

## **Microbicides 2006: Plenary Sessions April 24, 2006**

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**ZEDA ROSENBERG:** It is my great pleasure this morning to introduce our first speaker for the scientific plenary session here. It is Dr. Sharon Hillier who, many of you will know has been in the field for many, many years and has really been a pioneer in the microbicide research field. Dr. Hillier is a professor and director of reproductive disease research in the department of Obstetrics, gynecology and reproductive sciences at the University of Pittsburgh School of Medicine. Since 2000, she has served as director for the National Center for Excellence in Women's Health at McGee Women's Hospital in Pittsburgh, Pennsylvania. And as I said, Sharon has been working in this field and has been promoting women's health for many, many years and I would like to welcome her to the podium. Sharon? [Applause]

**SHARON HILLIER, Ph.D.:** Well, it's wonderful to be here this morning. And I was just sitting in the front thinking about how today differs from the way I spend most of my life. It occurred to me that I spend a great deal of my time speaking to groups of physicians and scientists about "what is a microbicide? Why do we need a microbicide? How will a microbicide? Who is working on microbicides?" And this morning, the is probably one of the most exciting for three reasons. In front of a group of people and talking, I'm with the people who [skip in audio]. And instead of standing in a room [skip in

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audio] I'm in Africa. [skip in audio] to change the face of this epidemic. And we're going to do that.

So thank you. And it's wonderful to be here. And thank you for all the ministers this morning, for your kind welcome. I was given a very simple task. They said, "Sharon, please just go over [skip in audio] and its evolution." I said no problem. To give you, as we begin to [skip in audio] we're going to hear a lot about [skip in audio] particular talk I'm giving is [skip in audio] in basic science. [skip in audio] take you through in a very [skip in audio] at a high level look. [skip in audio] the classes of action, [skip in audio] the challenges are for each of these approaches.

Everyone knows that microbicides are going to work in different levels. And the important thing, I think, is to understand where the target is. Where the target cells are for that virus. And how do we get the active molecule in a microbicide to the right target at the right time? And so, as we talk through some of the various approaches today, we'll talk about some of the pros and cons of these approaches. We know that some of the products that are in clinical trials currently really provide barriers in a couple of ways. They provide physical barriers and lubrication. And some actually may enhance the vaginal microbial flora and enhance the safety and the immune function of the reproductive tract. Some may have an important role, not only in preventing HIV or killing

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HIV in the vagina, but also in preventing other sexually transmitted infections. Some may actually disrupt the virus. Some will act at the level of stopping fusion or absorption, or even through inhibition of co-receptors through the antagonism. Some are going to work intracellularly as reverse transcriptylases.

And so I think the important thing, when we talk this morning about the spectrum of molecules that are in development, is that microbicides are not a thing. Microbicides are an approach. They are a real spectrum of approaches that we're taking forward that are going to be used in different ways by different people.

In the laboratory, and I have a laboratory, and I also do clinical trials work; and I'm also a mother. And so when I sit in the laboratory and think, "what's going to be an exciting active?" I think about, "will it have a great activity against HIV?" "Will it be very safe?" because my personal rule is any microbicide that we test in any population will have to be safe enough that I would recommend it for my daughter or my sister. And so we think very, very hard about insuring that these molecules will have low toxicity. Does it have activity against other STI's? Maybe it has activity against sperm and will be contraceptive. And maybe not.

And so when we sit in the lab, sometimes we get really excited because we're thinking about those in vitro tests. And

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we think, oh my gosh, we found the perfect microbicide. And shown here is my favorite microbicide as a Lamborghini called microbicide. And then when we begin to compare it in the laboratory, we use as our comparator Nonoxynol-9, which we know does not have any of the attributes that we want to see in a microbicide. That is to say, it has very low selectivity against HIV, at the same time having fairly high levels of toxicity when used at high frequency. And so, as a joke I've put here a picture of a bicycle on a gravel road. So what we do is we compare our new Lamborghini to the bicycle and say, well goodness. This is quite a perfect molecule. And then we talk about it and we publish papers. And people say, oh that's so exciting! You've discovered the new microbicide. And today, I want to sort of think beyond these attributes and how we need to think about our pipeline of products that are going to move forward.

There's a long road from the bench to scale-up and development before we come into clinical trials. We have to be able to scale-up these molecules. They may be exciting, but difficult to manufacture. We have to figure out how to formulate these and put them into a product that women and men will like to use. We need to understand pharmacokinetic and pharmacodynamic parameters to understand, where is the molecule? Is it transported into the sub-epithelium? Does it go inside the cells where it can exert its effect? Is it active

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only in the vaginal lumen? Or is it there and really active intracellularly in the sub-epithelium? And only then can we move forward to the first studies of safety and the second studies of expanded safety. And finally, the expanded two- and three-phase studies which tell us whether or not a product is effective. And at the same time, we have to be aware that this molecule, this microbicide Lamborghini that we've identified will have to be stored, it will have to be at low cost, it will have to withstand high temperatures and it will have to be utilized and exported all over the world in a safe way.

