Good evening and welcome to the second presentation in the second annual Voices series. Each of these sessions brings to our campus an individual hero in the battle against global infectious diseases. The series is co-organized by Dr. Dan Colley who's director of the Center for Tropical and Emerging Global Diseases and me. My name is Pat Thomas and I run the Knight Health Programs at the Grady College of Journalism and Mass Communication. Dan is missing this session because he's in Kenya where he conducts research on Schistosomiasis, that's another one of those terrible diseases. So it's up to me to thank the Office of the Provost, the Center for Tropical and Emerging Global Diseases, and Grady College for making this 2007 series possible. The next two voices lectures are listed on the back of the program which I hope you picked up when you came in. And I hope you'll mark your calendars and join us on Monday March 26th and Tuesday April 24th. This is a blue card event and I saw the blue card person out there.
at the back door handing them out. After Dr. Rosenberg's talk I hope you'll all step next door to Demosthenian Hall where we'll have refreshments and conversation. And now I would like to turn things over to Dr. Chris Cuomo a professor of philosophy and the new director of the Institute for Women's Studies. Dr. Cuomo came to UGA just last fall. And one of her many interests is the interaction of Western Science and traditional cultures. And she has a lot of other interests as well. Dr. Cuomo, [Applause] Good evening everybody. Thanks so much. I was so excited when Pat invited me to be a part of this series and especially to welcome this speaker because this is just an example of such wonderful research. And that's what I want to say a little bit about before we welcome Zeda Rosenberg. Zeda Rosenberg is the founder and CEO of the International Partnership for Microbicides. And a leading researcher herself in the development of microbicides that can help women around the world protect themselves against HIV prevention. Now, the promotional materials for this lecture series emphasizes that these speakers are
Heroes.

They're heroes in the fight for global health, and heroes as kind of paradigm brilliant researchers.

And I was, as I was reading about Dr. Rosenberg's work I was thinking about this notion of a hero. What does it mean to be a researcher, a scientist who's a hero?

A hero of course is someone who does something really wonderful but through some extraordinary effort.

And in thinking about Dr. Rosenberg's work, there's the extraordinariness of the, many years of work in HIV prevention, working for the National Institute for Health, and NIAID. But also, prioritizing women's health around the world and increasing real options for real women who want to be healthy, promote their own survival as well as well being.

So, there are these extraordinary what's to create so much useful research and to be a champion for the disempowered and for folks who really need certain forms of health care. But, also the extraordinariness of how she does, and I think that's what we're going to hear about tonight.

I know that some of you, as
Lecture's sponsored by the Grady College:
I know that many of you are here because this is an amazing story.
This is the sort of story that someone would want to write about as a journalist or as a novelist.
However, we're all at the university here also dedicated to promoting research and the production of knowledge.
And that happens at the university here in so many different ways.
Well, Dr. Rosenberg's work is an example of research that is focused on the neglected and the disempowered.
But it doesn't just look at them as one big lump of mass victims, but instead looks at real women's lives, their real needs and what will work for them in preventing HIV.
There are two comments that I saw in researching the work of the partnership for microbicides that struck me as just so wonderful.
Dr. Rosenberg emphasises that women's needs for HIV prevention are like their needs for birth control.
They're varied, they take various forms in different life stages.
and so we need a multiplicity of options for women. And secondly she emphasizes that we must develop microbicides that are interesting to women, that women will use and they will feel good about using. And so, she talks about developing microbicides that might have double use as a lubricant or something that women would feel very comfortable and happy using. So, this is not just a matter of figuring out what's good for women and then making them do it, but developing technology and medical innovations that really are good for women as they live their lives. Now, this is a perfect example, I think, of feminist science, science that aims for the interest of people who are disempowered and oppressed and takes their perspectives into the research. But, it's also such a fine example of the very best of public health. And I think with all the talk, there's a new culture of public health on campus and a lot of buzz about the importance of public health care, and so, I think that in learning about her work we'll see a great model of research for all of us. One other thing that I wanted to say about Dr. Rosenberg and I'm sure that we'll hear a bit.
about this tonight too, she really breaks the mold I think, as many women like her do and many scientists these days do, breaks the mold of the great researcher as the brilliant mind working alone in the lab, the isolated genius. No doubt she is a genius and has a brilliant mind is a master of her practice. But, as you will hear tonight she's also an expert community builder, an incredible fund raiser and conductor of many different researchers and many different aspects of this work. She has, the work extends to four different countries. And think that she has over 60 employees. So, we'll learn a bit not only about the specifics of the research, but how one masters such a fabulous research program. So, thanks for your interest in coming here tonight. we're very excited to welcome Dr. Zeda Rosenberg. [Applause] [Silence] Well, good evening everybody and thank you so much of that introduction. It's embarrassing and I don't think of myself as a hero. And in fact, I think of myself as incredibly fortunate to be able to work on something
that I care so much about and that is also very useful hopefully for public health.

