships between communities and researchers.

International principles of ethics in biomedical research provide a starting place for designing and implementing clinical trials that ensure autonomy, beneficence and justice to trial participants and communities where research takes place. However, declarations and documents cannot by themselves resolve the more complex issues that arise in the implementation of HIV prevention research.

A core goal of the Global Campaign for Microbicides is: “To ensure that as science proceeds, the public interest is protected and the rights and perspectives of trial participants, users and communities are fully represented and respected.” We work toward this goal through two complementary initiatives on *research ethics* and *community involvement*.

“Community involvement” represents on-the-ground implementation of science’s accountability to society, at the local as well as global level. Engaging a wide range of stakeholders as active and informed partners in decision-making about the research and its implementation enhances both the scientific validity and ethical integrity of clinical trials.

This has been widely recognised in the field of AIDS research, and almost all publicly-funded research networks require a community involvement component. Generally this has been done by forming a community advisory board (CAB) or similar structure, a model developed in the US in the early days of activist involvement in HIV treatment trials. Recently, however, research networks are questioning whether the CAB model is the best or only approach to developing partnership with communities. The community liaison teams at various trial sites are exploring a variety of strategies to engage with communities as partners in the research enterprise.

For more information about the Global Campaign’s work on community involvement and ethics download the following reports:

- *“Rethinking the ethical roadmap for clinical testing of microbicides: Report on an International Consultation” was published by the Global Campaign for Microbicides, May 2005. It is available on line at <http://www.global-campaign.org/researchethics.htm>.*
- *“Mobilization for Community Involvement in Microbicides Trials: Report from a Dialogue in Southern Africa” at <http://www.global-campaign.org/clientfiles/SA-community-involvement.pdf>. This report describes a framework for developing community involvement plans that are grounded in principles of partnership, mobilisation and sustainability, to help communities and research institutions to work together to implement scientifically rigorous and ethically sound clinical trials.*

Presentation III:

Advocacy for microbicides: *Paramita Kundu and Ananth Thambinayagam*

Paramita and Ananth presented the advocacy initiatives of the Global Campaign for Microbicides. The Campaign is a broad-based, international effort to build support among policymakers, opinion leaders, and the general public for increased investment into microbicides and other user-initiated prevention methods. Through advocacy, policy analysis, and social science research, the Campaign's diverse network of over 250 NGOs works to accelerate product development, facilitate widespread access and use, and protect the needs and interests of users, especially women.

Specifically, the goals of the Campaign are to:

- Raise awareness and mobilise political support for increased funding for microbicide research, female condom and cervical barrier methods;
- Create a supportive policy environment for the timely development, introduction and use of new prevention technologies; and
- Ensure that as science proceeds, the public interest is protected and the rights and interests of trial participants, users, and communities are fully represented and respected.

The Global Campaign pursues its work through a small core staff and by funding partner organisations to pursue activities that directly advance the Campaign goals and objectives. The Campaign Secretariat is housed at PATH, an international, non-profit organisation that improves the health of people around the world.

A civil society-driven advocacy campaign for microbicides has existed in India since 2001. The National Working Group on Microbicides formed in 2003 to help strengthen a supportive policy environment for microbicides development and introduction in India.

The presenters went on to highlight the global resource needs for the field of microbicides development:

- Global investment for microbicide research, development, testing, policy and advocacy has more than doubled from roughly \$65 million in 2000 to \$142 million annually in 2004, due to sustained activism and growing scientific promise.
- The vast majority of investment was then, and still is, provided by governments and the philanthropic sector.
- Projections developed by advocates and researchers estimate that the global annual investment to ensure timely development of a safe and effective microbicide must double to at least \$280 million per year over the next five years—and remain at approximately \$280 million a year until satisfactory microbicides are licensed.

The presenters also highlighted some of the work of the GCM with positive people's networks and the importance of working these networks. They reiterated that 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 more effectively for the development of user-controlled interventions, such as microbicides, that promote sexual and reproductive health and rights.

Finally the presenters concluded by informing the participants that India will host the next Microbicides conference. This international meeting is scheduled to take place in New Delhi on 24-27 February 2008 and will be an important opportunity through which to profile the work of India in microbicides research as well as attract new advocates and scientists.

