# 5. What to Do About Male Partners?

Some of the most difficult questions related to informed consent revolve around male partners—in particular, should *they* be required to consent to their partners' participation in the research trial. Especially among women's advocates, the commitment to preserving—for that matter, to greatly strengthening—women's autonomy may run flatly at odds with cultural norms that grant decision-making authority to men.

At first glance, it may seem paradoxical to consider men's involvement, much less their consent, to test a product that allows disempowered women to protect themselves against men's pervasive unwillingness to negotiate condom use. In this regard, the 1997 Symposium, among other meetings, affirmed that *women's* consent is paramount and that women should determine if and how their male partners are to be involved.[1] Nevertheless, these are not open-and-shut questions. Men's safety, their eventual acceptance of microbicides, and their attitudes toward women's participation in clinical trials are highly relevant.

In considering what to do about male partners, it is important to distinguish among men's levels of engagement. Reaching out in the community to encourage men's support for clinical trials is one thing; requiring their consent for women to enroll is another. Similarly, assisting women to engage their male partners in a trial is quite different from accepting men's culturally reinforced "right" to decide for women regardless of their wishes.

Men's consent is legitimate and necessary to the extent that men may be exposed to an experimental product involving risk. However, this obligation can be addressed in several ways that respect women's autonomy. For example, safety of the product for penile exposure can be established early in the research process through men-only trials. Requiring male partner consent in Phase 3 clinical trials is not the only means of ensuring that products are safe for men.

## The pros of involving male partners

There are many reasons to involve men in the clinical testing of vaginal microbicides. Among others, these include:

- All outcomes and effects of the products need to be studied and understood. This includes effects upon second parties as well as principal users.
- Partner safety is an unavoidable ethical issue, since men whose partners are participating in clinical trials will be exposed to vaginal microbicides during sexual intercourse without a condom, or possibly during oral sex.

[1] Heise L, McGrory CE, Wood S. *Practical and Ethical Dilemmas in the Clinical Testing of Microbicides*. New York: International Women's Health Coalition; 1998.

- Microbicide's acceptability to men will be critical to if and how women eventually use vaginal microbicides. Whether or not a product is capable of stopping HIV transmission, it will not be "effective" if men prevent women from using it.
- Involving men in microbicide trials may help to improve couples' communication, opening discussion on the question of HIV risk and protection.
- Male partners' active support would likely improve overall adherence to the study procedures and would encourage women to remain for the full duration of the study.
- Partners discovering women to be using the product without having informed them may become abusive or violent.

## The cons of involving male partners

There are also good reasons *not* to involve men, and these too are compelling.

- Men's participation may reduce women's enrollment—men may refuse to allow women to participate, or women may decline because they do not want their partners to be informed or involved.
- Men's participation adds additional expense, complexity, and effort to conducting the trial. Moreover, many women may have more than one sexual partner.
- Men may further refuse to use condoms because they believe that the microbicide product now provides protection, which may expose both partners to greatly increased risk.
- Men may resist or hinder women's participation in the trial or their use of the product—for example, not allowing her to visit the clinic, taking the product away from her, or telling her that it is messy or decreases his sexual pleasure.

Engaging men too closely in the trial is ethically problematic if they pressure or coerce their partners to participate (or not), thereby infringing on her basic right to autonomy. The result could be disempowerment of women, precisely the opposite aim of microbicide development. A fundamental cornerstone of the microbicide agenda is that women must have control of the method and decide whether to inform their partners—or not.

## Experiences from India and South Africa

Men are the principal decision-makers in many cultures; and whether or not their permission is explicitly required, their attitudes greatly affect women's participation. In many settings, women may find it unacceptable (or simply unthinkable) to participate without informing and involving their partners. Experience with field trials in many setting reveals that women typically *want* to include their partners in the research.