And I think the passion comes from that.

And I want to talk to you tonight about microbicides. It's something I've been working on for a long time. I've been an HIV scientist since the epidemic began and was working on viruses before HIV was ever discovered. We've learned a whole lot. And luckily all that work had been conducted in different species so that when HIV emerged, and it was a human condition we were able to figure things out much more quickly than if the research hadn't been done.

And I think that's a plug for basic research in general, that you never really know where the leads for basic research will take you for future diseases and that it's really critical to be able to be doing that.

And I know that there's a lot of work going on here at UGA. So, I will start. I'm not going to get this right away, so bear with me.

I don't think I probably need to give you a whole lot of background about the HIV epidemic. It is a clearly one of the greatest pandemics of all time. It really eclipses small pox.
I mean this is something that has been going on for a much shorter period of time in terms of chronologic history, but is really taking its toll so many places in the world. And what has happened in the epidemic over time is that it is becoming an increasingly female epidemic. And that is occurring for a variety of reasons, which I’ll go into in a little while. Let me get back from that one. But, in general, especially now in Africa, the vast majority of young adults that are living with HIV infection are women, nearly three quarters. And for a variety of reasons which I will explain as well, why that, there is that predominance in women. And in South Africa one in four women are infected by the age of 22 and I have some pretty horrific stories when we talk about some of the clinical trials of this. But we’re also seeing HIV infections increasing in women all through the world, not just in Africa. And in some places, especially in India, the majority of cases are in women who’ve had a single lifetime sexual partner which has been their husband. And so this whole notion of the promiscuous woman that is the one at risk.
of HIV infection has really gone by the wayside. I mean it is not. Every woman in the world is at the risk of HIV infection especially in countries where so many men have HIV infection. And in some countries, as example, in Swaziland, 56 percent of pregnant women between the ages of 26 and 29 are HIV infected, which is the highest prevalence in five years. So though, although we keep seeing statistics that are showing that many countries indeed are getting a grip on the HIV epidemic there are so many places where that is not occurring, and that the infections continue and they're continuing to concentrate in women. So, why are women at such high risk? First of all it's biology. HIV is transmitted during sex. And during sex women see more biologic fluid than do men. It's just a matter of fact, there is more semen than there are vaginal fluids. And so, all things being equal women having economic and social empowerment, women would still be at greater risk of HIV infection because there is more virus that is in the semen than there is in the vaginal fluid. So that's number one.
But young women are even higher risk and that mainly is because in many parts of the developing world young women have sex with older men and older men are more likely to be infected because they've had more years of sexual experience. And the need, or the occurrence of sex with, they call it intergenerational sex, is because women are generally very poor, older men have more money, and it is a relationship that is built on necessity for providing food for children. And so the notion that most young women are not having sex with men their own age, they're having sex with older men. And then you add in the inequality of women which leads to exploitation during war, their rape, all of these issues make women at much, much higher risk. And then there are cultural practices as well, such as very early marriages. And there's one thing about the biology of sex and women, young women is that vaginal tissue in young women is much more fragile than it is in more mature women. And I actually think I have some schematics on that which I think would be helpful. So I will continue in that vein. So, it is clear that we always used to think, you know, just get married.
Everything will be fine if you’re married and monogamous. Well, the notion has to be that the monogamy has to be both ways. And so, right now marriage and motherhood is not a protection against HIV. And a woman’s own fidelity is not a protection against HIV infection. And so many women are infected despite staying faithful to one partner. And that was certainly the case in India. There’s also data now out of Zimbabwe and South Africa where 66 percent of women who are HIV positive report having a single lifetime sex partner. And so we certainly have issues here. So there clearly is a need for microbicides or at least a women-controlled HIV prevention. I mean we have condoms. Condoms are not used for a variety of reasons. Men don’t like condoms. Women don’t like condoms. If we would like the society to continue and have new children every year you can’t use condoms as a method of HIV prevention for all people all the time because it is contraceptive and people want to have children and especially women in developing countries. There is a cultural status.
Rosenberg.txt