For copies of all presentations, please visit: <http://www.global-campaign.org/india.htm>.

For more information on microbicides research that has taken place in India, please visit: <http://www.global-campaign.org/india.htm>.

Question & Answer Session

The participants of the meeting went on to ask questions about the information presented. The following is a summary of responses from the meeting, the Global Campaign for Microbicides resources and communication with several experts in microbicides development.

Q: If microbicides are effective can they be used without condoms?

A: When used consistently and correctly, male or female condoms are likely to provide better protection against HIV and STIs than microbicides, so they will still be the preferred option. But for people who cannot or will not use condoms, and particularly for women whose partners refuse condoms, using microbicides can save lives and have a substantial impact on the spread of HIV. In fact, researchers developed a mathematical model that shows that if even a small proportion of women in lower income countries used a 60% efficacious microbicide in half the sexual encounters where condoms are not used, *2.5 million HIV infections could be averted over 3 years.*

Q: Will microbicides be contraceptive?

A: Some of the microbicides being investigated prevent pregnancy and some do not. It is important to have both non-contraceptive microbicides and “dual-action” microbicides that prevent pregnancy and infection, so that women and couples can protect their health and still have children. This is not possible with condoms.

Q: Can microbicides help reduce transmission of HIV for women with damaged cellular walls (perhaps caused by STIs)?

A: Women in clinical trials are treated for symptomatic sexually transmitted infections diagnosed when they attend clinic visits. Therefore, very little information exists on microbicide safety or efficacy in the context of untreated symptomatic STIs such as ulcerative genital diseases or other infections. It would be unethical to observe this in the context of a clinical trial. Data on these effects will likely be retrospective—in other words, they would be gathered by looking back over records from women who have used the product during trials or after licensure.

Q: What is a placebo?

A: A placebo looks just like the product being studied but does not contain the active ingredient. It is often used in a study to provide a comparison to a product being tested. This comparison helps to determine if any effects of a candidate product (including both side effects and efficacy) are due to the product itself or if the effects would have happened without the use of the active product.

Q: How will you assess the effectiveness of products if both groups are using condoms?

A: If all trial participants were able to use condoms consistently, it would indeed be impossible to evaluate microbicide effectiveness. The very reason we need microbicides, however, is that even with state of the art prevention counselling and access to condoms, not all women can get their partners to use condoms every time. Microbicides trials measure whether use of the active

product offers any protection among those women who do not manage to use condoms 100% of the time during the trial. It does this by comparing ser-conversion rates among women in the product arm with those of women in the placebo arm, after providing women in both arms with condoms and condom counselling and it assumes that the rate of successful condom use is likely to be the same in both arms.

Q: How can we ensure that trials participants have sex with positive men?

A: Microbicide trials cannot ensure this. But a Phase 3 trial assumes that the behavior of the trial participants is like the behavior of women who would be using the product in real life, if it came on the market. By enrolling sexually active women in sites that have a relatively high HIV incidence rate, the probability is that many of the women will, at some point, be exposed to HIV during sex. All trial participants are given state of the art prevention counseling, access to condoms and encouragement to use condoms. But the reality is that many of them may not be able to insist on condoms (just as they are not able to in their regular lives) and that, if they are exposed to HIV and using the gel, it will be possible to determine whether the gel is protective.

Q: Have “vulnerable” populations been involved in trials in India?

A: The term “vulnerable” populations or participants can be interpreted in many different ways. A recent commentary defines this term as subjects lacking basic rights.^[3] In India microbicides clinical trials have not targeted vulnerable participant, such as people living with HIV or adolescents. Some safety trials, however, have included HIV negative sex workers.

Q: What have been some of safety tests for microbicides among positive people?

A: Before a microbicides can be licensed, candidates must go through a series of tests to evaluate their safety. Product developers tend to think about safety as a person’s ability to use a product without it negatively affecting their body. While communities share these same concerns, community members sometimes conceptualize “safety” more broadly. For example, when asked about their safety concerns regarding an upcoming microbicide trial, community members wanted to know if the product would cause relationship problems between spouses, or cause people to be stigmatized who participated in trials. Others wanted to know if the microbicide would cause problems if they ingested it during oral sex, or if the drug would negatively affect a woman’s fertility.^[4]

In order to get a drug approved for human use, however, researchers and drug regulators concentrate on a very specific notion of what it means to be safe. Generally, they focus on whether and under what conditions the product might cause harm. If the potential benefit a new drug provides does not outweigh any harm it may cause, the drug regulators will not approve it for use.