And so, sometimes we think about the road to development being a straight road. We say, well, you find the molecule, you scale it up, you put it into a formulation, you do a phase one, you do a phase two and you do a phase three. But in actuality, there's a lot of hidden dangers around every corner. And so, although we sometimes think we've found the perfect molecule in the laboratory, I think we won't know until we do the road test. Until we find out which ones actually work best in the setting. And by 'work best' I mean not just stopping HIV. But having the best safety profile. Having the best level of acceptability. Having the lowest cost and ability to be transported and made available around the world.

So I'm going to start with the first class of products that most of us have heard a lot about. And that's surface activated agents. Nonoxynol-9 is a surface-active agent. But

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it's an older type of molecule that has some attributes that all of us understand, are not really optimal. There are some new ones that are in development right now. Including something called 'the invisible condom'. There's one we've been working on in Pittsburgh for a long time with Charles Isaacs called Octoglycerol, which is a synthetic breast milk lipid. And there's another, called Savvy, which is one of the products that's in clinical trial, C31G.

Now, all of these surface-active agents have in common the fact that they're pretty low cost; they're pretty cheap to make. Most of them have contraceptive activity. And all of them have some activity against other sexually transmitted disease, particularly Herpes Simplex virus. And how they are really distinguished from Nonoxynol-9 is, when these are placed into the rectum in a monkey model, they are very safe. They don't have the same effect of sloughing epithelium that we saw with Nonoxynol-9. But there are some real challenges even though these are inexpensive and effective and appear to be much safer than Nonoxynol-9, they do have a low therapeutic index. That is to say, a fair bit of the molecule has to be present in order for them to exert their activity. And it's the window between their therapeutic level and their toxicity window isn't as wide for some other classes.

There's still significant surfactant stigma. That is, people think, well Nonoxynol-9 was dangerous. How could another

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surface-active agent be the best? And the third thing is that they really are active in the lumen only. And therefore will always need to be used only during coitus. They'll never be used independent of coitus. Nonetheless, there are a number of these that have been identified that are moving forward. The Savvy trial is funded by the U.S. Agency for International Development. And FHI is implementing that study. And you'll hear more about that at a session this afternoon. And this is one of the large-scale trials that's currently underway.

Cellulose acetate fellate [misspelled?] is being identified as Centers for Disease Control and The National Institutes of Health. And the good thing is that these agents do have lower toxicity than Nonoxynol-9. And I do think could potentially replace Nonoxynol-9 in products used for topical contraception in the United States and internationally. A study comparing Savvy versus Tenofovir gel, PHPAL, versus placebo is being currently planned through Caprisa through Dr. Slim Abdul-Kareem and Karesha Abdul-Kareem [misspelled?] funded by The Family Health International with helping with implementation and CONRAD. So we do have the first planned trial of a surfactant agent, C31G, directly against a anti-retroviral specific approach.

How about acid buffering agents? Well, these seem to be a no-brainer. They seem to be very simple. The vagina is acidic. And by acid buffering, we can restore or maintain

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vaginal acidity in ecology. They have very low toxicity. There is no systemic absorption, and therefore, very high levels of safety. All of these agents have in vitro activity against acid sensitive STI's such as bacterial vaginosis, Herpes Simplex, Human Papillomavirus, Chlamydia and Gonorrhoea. And some of these are actually fairly contraceptive. But again, these are somewhat less specific. They have low potency against HIV. They will be available only for coital dependent use. And as I'll mention a little bit later, I think this class of products is going to be really important in using in combination with other higher specific actives.

It's important to note here, at this meeting you are going to hear some early results about lemon juice which has been promoted as a natural microbicide by some people. And there, I think, teaches us an important lesson. What you'll hear in this presentation is that lemon juice actually showed a fairly high level of toxicity during human studies. And so that teaches us, again, that when we try to develop microbicides, we can't look at something that's on the shelf and say "because it's natural or because it's been around a long time, it must be good." We must apply the same degree of rigor about safety for any molecule irrespective of how long it's been around or in wide use. And that's the lesson we learned from Nonoxynol-9. And we have to remember that lesson.

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So where are we with acid buffering agents? They can be used, maybe, with cervical barriers for HIV and STI prevention because of their excellent, outstanding safety profile. Again, I think this class of products could replace Nonoxynol-9 as topical contraceptives. And they can be combined with other high potency microbicides as our first generation combination products.

How about fusion inhibitors? These are molecules that you'll see at this meeting like cellulose sulfate, Pro 2000, CareGuard, which are in clinical trials. Again, these are low cost molecules, they have a low potential for resistance from the virus, many have activity against other envelope viruses; particularly Herpes II, and they do have contraceptive potential. Cellulose Sulfate has been found to have, actually, very high levels of contraceptive efficacy; in the high 80's. But again, this class of products, because they're somewhat non-specific, have a lower potency. And there is undefined activity against the other STI's. And again, these will be coitally dependent. But this class of products is very far along in testing. Pro 2000 is currently in effectiveness trials, HPTN03-5 and the microbicides development program trials. Cellulose Sulfate is currently in effectiveness studies funded by Conrad and Gates, FHI, funded by Gates and USID. CareGuard is in late phase effectiveness studies through the POP council. And I think all of these products have the great

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potential as being considered as the case for secondary active for combination products as we move forward.