Issue of having children. They need children to help out in the fields and in the different kinds of work. So children are necessary. And if you can't have condoms there needs to be something else that will allow women to conceive, but be protected against HIV protection. So what's a microbicide. We define a microbicide as something that a women could use vaginally that will prevent HIV infection. And it can take a lot of different forms. It can be in a form that many of you are probably familiar with. There are over the counter contraceptives that are in the form of gels or creams. And they come in applicators. And so, that's something that most people are pretty familiar with. There're also contraceptives that come as intravaginal rings. And they can protect against pregnancy for a month. And so these are some of the kinds of delivery mechanisms that we're thinking about for microbicides. How do you deliver something that will kill HIV in the vagina and stay there when you need it during sex?
And there also could be different ways. There could be tablets that could be inserted so that you wouldn't have to have any kind of applicator. There are disposal and environmental issues with applicators. And there are suppositories and even diaphragms. But, ideally whatever is designed has to be safe above all and it has to be low cost because it has to get out there to women who need it, who really can't pay for it and user friendly. And you talked a lot about what women want. In fact we had the what women want study. We need to really figure out what will make the most sense in the context of women's lives wherever they may be. And it's not going to be one size fits all, it can't be. So we actually look at microbicides as a human rights issue for women. And so again, it's this wonderful blend of science and politics because you really want women empowered. Although the goal is HIV prevention, ideally if you can keep women alive long enough they will then be able to empower themselves. And so, that's the whole...
goal, keeping women alive
and then everything else will fall into place appropriately.
And the notion of a microbicide that could be both a contraceptive and not a contraceptive is very critical because again, women want to have children, couples want to have children. The survival of the species depends on having children. So we have to come up with some other ways of doing this. Up until about two years ago nobody knew about microbicides. Not very many people still know about it. But it was something that we were all working on that wasn’t a vaccine. In fact most of the prevention that was going on was called non vaccine prevention because everyone wanted a vaccine and we all still clearly want a vaccine. But I think everyone has come to the realization that HIV is an incredibly difficult virus. It’s a very difficult virus to develop immunity to. No one recovers from HIV. So, we don’t know what to imitate when it comes to prevention and a vaccine. And so the development of a vaccine
is going to be very, very difficult. And it has now become clear

and well accepted that we are ten, 20 years away from a vaccine. So, some of us in the mid 90s were already thinking, okay, we can't really wait for this. And even when you do have a vaccine it's going to take a long time to roll the vaccine out to get it manufactured in enough quantity, to set up the systems in place, to have vaccination campaigns. Things just don't happen like overnight. You know, hepatitis B vaccine was in this country for 15 years before it ever saw a developing country. And the whole paradigm for microbicides is slightly different. The goal is to develop these first for women in developing countries where the risk of infection is highest, and to really put all the effort into that. But, a few years ago people started thinking about microbicides because the notion of a vaccine was much harder to come by and everyone started realizing you know what this is a women's epidemic. Kofi Annan at the UN said the HIV AIDS epidemic has taken on a woman's face. So, all of a the sudden microbicides became something that people were interested in.
August at the AIDS conference there, you know, you had Bill Clinton, and Bill and Melinda Gates and we've got Barack Obama and it actually is very cool, you know. For about the last several months we've had a few kind of moments in the sun which I will also then explain to you how quickly they evaporate because drug development is incredibly difficult. No matter how you develop these products, it's difficult to get to a successful product. And, I'll explain a little bit about why that's the case. So, it's very critical for us in transparency and gaining trust in communities all over the world that we be very honest about the chances of success and how long it's going to take. Because, I think people are tired of hearing about the magic bullet, the magic cure. With HIV it is not going to be that easy. And there's going to have to be a whole panoply of approaches to HIV and AIDS if we are going to make a dent in this epidemic. It is unlikely that we will ever have a hundred percent protective vaccine the way we're used to having something for measles or mumps. What we will have is a partially effective vaccine at some point and time.
Rosenberg.txt

So, what we are going to need are a whole group of prevention strategies each one in themselves is not going to be 100 percent protective but together we’ll be able to ramp down the epidemic. And so, and treatment and cure is going to be critical. So, we can’t do one at the expense of the other. And we’ve seen recently how the world has rallied to providing treatment and care all over the world. And the Global Fund and the Clinton Foundation and people now all over the world are successfully taking antiretrovirals and adhering to them. I might add, better than most people in Europe and the US. Everyone said no. No one will be able to take them. And even the head of USAID, one of our premier development agencies, said “Well, people in Africa don’t have watches; they won’t know when to take the medication.” I mean, it was just this kind of mindset that people can’t figure out strategies to keep themselves alive. And they are doing amazing jobs in providing care and adhering
and the patients and adhering to care. And I was in a slum in Katanga in Nairobi where in one little corner there must have been about 12 women in little room huts, all who were HIV infected. And there’s a group called The AIDS Service Organization in Uganda, TASO, that is providing antiretroviral care. So, they send workers out to meet with the women. And you have GPS coordinates because there’s no street signs, there’s no nothing. I mean you have these maps and you figure out where you are going. And there is a woman there with four children. And she was sitting up and very excited to talk to us. And here daughter, who’s 12, and taking care of the three younger siblings said that they were planning three months earlier for her mother’s funeral because her mother had wasted away and was not getting out of bed. And they managed to get her antiretrovirals. And this woman was not perfect yet, but she was doing amazingly well. And they asked her the question, what and you know that many of these drugs have to be taken on a certain timeframe and...
some of them have to be taken with food, some without.