In India, observations of couples enrolled in an early Phase 1 safety trial revealed significant differences between men's and women's concerns and how they make decisions. During the informed consent process, women primarily worried about possible side effects. By contrast, men expressed many more concerns, including the amount of time that would be required and the possibility of lost wages related to study visits. They too expressed concerns over side effects, for themselves as well as their partners.

The rationale for participation also differed between men and women in India. Both groups were influenced by possible benefits, such as access to services, and by assurances that side effects would be appropriately treated. Both were also motivated by a larger sense of social responsibility. Men, however, were notably more influenced by the means through which they received information. If doubts emerged during the consent process, they often became quickly suspicious. For this reason, a detailed informed consent process was found to be essential in involving men. In contrast to women, men generally perceived far less need for a microbicide. Women discerned risk of HIV infection, and they understood the need for protection. Nevertheless, the *most* important factor influencing a woman's decision to participate was the approval from her male partner.[2]

Focus group research in South Africa revealed different issues related to male involvement. Men were concerned about women touching ("fidgeting") with their vaginas, and they worried about exposing their own genitals to the product. In a setting where men generally prefer "dry sex,"[3] men expressed concern that the product might be wet, messy, or interfere with their sexual pleasure.

The South African focus groups observed that men might find "subtle" ways to interfere with their partners' participation—for example, sending their wife to the rural areas "to look after the house or family," as one focus group member observed. On the other hand, concealing women's involvement could have worse repercussions, including violence. As one man put it, "If I find my partner using something in her vagina—that will be the day! This will mean that there is no trust in the relationship." In adherence with traditional law, a man might report a woman to community elders, who could pressure her not to participate, if not punish her.[4]

In both India and South Africa, the point was reiterated that involving men could increase men's sense of responsibility and their accountability. This applies not just to the study but extends to greater openness between partners in discussing safer sex practices. As with contraception, men often prefer that their partners take on the burden of using a method. Many men find the idea of a vaginal microbicide appealing for similar reasons, especially for sex with their regular partners.[5]

## An emerging consensus on male participation

Despite strong encouragement to use condoms, some men will undoubtedly not do so. They will be exposing themselves to the product topically during Phase 3 trials—and to any harm that it might cause to them. It is therefore widely agreed that the safety

[2] Joglekar N. Involvement of men in vaginal microbicide trials: An Indian perspective. Presented at: International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23-24, 2003; Warrenton, Virginia.

[3] In many parts of southern Africa, men are said to prefer "dry" rather than lubricated sex; and women routinely insert herbs or astringents to dry and tighten their vaginas prior to sex.

[4] Nkala B, Dickson K, Kubeka V. Male involvement in microbicide testing: Insights from South Africa. Presented at: International Consultation on Ethical Issues in the Clinical Testing of Microbicides, October 23-24, 2003; Washington DC.

[5] In India, many men said they would continue to use condoms in casual sexual relationships because they could not rely on unknown partners to use a microbicide.

of microbicides for men must be established before large-scale trials can be launched with women.

One option for establishing safety for men is to enroll couples in Phase 1 studies, which allows safety for men and women to be studied simultaneously. In addition to evaluating safety endpoints, male participants in Phase 1 vaginal safety trials could provide useful feedback on their experiences and attitudes toward the product. Researchers can use urine tests and visual exams to flag instances of penile irritation or inflammation that could be product related.[6]

Alternatively, researchers can mount separate male tolerance studies, which test whether the experimental product causes irritation to the penis or other negative side effects. In the microbicide world, male-only safety studies generally occur shortly after safety testing in women. They are repeated later in men who are HIV-positive and among men with other STDs to establish microbicide safety for these user groups. In early safety studies of this sort, men's consent is of course required.

In weighing the pros of involving men in microbicides trials—yet cognizant of the potential infringement on women's autonomy if men's formal consent is required—Consultation participants considered alternatives for Phase 2 and Phase 3 trials. One option would be to enroll only women who are comfortable including their male partners, despite the added complications to enrollment and possible dramatic reduction in the number of eligible women. This strategy could bias the study toward women in lower-risk relationships, possibly at the expense of fully representative data.