I think there's a lot of talk now about the use of anti-retrovirals for prevention. Just as we have used these for treatment. Things like Tenofovir, MIV, UC-781, TMC-120. You'll see papers on all of these products at this meeting. Now these have tremendous potential. High levels of potency, documented efficacy as therapeutics. They can be delivered vaginally or orally, or both. Some ARTs do have poor systemic absorption and may be perfect because they would have, in fact, lower levels of systemic toxicity. We have extensive pre-clinical and clinical data from many of these molecules. And they can be modified to other delivery forms, not just water-based gels. So we would have, with this class of products, the first coitally non-dependent use. Which I think would move us away from many of the concerns we have about adherence.

But again, with any Lamborghini, there are deficiencies and challenges. There is limited activity against other sexually transmitted diseases for this class of product. And there is significant concern that we all share. The use of these agents for prevention could give rise to resistant virus which would in turn, render the use of these drugs non-applicable, should a person seroconvert. And so, I think we need to always really weigh the pros and cons and think about

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putting these approaches together in a way that will give us the best possible approach.

I think you know, right now, Tenofovir is being evaluated as an oral agent for prevention of HIV by several groups, but a large study ongoing in Botswana funded by the CDC. Tenofovir gel is moving forward into expanded phase II safety testing. And those studies will be conducted in Pune, India and in the U.S. under the HPTN059 protocol. TMC-120 gel is moving into expanded phase II testing at the IPM. And the vaginal ring, which will be our first coitally independent method for testing TMC-120 is in phase I trials, again, by the International Partnership for Microbicides. Several NNRTIs such as UC-781 are moving forward in early clinical studies. And some are going to incorporate sustained-release technology. This, in my view, is the richest pipeline of products ready to move into effectiveness studies.

How about the CCR5 antagonists; another group you'll hear about at this meeting? These include molecules like PSC-Ranties, [misspelled?] the sharing-D molecule, Merck-167, the GSK molecule; Pfizer has a molecule. And these are an exciting new group having a completely different mechanism of action. High potency against the R5HIV, long-term binding to CD4 with the therapeutic products, up to five days after the last dose. So again, we have that opportunity to provide microbicide potentially apart from the coital act. These have proven

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activity as an HIV therapeutic. And we have proof of concept in simian models. And we already have a small molecule scale-up because of the therapeutics. And some of the problems with the larger molecules, like the PSC-Ranties are really being addressed.

There are some concerns with this class of product. And we don't know how widely it will affect the whole class of this group. There were safety, toxicity signals for some of these molecules when they were used as therapeutics. The larger molecules, such as PSC-Ranties, may in fact be difficult to formulate. And there are concerns regarding selective pressure towards X4. But, none of these agents are in trials as topical microbicides. Although PSC-Ranties is being developed specifically for vaginal applications. Although formulation challenges are considerable. But it's important to note that two molecules, Merck-167 and two other related molecules, have recently been licensed and will be available on a royalty-free basis for microbicide development through the IPM.

CCR5 antagonists, developed as therapeutics, have had safety signals which may limit their further development. But I think that with the careful decision and pipeline management about which of these molecules can move forward, there may be yet one or more of these molecules that has a real future as a topical microbicide.

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How about GP-120 binders? These are things like Cyanovirin and dendromers. There are other molecules from Bristol-Myers which have been licensed to IPM. These have wonderful activity against Herpes II. Things like hydrenomer [misspelled?], the Viva Gel product. There is, again, proof of concept in simian models. Cyanovirin has been proven to prevent SIV infection when administered rectally. Dendromers have been shown to prevent infection when vaginally delivered. And we know that, for even some of the more difficult to produce molecules, that plant expression systems can actually help increase their availability. But these may be difficult to formulate. And they probably will be for coitally dependent use. But we hope these can be modified for use in rings or sustained-release products which will allow them to be used independent of sex.

Where are we with this group of products? The dendromers. Viva Gel is in phase I clinical trials and beginning studies for STI prevention through funding from the MIAID. Cyanovirin formulation is very complex. But there are really innovative strategies underway to try to use genetically modified organisms to express Cyanovirin. And again, the Bristol-Myers molecules were recently licensed royalty-free for microbicide development.