For more information on how safety is evaluated in microbicide trials, see the Global Campaign’s briefing paper on the subject at <http://www.global-campaign.org/clientfiles/GCMBrief-Safety-Evaluation-Fundamentals.pdf>.

It is important to enroll positive women in microbicides safety trials to understand if and how general safety concerns affect HIV positive women. The safety tests often require the participants to remain sexually abstinent over the course of the trial. They are then asked to apply the gel a few times a day for a couple of weeks. Comprehensive safety assessments are then performed that may address a variety of questions:

- Does the product harm the vaginal lining (epithelium) or create an inflammatory response that may facilitate HIV or other STI transmission?
- Does it affect the natural vaginal environment that helps to keep the vagina healthy?
- Does the product penetrate the vaginal epithelium?
- Is it absorbed into the blood stream? If so, to what degree?
- Are there any negative effects of using the product on other body functions?

All of the current lead candidate microbicides have been tested in HIV positive women for safety in the USA, Europe or Africa, except for BufferGel. Although studies in HIV positive women will be needed if BufferGel proves promising in Phase 3 trial, the developers of this gel feel it is appropriate to wait until BufferGel's effectiveness is assessed before doing those studies.

Although it has become more routine to do Phase I studies in HIV positive women at an early point of development, some developers believe it is better to assess the safety of a microbicides among HIV positive women only after a microbicide is shown to be effective and before the product is available on the market. They argue this for the following reasons:

1) HIV positive women are a potentially vulnerable population, and generally, ethical guidelines ask that we do not study such populations without a compelling reason. Until a microbicide is to be released to the unscreened general population, they are not sure there is a compelling reason. Thus, a better strategy may be to study HIV positive women only after a microbicide is shown to be effective, and widespread use is going to happen.

2) Currently our tools for detecting this most important toxicity during early phases are very limited. We should try to develop more sensitive tools, but at present, we cannot. Therefore, even though some studies are, in fact, looking at safety among positive women, the findings are limited by the current tools.

The counter-argument to this position is that, once a microbicide is publicly available, it will be used by many women who do not know their HIV status. It is critically important to assess whether using it poses any greater risk of side effects to HIV positive women than to HIV negative women. If it does, then the product should be labeled with a specific caution that it may be risky if used by women who are HIV positive *or who do not know their HIV status*. It will not sufficient to assume that labeling such products as "for HIV prevention only" will adequately warn women who don't know their sero-status of the potential risk it could pose to them.

Significant discussion also surrounds whether it is ethical to test ARV-containing microbicides in women who are already HIV positive given the threat of resistance and the that that such products may compromise their future treatment options and/or the prevention of mother to child transmission. Currently we know very little about this. In microbicide clinical trials, women who seroconvert during the trial are instructed to stop using the ARV-containing product and are monitored to determine if resistance develops. Exposure during a microbicide trial, however, is unlikely to present a realistic picture of a microbicide's potential to induce resistance in the real world, because women who seroconvert during trials will be exposed to the product for such a short time.

In real life, women will not get tested as frequently and thus will likely be exposed to an ARV-containing microbicide for longer before they become aware that they are HIV positive. Thus, it is important to understand the effects of using an ARV-containing microbicide when someone is HIV positive.

As such, an argument can be made that positive women should be enrolled in safety trials (Phase 1 and Phase 2) trials of ARV-containing candidate microbicides as long as the following conditions are met:

- 1) Their immune systems are not compromised to the point where they need access to ARV treatment
- 2) They are fully informed of the risks they take by participation in the trial
- 3) They are guaranteed free access to other treatment options, should they develop resistance to first line treatment medications

Another argument in favor of early safety trials in HIV positive women is that trials could be used to screen out and stop development on a microbicide that would eventually have to be discarded due to their toxicity in HIV positive women. However, currently there is little evidence that HIV positive women are more susceptible to any microbicide toxicity when compared to HIV negative women, and that any microbicides would actually be discarded due to the results of these extra trials. [Either Tom Moench or Salim will provide us with the citation for the study that shows this]

Q: Why have none of the microbicides been tested among positive people in India?