Most Consultation participants agreed that the involvement of men in Phase 2 and 3 trials is preferable, but that male partner consent should *not* be required. Depending on the specific characteristics of the trial, it may be appropriate and possible to enroll couples in earlier safety trials. Yet in the large-scale Phase 3 effectiveness trials, Consultation participants generally viewed requiring partner consent as neither practical nor desirable, especially since many women may have more than one sexual partner.

In summary, there are many good reasons to involve men in trials, but this stops short of requiring men's formal consent for women's participation. It is sufficient that women be encouraged to inform and involve their partners. Where women do choose to involve men, researchers should support their decisions by providing materials that are designed for men and by creating male-friendly clinic environments.

## Further safety precautions for men

While Phase 1 safety trials should help to uncover serious safety issues for men, short-term safety trials may be inadequate for establishing longer-term safety among men who have sex more frequently. As a further precaution to enhance male safety, a "passive surveillance" system could be established to help capture any adverse events for men in Phase 2 and Phase 3 trials. In other words, researchers would ask women to refer men to the clinic with suspicious symptoms that could be product related. Whether or not men are actually

[6] A generic inflammation marker—urine leukocyte esterase—in the absence of an STD might indicate product-related effects.

enrolled in the trials, treating partners for these side effects should, of course, be part of the study protocol.

A more active alternative might be to test penile safety in higher-risk men by carrying out an ancillary study with men during or after the Phase 3 trial in women. Once a microbicide product is on the market, a post-approval surveillance system should also be established for reporting additional adverse effects.

## Rectal use of microbicides

Regardless of its labeling, a microbicide that is marketed only for vaginal use is sure to be applied rectally by both men and by women. Studies have confirmed that anal sex is not uncommon among heterosexual men and women. One review of studies on the incidence of anal sex in sub-Saharan Africa found percentages among respondents ranging from 8 to 75 percent.[7] For this reason, advocates have long argued that it is important—both for men who have sex with men, and for heterosexual women and men who engage in anal sex—to establish whether products designed for vaginal use cause irritation or inflammation of the rectal mucosa. If that occurs, a considerable amount of effort must be invested in order to actively discourage rectal use of microbicides intended for the vagina.

Still under debate, however, is when rectal safety studies should be undertaken in the course of product development. Some argue that rectal safety studies should be pursued before a product goes into large-scale effectiveness trials for vaginal use among women. Although Phase 3 participants are routinely advised not to engage in anal sex—and explicitly, not to use the microbicide product rectally—they may do so anyway. This argues for establishing the rectal safety of vaginal products early on.

Others argue that it is sufficient to evaluate rectal safety once an experimental product demonstrates some effectiveness when used vaginally. Evaluating rectal safety earlier will require considerable expenditure of precious resources to test products that may not prove viable as vaginal products. Arguing from this perspective, the time between preliminary analysis of the data and regulatory approval should be sufficient to assess safety for rectal use.

Biologically, the rectum and the vagina are vastly different.[8] Regardless of when safety testing occurs, it is critically important to avoid any assumption among users that vaginal microbicides will be protective for anal sex. There can be no ambiguity allowing anyone to take for granted that a product meant for vaginal use will also protect when used rectally.

[7] Brody S, Potterat J. Assessing the role of anal intercourse in the epidemiology of AIDS in Africa. *International Journal of* STD *and* AIDS. 2003;14:431–436.

[8] The rectum and the vagina differ significantly in structure and natural ecologies. The vagina is a closed pouch while the rectum is part of an open-ended cavity. The rectal lining is more fragile than most of the tissue lining the vagina. It is also richer in CD4 receptors, cells particularly vulnerable to HIV infection. These factors further enhance rectal vulnerability to irritation, tearing, and infection during sex.