Now, I think another strategy that really deserves another mention are the idea of putting some of these

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microbicides with cervical barrier systems. This is a nice slide from the Program for Alternative Technology and Health which shows a buffer gel cup and in this particular manifestation, it's a single-sized disposable, pre-filled with microbicide agents. So this would come pre-packaged, ready to use and the gel cup itself becomes the applicator. They also will have a reusable model which would obviously reduce the cost. There's also something called the Silks Diaphragm, which is one size, reusable, and can hold microbicide. The idea about this is that the cervical barrier would provide protection of the cervix which would be of likely benefit for prevention of cervicitis. It could be adaptable for multiple different microbicides. It's a familiar technology from the contraceptive field. And it actually might concentrate microbicide right at the cervix, which we know has a higher density of target cells. And it would replace the applicator. If we use it in a disposable form, it's going to be a little bit more expensive than an applicator. But if it's used multiple times, it's actually going to be a very cost-effective way to apply microbicide. Some people will have difficulty with insertion. And this is where acceptability studies are going to be really important to find out, do women prefer an applicator versus a cervical barrier? What's the best way? Which produces the least garbage? What's the best, most acceptable thing for them to use in their daily lives?

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And finally, we need to realize that anything that's there in a permanent or semi-permanent way, may produce local irritation. And they'll need to assess that very carefully. But currently, there are Phase I acceptability studies of the Duet pre-filled gel cup which was completed early this year by Conrad. Post-coital study for the Silks Diaphragm was completed in 2005. And the Silks Disposable Diaphragm will be moving forward to contraceptive effectiveness studies with Nonoxynol-9 as a non-comparative study, to begin in July 2006.

A lot of talk about rings. Well, rings look very nice. We all love rings. And the really exciting thing about rings is that they can be inserted and kept in place for a week or a month, and really provide a great deal more spontaneity because we don't have to worry about application of product right before coitus. So it will increase compliance and acceptability because it's coitally independent. It may be the optimal method to deliver molecules which are active intracellularly. And it's a flexible platform because you can add anti-bacterial agents or even contraceptive agents. Rings are used very widely in the U.S. for contraceptives. So you can envision a time when a woman might be able to get a ring if she feels like she's in a high-risk situation, a ring that's contraceptive and could potentially deliver anti-retrovirals and that would be replaced on a monthly basis. But, it may give you more exposure to drug because it's there all the time and therefore, may have greater

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potential for toxicity. And so that's a thing we'll have to look at very carefully in studies. Some people find ring insertion to be somewhat difficult. And getting correct placement can be a little tricky. And I think we have to consider that if we're using anti-retroviral based microbicides, that having a constant level of drug available all the time, that this could be an optimal method to induce resistance. So again, this is not something that should make us back away from this approach; but to be very careful as we move forward.

Currently, there are multiple technologies being developed. The Reservoir and Matrix type Phase I studies; with the reservoir type ring with TMC-120 has demonstrated great safety, good tissue levels. And new ring technologies are in development which would be biodegradable, with multi-drug delivery, with hydrofolate drug compatibility. So I see this as a really exciting future strategy that has tremendous promise.

And then, let's think really into the future. And this is a really exciting development; but a little ways off. Genetically modified bacteria. And these are my friends, the lovely lactobacilli. Positive attributes of these are there's a potential for continuous delivery. Imagine if we could put an organism into a vagina or into a rectum, and this organism would continuously release microbicide. And these microbicide molecules could bind CD4, they could produce Cyanovirin.

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There's extensive microbiological proof of concept so far with the idea. And the potential is obviously, that you would put these suppositories in, it would release the organisms, the organisms would grow and continuously produce the microbicide. Obviously, it would give you the option to use these independent of coitus. But there's a lot of work to do. And when you put a genetically modified organism into the normal flora, how will it compete with the other bacteria that live there? Concerns. Just about many people won't eat rice made from genetically modified seed. Well, how would we feel about having genetically modified organisms as part of our normal flora? It's very difficult, and I've done a lot of these studies, to predict success on how well an organism that's placed in a vagina will compete with the others and how many will be sustained. And therefore, it's very difficult to figure out what your pharmacologic dose will be. And finally, there is a potential for inducing immune response to the organism itself or to the product that it's secreting.

But there are some really exciting developments which you'll hear more about at this meeting. With respect to lactobacillus soluble CD4 receptors and 17B hybrid proteins were developed by Ed Berger, the chief of NAID Lab of Viral Disease. And this genetically modified organism to express soluble CD4 receptors has been scaled-up now, by O-Cell, who is at this meeting. And they've also developed a lactobacillus that

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expresses Cyanovirin. And some animal model studies are currently underway, funded by the National Institutes of Health, about the expression of these molecules in vivo, in animal models.

E. Coli is another approach that's been put forward by Dean Hammer at the National Cancer Institute Biochemistry Lab, who has engineered a strain of E. Coli which is a common organism in the gut, which will secrete an antiviral peptide. And this binds to GP41. The capacity of this organism to colonize in the mouse has already been documented. And simian models are underway to assess whether or not this actually will express the protein. And whether or not it can prevent infection with the simian immunodeficiency virus. And these studies are underway. Dr. Hammer is at this meeting. You should get an update from him.