A: An NIH-sponsored Phase I safety study of PRO 2000 Gel was conducted among low-risk and 'higher'-risk HIV-negative Indian women recruited in Pune and the investigators concluded that PRO 2000 Gel was safe in the study populations. Should future effectiveness trials be conducted in India, researchers for this gel feel that safety study among HIV-positive Indian women would be considered.

In order to conduct a Phase 3 efficacy study of microbicides, the research trial site must have a very high HIV incidence rate (meaning many new HIV infections are occurring annually in the population). Many microbicides researchers question whether India is now an appropriate location for future HIV microbicide efficacy trials because, thankfully, studies show that HIV incidence is probably decreasing in most of the areas where trials have taken place in India. Some argue that if incidence is decreasing where trial sites have been developed in India, then this country may also not be the best place for microbicide safety trials, whether in HIV negative or HIV positive women. It may be better to invest in conducting trials in the countries where the efficacy trials will also be done since the appropriate infrastructure to conduct them will already be in place there or be developed. Many however believe that safety trials should continue to be conducted in both high and low incidence areas in order to share the "burden" of research and to assess the safety and use of a product in varying conditions. Also, researchers continue to believe that HIV should be a major health in India, and even a modest incidence rate translates to a very large total number of infected people in such a large country. Microbicides, if developed, would therefore be an important tool for use in India. By studying them in India we will begin to pave the path for its eventual introduction by sensitizing by sensitizing eventual users, providers and policy makers to issues surrounding this.

Some researchers don't believe additional safety tests in HIV positive women in India should be conducted as little will be gained in terms of data but much will be lost in terms of time, cost and

the ethics of doing a study which is of dubious scientific value in terms of providing useful additional data.

Q: Can we enroll HIV positive female sex workers in microbicides trials?

A: They can be involved in safety trials. We are not sure if they are involved in trials in India

Q: So many agencies are doing clinical trials on microbicides. When (and if) microbicides come to the market how will the user know which one will be the best?

A: Marketing will play a major role in informing the consumer. Civil society and the community must also be very active in driving the education around these products.

Q: How should communities be involved in awareness-raising around microbicides?

A: The challenge for the microbicide field is to find the correct balance between building enthusiasm and political support for microbicides, while avoiding raising unrealistic expectations. Unfulfilled expectations can backfire and create doubt that could erode continued financial and community support.

Media and advocacy outreach around microbicides must similarly be attentive to the complex nature of drug development. Public discussion of microbicides must be sensitive to the desperation and powerlessness that many women feel in the face of their current HIV risk and their lack of ability to protect themselves. In this environment, it is irresponsible and potentially exploitive to be overly optimistic about the characteristics and likely availability of microbicides.

We will therefore need to strategically think through when, how and to whom we deliver information on these candidate products.

Q: What are the advocacy challenges? To whom will we address the advocacy strategy?

A: Both in the global north as well as the south, advocates for increasing HIV prevention options have focused on several key advocacy tasks:

- Awareness-raising among policy-makers, opinion leaders, the scientific community and general public about microbicides and prevention options for women
- Legislative advocacy and resource mobilisation in donor countries
- Policy advocacy in government and international organisations so that we can ensure the timely development, delivery and access to prevention options

The Global Campaign for Microbicides team in India is currently assessing how advocates in India could best contribute to this initiative both locally and globally. This may include signing a petition that will be presented to global health leaders on the need for increased investment for microbicides. Or perhaps we could mobilize the voices of India to help leverage resources for microbicides development both at home and abroad. You could even write a letter to a US representative urging them to support the 2007 MDA (attached weblink)

Q: What can we do to ensure efficacy, access and affordability of microbicides?

A: Scientists are currently working very hard to develop the most efficacious microbicides possible that is safe and easy to use. Despite increased funding and interest in microbicides

research the first generation products are still estimated to be approximately 40-60% effective. Even this level of efficacy, however, can have a major impact on the epidemic.

