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Around the globe, countless women are unable to protect themselves from HIV—largely because they lack access to condoms or can't count on their male sex partners to use condoms consistently. Potentially life-saving HIV prevention interventions are being developed with these women in mind, including microbicides and other protective products that can be used with or without a partner's knowledge, as well as strategies for boosting women's control over how and with whom they have sex.

A Conversation with Dr. Nancy Padian

At the forefront of research on HIV prevention for women is Dr. Nancy Padian, an internationally recognized expert on heterosexual transmission of HIV and the director of the Women's Global Health Imperative at the University of California, San Francisco. Dr. Padian, who led the recent Methods for Improving Reproductive Health in Africa (MIRA) study, spoke with BETA *about her research and the challenges inherent in trials of HIV prevention technologies.*

BETA: You head the Women's Global Health Imperative at UCSF. What are the program's goals?

Dr. Nancy Padian: The goals of the program, in a very general sense, are to reduce women's vulnerability to adverse outcomes associated with reproductive health. Mainly that's HIV, but it also includes other sexually transmitted infections and unintended pregnancy, for example. Essentially we have two major themes (although it's a bit reductionistic to winnow it down that way). One is looking at women-controlled methods of prevention. The study that I just completed was looking at whether diaphragms protect women against HIV. We're also involved in many microbicides trials, for example, and we've done some stuff with the female condom. It's a major theme: having tools that women can use to protect themselves against HIV that don't rely on negotiating male condoms with their male partners.

> An outcome is the result or consequence of a situation, disease, intervention, etc. Outcomes for participants in trials of HIV prevention methods include remaining HIV negative or acquiring the virus.

The other major theme of our work is—although I hesitate to use this word, because it's ill defined—"empowerment" strategies, trying to devise interventions that give women a voice so they're more in control over who they have sex with, under what circumstances. Those tend to have more of an economic or structural component, and they include things like microfinancing and vocational training, involving various aspects of society, like the health care system. For example, in India, how are [health care practitioners] interacting with women to uncover domestic violence? Domestic violence is another important one of our outcomes. We're studying that theme in India and Zimbabwe, and we're starting some new studies in Tanzania and possibly Kenya.

The MIRA Trial

Headed by Dr. Padian and an international research team, the MIRA trial assessed the efficacy of latex diaphragms as part of a comprehensive package for HIV prevention. The analysis involved nearly 5,000 sexually active, HIV negative women in Durban and Johannesburg, South Africa, and Harare, Zimbabwe. Along with intensive HIV prevention counseling and male condoms, women in the intervention arm received a clinician-fitted latex diaphragm and a supply of Replens lubricant gel. Participants returned for quarterly follow-up visits from September 2003 to December 2006.

During the three-year study period, 6.4% of women in the diaphragm arm acquired HIV, compared with 6.1% in the condoms-only arm. These HIV incidence rates, as well as self-reported data regarding participants' condom and diaphragm use, were reported in the July 21, 2007, issue of *The Lancet.* "Among women receiving a state-of-the-art HIV prevention package…we observed no added protective benefit of providing the diaphragm and lubricant gel in addition to provision of male condoms," the authors concluded.

Statistical power is the probability that a study can detect a real effect (such as lowered HIV risk in women using diaphragms) in an experiment or clinical trial. A trial's statistical power is strongly influenced by its sample size, the number of participants enrolled in the trial.

Another major component is the training side, working with women to be scientific leaders in these fields. With that regard, we have various training programs and we like to think of our program itself as being a fertile training ground. For example, more than ten people on our staff went back to graduate school this year.

***BETA:* You are also the principal investigator on the MIRA trial, which looked at diaphragms as part of an HIV prevention package. Why diaphragms?**

NP: There's good data from a variety of different sources to indicate that almost certainly the cervix is the most vulnerable site for HIV infection. That's not to say that all infection occurs at the cervix, but probably most. So our hypothesis was that if you cover the cervix, which is what the diaphragm does, you would protect women against HIV. That's it in its most simple iteration. Also there have been a variety of observational studies that have shown that the diaphragm could protect against other sexually transmitted infections, and many of those facilitate HIV. We thought it might work with that mechanism as well.