Finally, many people understand combinations are probably the way we need to go. Combinations are a proven therapeutic approach. We know now we would never treat a person who is infected with a single agent. And many of us believe that combinations are the long-term future. There's a lower risk of breakthrough infection, lower risk of ART resistance, and we may be able to really incorporate slow-release technology with using combination. But with anything, there are challenges. Formulation is going to be more difficult with multiple actives. And the current regulatory pathway for a

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combination agent, is, by law for the Food and Drug Administration, you have to compare one active, Active A versus B, versus A plus B. And if you had two very active molecules, each having 80% effectiveness—we could dream—it would be very difficult to size a trail to really show superiority of the combination. So we're really going to have think carefully about what things we put together and the way that we do it in order to insure that the regulatory challenges will not be prohibitory. And obviously, when you put multiple things together, you have to think about intellectual property and licensing issues.

So where are we today? Well, we have combinations of cervical barriers and non-specific microbicides. In my view, these are going to be our first combinations. We're going to take an acid-buffering agent and put that together with a specific anti-retroviral. Or we're going to take physical barrier and put it together with one of these first phase microbicides. Combining the high potency actives, the ARTs , the CCR5 activists will be challenging. But preliminary animal studies are really encouraging that, in fact, these multiple combinations are going to be very effective.

So as we sit in the laboratory and we think about how to discover new molecules that are really going to get us to where we want to be, to find a microbicide that really can change the face of this epidemic, we still need to think about

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HIV activity and toxicity. And whether or not it's active against other STIs. We have to really consider carefully, early, where the molecule is going to be. Is it going to be in the sub-epithelium? Where is the active? Where is the target? And we need to think very early on about how easy it's going to be to formulate these microbicides.

So in the pipeline of candidates, there's a broad diversity of mechanisms. This isn't a single approach. It's really a family of approaches. Each of these approaches as significant strengths and challenges. And we have to have our eyes open to those. The near-term pipeline of molecules which is entering Phase I testing is actually fairly modest. And we need a lot of work to really richen the pipeline of molecules that are ready to move forward. We need to define better what the target is? What target cells we're really trying to reach for each active? And make sure that the pharmacology matches that. That, in fact, the active agent is getting to that target.

So as we think about the pipeline and the molecules that we have in the pipeline, we have to have a lot of different approaches in the race. And it may not be that the Lamborghini is our optimal molecule. In fact, we may find, as we come out of the pipeline, that the Lamborghini was not the right one at all. We may find out that we needed a whole different approach. So I like to think that someday, what we

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really need, so we don't end up with an empty pipeline, is a group of eco-friendly hybrids that maybe approaches that are not anything that we have right now. But something that's going to be cheap. That's going to get the job done. That can be delivered where it needs to go, will be friendly to the environment, safe, and will make a difference in this epidemic. Thank you, so much. [Applause]

**ZEDA ROSENBERG:** Thank you very much, Dr. Hillier. Thank you for that very clear, comprehensive overview. And clearly, there are many challenges. But also, there are very exciting possibilities in this field. While we prepare for the next speaker, I'll just begin to introduce her in the interest of time.

Honorable Ministers, distinguished guests, ladies and gentlemen, colleagues; it is my pleasure to introduce the next speaker. The next speaker is the Honorable Minister of Gender, Labour and Social Development in Uganda. Minister Zoe Bakoko Bakoru. Minister Bakoru has been an activist for gender issues and in support of honorable groups, especially in the promotion of social protection. She has received a UN Award for engendering peace in Somalia and has been involved in peace initiatives in the Sudan and the Congo and has, herself, been a refugee in the Congo. Minister Bakoru is a widow, she is a mother of 40 children; ten sets of triplets and five sets of twins. That's four-zero, not 14. Four-zero. The minister is a

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public health nurse by training. She has a Master in Public Health and has been trained in psychiatry and midwifery. I see that everyone is smiling at that.

The minister is in charge of a ministry that really reflects a lot of her previous experience and training. The ministry that she's responsible for deals with advancement of women and gender, the promotion of employment and labor productivity, et cetera, and the rights of communities. I won't go into all of the details. But this is the profile of our next speaker. And today, minister will be speaking about vaginas and applicators. Expanding the national discourse on microbicides, sex and sexualities. For those colleagues who might have walked in a little late, this topic has been brought forward from the third day and is being presented this morning. Minister, please? [applause] Just a minute, please. [whispering]

**HON. ZOE BAKOKO BAKORU:** Good morning. The honorable minister of health from South Africa, the honorable minister of science and technology from South Africa, the honorable minister of health from Rwanda, and the honorable minister of health deputy; all of you that delegates, ladies and gentlemen. First of all, allow me to extend my gratitude to the government of South Africa for receiving us very warmly yesterday. And I always love to come to South Africa.