It is essential that effective microbicides get into the hands of women and men who need it at a price they can afford. In the past, new health technologies have rarely become widely available in developing countries until more than a decade after their approval in the US and Europe, an unacceptable delay for this life-saving technology developed primarily with public funds. Advocates are working with researchers and policy makers now to emphasize the need to address issues of access and affordability up front, in order to be prepared to deliver a microbicide rapidly as soon as one is proven safe and effective.

To get more involved in this effort visit the Global Campaign for Microbicides website: www.global-campaign.org to sign a petition, sign up for our electronic newsletter, write to your legislators, meet up with local advocacy groups in your region, and learn more about microbicides. We need your help to make a safe and effective microbicide available as soon as possible.

Q: What can advocates in India do to increase investment into microbicides research?

A: Sign the Global Campaign for Microbicides petition, which demands that governments increase funding for microbicides research. Also, you can participate in the Microbicides 2008 conference, which will be held in New Delhi. It will be very important for civil society to voice there needs and concerns around microbicides development and introduction.

Q: Right now our fight is secure assessible second line treatment within the NACP III – how do we prioritize microbicides considering this?

A: We shouldn't have to choose one over the other. We should advocate for both treatment and prevention.

The audience was then asked the following questions on advocacy. Below is a summary of the questions and the responses given by the participants at the meeting. The discussion was facilitated by Tilly Sellers and Anandi Yuvaraj.

Question: What are the key messages for positive networks?

Responses:

- General awareness should be raised on microbicides. Key message- such as the following - have to reach at the grassroots level:
 - Not 100% effective but is a good additional tool
 - Good for negotiation power of women
 - May be suitable for clandestine use (although the first generation products will probably be more obvious as they will be gels that increase vaginal lubrication somewhat).
 - Some non-contraceptive microbicides may reduce the risk of transmission among couples in which the women is HIV positive, the man is HIV negative and they are trying to conceive a child. But it must be noted that extent to which the man's risk is reduced (if at all) has not yet been determined.
- Education should be done separately for men and women
- We should consider diversity of language in India

- Messages should address misconceptions
- Hope is life – important to share with positive people
- Communities involved in vaccine trials don't know about microbicides
- Positive women are not yet involved in safety trials in India (notetakers questions: is this true? if so why?)

Question: What are the key advocacy issues for positive networks?

Response:

- Microbicides should be prioritized
- Positive women should be involved in research
- Microbicides should be affordable
- Clear misconceptions – maintain advocacy around condoms
- Sero-discordant couples need to know about future role of microbicides
- First figure out who are the “change makers” and positive people can advocate among them
- Good standard of care for those who sero-convert...during or even after trials – who is the one monitoring this. And will this information be provided in local language
- How can we step up watch-dog groups or be a part of this
- Advocates should push for increased funding in microbicides research in India
- How can we increase microbicides funding in the global north?
- Target migrant workers and rural people because they more vulnerable – in the future.

Question: How would positive networks like to address these issues?

Response:

- National Working Group should link with state-level advocates
- We should integrate microbicides with other HIV responses
- We need to involve all the positive network leaders – so they participate
- Review NACP III and integrate microbicides in the language and budget
- NRH Mission 1 – we can try to integrate microbicides advocacy
- We need to educate CBOs – GCM/PATH should organize the trainings
- We need to translate information in local languages
- We can raise resources to train positive people and include microbicides in that training
- We can link work on MTV and positive people

Question: India will host the next Microbicides conference. This international meeting is scheduled to take place in New Delhi on 24-26 February 2008 (correct dates?) and will be an important opportunity through which to profile the work of India in microbicides research as well as attract new advocates and scientists. ***How do you want to participate in M2008?***

Response:

- We should have representation from each district in India.
- Invite CAB reps to talk to community at M2008.
- National Working Group on Microbicides should advocate NACO to integrate microbicides in NACP III.

Possible follow-up advocacy support/tools from GCM India

- ✓ Add all participants to the GCM India list-serv/e-forum
- ✓ Distribute GCM film for participants to share with their partners and constituents
- ✓ Provide participants with CD-rom when it is released and finalized