***BETA:* But you saw no added protective benefit from diaphragm use?**

NP: Right.

***BETA:* Your recent article in *The Lancet* describes the disappointing results of the trial, but it also notes that women who used diaphragms reported lower condom use but did *not* have increased infection rates.**

NP: We can't rule out that they were as effective as condoms, but there's not enough statistical power to really be able to asses that in a rigorous way. Another equally viable hypothesis is that women in the condom-only arm significantly over-reported [using] condoms, because they knew that was the intervention they were supposed to be practicing—which highlights another issue: not only is adherence challenging, but how you measure adherence is also extraordinarily challenging.

BETA: What are some of the other challenges that researchers face when studying a product that may—or may not—prevent HIV infection?

NP: There are a lot of challenges. One is a point that you just made: we don't know whether these things are effective, and a number of things can result from that. One is that, even though you're telling them that they're participating in the study to actually determine whether the method is effective, people may nevertheless think that it might work (or just want so badly to think that it works because they have no other options), in which case they may reduce their condom use and end up using a method of unknown efficacy, or one that turns out to not have an effect. So that's one problem. And that's in part what I think we saw in our study: [in the diaphragm group] women reported less condom use.

The complete other side of the coin is that, because we don't know whether these new methods are effective, it's our ethical imperative to counsel them very, very heavily about condom use. And what you can do, as we did in our study, is really significantly increase the rates of condom use (although not as much in the diaphragm arm), which then makes it very difficult to detect an effect of the new intervention. So you might conclude that we need to do more in promoting male condoms, which I think is true. This study is really geared for those women whose partners don't use condoms, and the most vulnerable women are probably the women who didn't participate in the study.

Even though condom use may have increased in this study, it cannot be sustained. What's in place in the community to sustain those high levels? That highlights our need to keep up these intensive condom programs, but also that [it's possible to] raise condom use to a standard that perhaps is not sustainable in a community. And you also make it very difficult to detect an effect of a new intervention.

BETA: Given the recent closures of trials evaluating two vaginal microbicide candidates, Savvy and cellulose sulfate (UsherCell), and the results from the MIRA diaphragm study, where are we in terms of a woman-initiated HIV prevention approach?

NP: I think everyone is really looking forward to those methods that have an antiretroviral component. People are looking at both vaginal methods and vaginal microbicides, and also at PrEP, pre-exposure prophylaxis. (Even though that is not gender specific, it's something that women can use; clearly, you're in control of taking a pill.) So that's one direction.

And also, I think we do need to step back and look at the methodological challenges of these studies. Are there other ways to analyze the data? Are there other ways to design them so that we have a better chance of detecting an effect? I think it's really important to point out that in our study, the methodological challenges were such that our hypothesis that covering the cervix is protective is still viable; it's just that we felt we could not really say that in our study.

BETA: What do you think would facilitate more definitive results in trials such as these, where the inherent challenges are so numerous?

NP: It could be that there are methodological advances—for example, one which is not nearly as sexy as testing a new intervention is coming up with better ways to measure adherence. Hopefully, in addition to seeing testing of new methods, we'll also see advances in how we do these study designs themselves. That will make it easier to sort out what the results really mean.

BETA: Looking back, is there anything you would have done differently in the MIRA trial?

NP: Off the top of my head—and this is *really* off the top of my head—I think maybe we would have had more frequent visits, because that might have been a better way to enforce adherence (of course, [it] would have made the study more expensive, and more arduous for the women who participated). We also might have thought about some sort of strategy to really target those vulnerable women who could not use condoms. Some thought needs to be given to that.

Selected Sources

Padian, N. Synthesizing our options: biomedical prevention technologies in the context of behavioural interventions. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Sydney. July 22–25, 2007. Abstract WEPL103.

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For more information on microbicides, see "Microbicides for HIV Prevention" in the Summer 2006 issue of *BETA*.