Ladies and gentlemen, this morning we are going to talk about a topic which I believe is very dear to all of us. And

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that is vaginas and applicators; expanding the national discourse on microbicides, sex and sexuality. The purpose of this discussion is going to be for all of us to reflect on the implications of the current political and public health climate of efforts to raise awareness and focus public attention on microbicides. It will also help us to further discuss the special vulnerabilities of women, focusing on gender and cultural perspectives. It will also attempt to provoke an open discussion on the need to support and fund existing and new efforts to accelerate microbicides research and development.

Microbicides are substances capable of reducing the transmission of HIV and other sexually transmitted pathogens when applied vaginally. Microbicides being in the pipeline are very difficult products to promote. The task is even made harder by the fact that they are branded to be female controlled or aimed at empowering women in sexual encounters. Which threatens the traditional gender roles and societal norms. And I think you know this very well. Within your societies, you know who is in charge of sex and how it is played and who enjoys it most, and who doesn't. {laughter}

Being a new HIV prevention technology under research and development, it is not surprising that it involves multiple state quotas and interest groups with different focus, which needs to be worked synergistically. There are difficulties in generating a public discourse about sex and sexuality which are

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required in order to discuss the most basic description of microbicides. And that is vaginas and applicators.

The background. Over 20 Million persons have dies of AIDS in Sub-Saharan Africa since the early 1980's. And most of them adults under the age of 35. that is a UN AIDS report of 2001. Three-quarters of the persons estimated with the disease worldwide are in Sub-Saharan Africa. It is a reflection of global health research priorities that the question of why HIV prevalence rates in Africa are so high compared to other parts of the world remains, to a great degree, a matter of speculation. Africa's HIV/AIDS epidemic is distinctive in that more than half of the persons living with the disease are women and girls. A higher proportion than in any other region. And this aspect of the epidemic in Africa, as much as the overall high prevalence of HIV in the population, is a grossly neglected aspect of research on the epidemiology of the disease.

HIV/AIDS and Women. Today, women and girls account for nearly have to the 37.2 Million adults living with HIV/AIDS worldwide. Over the past two years, the number of women infected with the virus has increased in every region of the globe. And if current trends continue, women and girls will soon outnumber men and boys infected with HIV/AIDS. Already 60% of adults living with HIV in Southern Africa are women. In Sub-Saharan Africa, young women aged 15 to 24 are three times more

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vulnerable to HIV than they their male peers. This increasingly disproportionate pattern of HIV infection threatens to have devastating long-term consequences. Not just to the women affected, but to their families and communities. Despite global effort to prevent and control the further spread of HIV/AIDS, the incidence, prevalence and impact of the disease have continued to grow. By the end of 2003, global estimates place the number of HIV/AIDS infected people at about 38 Million, with variations among different regions as indicated in Table One.

Regional aspects of the disease notwithstanding, there are important demographic, social, and economic aspects of the pandemic. First, the epidemic has hit the 15- to 49-year-olds the hardest in almost every region. Thus depleting the stock of human-human capital. Second, women have borne the brunt of this pandemic due to their biological susceptibility to infection and the socio-economic inequities prevalent in most Sub-Saharan Africa. Throughout the region, there has been a steady increase in the number of women infected with HIV. And by 2001, almost 13 Million women were infected. And Sub-Saharan Africa was the only part of the world where infected females outnumbered infected males.

This pandemic has left in its wake a horde of HIV infected people. On average, the effect of HIV/AIDS on the household is so large that some households just fall apart. In most cases,

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and based on the socio-economic status of a household, HIV/AIDS leads to depletion of household savings and assets as money is used in medical care for those affected.

While cases of AIDS have been reported in every nation of the world, the disease affects from countries more than others. More than 95% of all HIV infected people live in the developing world. In these areas, the disease has sapped the populations of young men and women who form the foundation of our labor force. Most die while in the peak of their productive years. Moreover, the epidemic has overwhelmed healthcare systems, increased the number of orphans, and caused life expectancy rates to plummet.

These problems have reached crisis proportions in some part of the world already burdened by war, political upheaval or unrelenting poverty. Nowhere is this better demonstrated than in Sub-Saharan Africa where the number of AIDS cases far exceeds that of all other geographic regions. Of the estimated 14,000 HIV infections that occur each day worldwide, about half of these infections occur in Sub-Saharan Africa. And about 70% of all people infected with HIV live in this region. In some countries, in the southern part of the continent, including Botswana, Lesotho, Swaziland, and Zimbabwe, more than 30% of the populations has HIV infections or AIDS. HIV/AIDS is the single biggest war that demands our attention.

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Countries in West Africa, with few exception, have far lower infection rates; less than 3% than the rest of the sub-region. The HIV prevalent rates in this sub-region are highest in Cote d'Ivoire, Burkina Faso, and in the low west in Mauritania, and Senegal.

A case for Uganda. Tuberculosis, Malaria and HIV/AIDS constitute the most critical disease burden in our country. In the last 20 years, a cumulative total of approximately 2 Million people has been infected with HIV. While about 900,000 deaths arising from AIDS have been reported. It is estimated that prevalence rates in the adult population start at 6.15%; while 100,000 people live and die with AIDS each year. The Uganda demographic Health Survey, 2001.

In spite of these grim demographic characteristics and the tragic effects of the AIDS epidemic, Uganda is currently being held as an example of a success story in reducing the prevalence of HIV from an average of about 20% in 1992 to the current reported rates of between 6.1 to 8%. There is no doubt that Uganda has made tremendous strides in sustaining effective prevention programs. And this, together with other factors, has lead to this and presented decline. We believe that this [inaudible] 6% could be due to the factor that we have not addressed the cultural and gender perspectives of HIV/AIDS.

A recent study which was conducted reflected that, among the young people in the detention institutions, there are

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young girls who are trying to learn some methods—you know, we have 56 ethnic groups in Uganda. And these 56 ethnic groups play sex differently. In my culture it is different from how it is played in the South. And so girls from my area, if they want to access boyfriends from the south, they would have to learn how it is done in the south. And we have aunties we call "Senga's" [misspelled?] who are the experts in what to call in creating arousal factors in the young girls. And so these girls have to undergo a process where they are trained by these Sengas.

The challenge is to maintain the low rates. And better still, to lower the relatively stagnant figures of new infection. It will, however, take an number of years before this prevalence declines; translating to lower numbers of people with AIDS. As the cases we now see were probably infected in the early 1990's.

Women's vulnerability to HIV/AIDS. There is a direct correlation between women's low status , the violation of their human rights and HIV transmission. The reason that AIDS has escalated into a pandemic is because inequality between women and men continues to be pervasive and persistent. It is time for the AIDS community to joins hands with The International Communities to hold governments accountable. UNIFEM Executive Directive by Noreen Hazel in June, 2001.

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And it's unbelievable to appreciate what women face behind these walls called the bedroom. A married wife—and I remember nursing a lady every year. I'm not breaking confidentiality here. And this woman used to come and delivery every year. And her husband would be the first person to bring milk and several other products to feed the baby and buy wonderful things and put her in the private ward. But the woman was never happy. And we wondered what was happening. So one day, she was able to explain to me that the man was not just being wonderful. He had never grown out of his childhood. What actually was happening was as soon it delivered, the husband would be the one sucking the milk. And therefore, if he was sucking the milk, you know what follows. And that meant every year, the woman had to come back to the labor ward and deliver. And so he wanted the baby to be fed on the milk while he would be the one sucking the milk from the wife. And then playing sex with her at the same time.

And so you see, there are so many stories I could tell you. But I think time is against us. Vulnerability to HIV/AIDS is one's inability to control her risk to the infection. The special vulnerability of women and girls in Sub-Saharan Africa overall, where women are 30% more likely to be infected with HIV than men, is well documented. Vulnerability to HIV transmission is heightened for girls and young women because the vaginal lining is less well developed and the cervix more

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vulnerable to injury and erosion. And women are denied the knowledge and tools to protect themselves from HIV/AIDS. Additionally, the legal, social and economic disadvantages faced by women and girls in most societies greatly increase their HIV vulnerability.

In certain societies and our communities, people enjoy what you call "dry sex." And this thin lining exacerbates the vulnerability in the woman getting HIV/AIDS. And the fact that you must now play dry sex is not a pleasure for the woman. But a pleasure for the man. The increased physiological risk borne by women and girls in Africa is compounded by the HIV risk they bare from insubordination, discrimination and inequality and how they [inaudible]. Ironically, trust and affection within marriage and other long-term relationships are sometimes part of the problem.

Women's sensitive approaches are key in designing prevention programs. We have been preaching a lot about the use of condoms. And we know that condom use is also decided by the man. And in many relationships, the research has also shown that when people use condoms three or four times, then they question comes, "Don't you trust me?" And the condom is thrown on the other side and to go, as they say in my country, body-to-body.

Although women are vulnerable to HIV/AIDS than men, statistics suggest that not all women are equally vulnerable to

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infection because women are also not equal. Thus, not only is women's vulnerability to HIV/AIDS rooted in sexual, social and economic inequality based on gender, but that gender inequality is farther fragmented by a combination of factors such as race, class, urban, rural location, sexual orientation, religion and culture. In the rural setting, sometimes it's even more difficult to use a condom because many of them, I don't know if we are aware, don't even have electricity. And sometimes they cannot even afford to buy kerosene to light their rooms. So, in that case, does the women have to help the man with a piece of stick or grass, light it so he can put on the condom? Those practicalities are real. Demographic portrayals of the epidemic in South Africa, for example, suggest that it's more marginalized and vulnerable groups of women that are most at risk of the infection. People living with HIV/AIDS are not only more likely to be women, they are more likely to be the poor.

African Women. Young African women and girls are increasingly at risk. However, infection rates are also particularly high among monogamous married women. Vulnerable groups also include sex workers, migrants and refugees including the internally displaced persons. I think it is becoming clear that the women in the house, the married women, are actually the ones who are at risk more than the ones who are outside [skip in audio]

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..as a strategy for prevention [skip in audio]HIV infection. Microbicides, if successfully developed, will greatly improve a woman's ability to protect their [skip in audio]. Various studies have indicated that behavioral change [skip in audio] sexual practices. And utilization of preventive [skip in audio—too many to discern anything clearly until 59:12]

Young people, too have developed their own code language that adults cannot understand. [skip in audio] information on sex and sexuality. I was introduced to you [skip in audio] and when it comes back, I cannot understand the messages. The language—I tried to talk to my girl and one time she was like, "Mommy? You know when boys want sex from you, they'll give you [skip in audio]" I said [skip in audio until 60:09]

..need to promote open but sensitive talk. [skip in audio] The political backlash against [skip in audio] for safer sex [skip in audio until 60:40] Uganda will use the ABC strategy. That is Abstinence, Be Faithful and Condomize. The President and the first lady have launched [skip in audio until 61:15] being faithful in the marriage [skip in audio until 61:33]

Working with commercial sex workers, we have a society of women in Africa living with [skip in audio]. They are women in my ministries working with these people. Sometimes I'll have

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to disguise myself and get out at night so that I can reach out to these [skip in audio]. And just after the women [skip in audio] experience where some of them were able to come out and tell their story of how they got sex work. How they came out of it, and how they believe that the girls who are on the streets are not their [skip in audio] sex work needs us to also handle it to the people who buy it. You know, when you have a commodity and there are no purchasers, it can never be bought. So you have to get to the guys [applause] who find that commodity enterprising. And they're always buying it. And tell them that I think keeping those girls on the street is not the best thing.

The common description of microbicides is women controlled and empowering, women in sexual encounters. Which threatens traditional gender roles and norms. It is true that there is no single tool or technology that can overcome the structural, cultural and the institutional disadvantages that increase women's vulnerabilities to HIV infection. However, it should be noted that such reactions should be expressed in personal interest. As we are all aware that some men believe that sex makes up for all the injustices on women. They use rape as a tool, you know, to make this woman dishonored. And we also know that there are men who think when they beat you up or when they sleep out or something like that, they come back and when they play sex with you, they make it up to you. So the

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woman must understand some of these problems and not allow the injustices to happen to them.

And some activists may be worried that the development of microbicides is eventually leading to taking power away from the men. We therefore need to answer the question on how, at national levels, discourses on microbicides can promote the rights of women to have control over their sexuality without trivializing the profound injustices that they face.

Concerns from public health and provider sectors that partially effective methods like the first generation of microbicides will undermine the level of prevention achieved by promotion of highly effective methods like condoms. However, a mathematical model study has specifically tried to address this concern by predicting what the potential impact would be if people started replacing condom use with microbicides. The modeling shows that the lower efficacy methods, like microbicides, used with greater frequency can provide more or equal protection than high efficacy methods, like condoms used less frequently. Because we know that consistent condom use is hard to achieve for people in long-term relationships such as marriage, professors propose that the overall impact of microbicides as an additional prevention method would enhance overall HIV prevention rates.

People also have to know that condoms are actually just—that they can fit. I know that in the late '80's and the

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early '90's in Uganda we received a donation of condoms from China. And our men thought they were too short. {Laughter and applause}

The need for preparation to achieve rapid introduction and scale-up of access programs once a safe and effective microbicide is developed. The national leadership is needed to demonstrate country-level demand, negotiate with donors for procurement, create systems for distribution; such as effective integration into their productive health and family planning services with HIV/AIDS services. The perception based on reality that microbicide research is generated from outside Africa and the push among African advocates for greater involvement of African governments in supporting research or it's associated processes. For example, one of the frequent concerns with all HIV prevention trials is, what happens to the people who seroconvert while enrolled in the trial? And what happens to people too sick to enroll but are not ineligible because they are already HIV positive?

While research sponsors are trying to provide an anti-retroviral therapy, treatment programs for enrolled participants who seroconvert and establish referrals for those who screen positive. Collaboration with national government is required to sustain these programs and insure that the research can be carried out in an ethical environment.

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Strategies for promoting political discourse to address obstacles in advocacy for microbicide research and development. Enlist political commitment for funding open-policy destigmatization and demystification of HIV/AIDS. A doctor may accept your collaboration and approach to form networks and partnerships among researchers, scientists, civil society and advocates; including people living with AIDS. Initiate and support effective information, education and communication programs on HIV prevention and microbicide research and development. Develop and sustain avenues for insuring access to treatment and prevention of opportunistic infections; including anti-retroviral therapies. Design and develop targeted abstinence, be faithful and condomize approaches to address specific needs of youth, married and unmarried persons. Provide structures for working with high-risk groups like commercial sex workers. I thank you for listening to me. [Applause]

**ZEDA ROSENBERG:** Minister Bakoru, thank you very much for that very interesting presentation and for truly expanding our discourse on microbicides.

[END RECORDING]

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