That assumes A, that you have food and that you have clean water.

And they asked the woman, we were there Wednesday and they asked her, when was the last meal she had eaten?

And she said it was Monday.

And so, the notion that we're going to have antiretrovirals working well in a population of people that we can't get into the world hunger program and get food to them is another issue.

So, treatment alone is not going to be the answer.

And in fact, in history we've never treated our way out of an epidemic.

You can only prevent your way out of an epidemic.

But treatment is critical for those who are afflicted.

You have treatment and care and then you have male and female condoms. And for those who can use them it is terrific.

And you don't want anyone to change from being able to use condoms if they can.

You want them to stay using condoms because condoms are the best form of protection.

It is a physical barrier.

And if you can use them you
Rosenberg.txt
definitely should want to use them. And you don't want people switching. In fact there's even a term now called condom migration. That you don't want them switching from a condom to another form of prevention because condoms are the best. But many people don't use them, so you need other things. And there are a number of cervical barriers that are being tested. There's a diaphragm that is being tested for HIV prevention. And then prior to exposure, we're looking at vaccines. We're looking at drugs for prevention rather than treatment. Male circumcision was just announced as being very effective for HIV prevention. 50 percent lower risk in men who are circumcised than those who are not. And that's because the target cells for HIV, many of them reside in the foreskin. And the foreskin can get easily damaged during sex. So, circumcision is protective, not 100 percent, but it is highly protective. And so many countries especially now in Africa are trying to figure out how do we roll out adult circumcision programs. And all you men are getting
very nervous but it's what has to happen, alright.

And then there's also treatment of other sexually transmitted infections because if a person has herpes and has lesions they are much more likely to develop HIV infection.

So, there are a lot of different approaches to HIV and AIDS. And microbicides would offer one approach that would be a woman initiated method to reduce HIV transmission.

So, how do you develop a drug? I mean, we want to develop a microbicide. It's not simple. And there's a whole process that has to go through in order to be approved by any regulatory body anywhere in the world. You just can't put anything out there on the market. And the basic research we've kind of already talked a little bit about why that's so critical. And then you discover the chemical that you want to use, the drug, then you need to figure out how to formulate it and do all the preclinical before you get into people assays, and then into clinical trials, which is when it's being tested, excuse me in women.

And then you have to launch...
it and have to be able to provide it to people. So, not a small task.
This is a schematic of the vagina and what it is we're trying to do.
We know that the vagina is open to the environment. It not only sees HIV, it also sees human papilloma virus.
It's only sees HIV, it also sees human papilloma virus and there was just recently a vaccine that was produced for that and cytomegalovirus, hepatitis, tons of bacteria. There's some good bacteria, lactobacilli which many of you probably have heard about. They consider in yogurt for gastric lining but lactobacilli are also very important in the vaginal tract. And they're natural producers of hydrogen peroxide and then there are lots of others there's yeast and there's tricamomious, so lots of assault in the vagina. The vaginal tissue is actually very thick. The vaginal epithelium is made for a purpose because sex by itself traumatic. And it's not just emotionally traumatic, it actually can be physically traumatic, even normal sex, where we think everything is perfect.
Rosenberg.txt

micro-<br/>
abrasions, which you don't see,<br/>
<time begin="00:26:03.40"/>you don't feel, but they can<br/>
let in HIV.<br/>
<time begin="00:26:06.95"/>So if this whole layer is<br/>
too thin HIV will get right through it.<br/>
<time begin="00:26:11.27"/>So, nothing that we put in<br/>
the vagina should do any harm to the vaginal epithelium.<br/>
<time begin="00:26:16.45"/>And then as you move up into<br/>
the cervix the<br/>
lining of the cervix is much thinner.<br/>
<time begin="00:26:21.40"/>It's literally one cell layer thick.<br/>
<time begin="00:26:23.47"/>And so HIV can easily get<br/>
through the spaces between the cells<br/>
<time begin="00:26:29.64"/>which is why young women are<br/>
actually at higher risk of HIV infection than older women<br/>
<time begin="00:26:34.90"/>because in very young women<br/>
this cervical<br/>
tissue naturally extends into the vagina.<br/>
<time begin="00:26:40.89"/>It covers more of the surface<br/>
and can be damaged during sex.<br/>
<time begin="00:26:44.93"/>So, if a girl is 13, 14, 15, 16 and having sex, she is much more likely from an exposure<br/>
<time begin="00:26:51.18"/>to get infected than<br/>
would a woman who is over 21.<br/>
<time begin="00:26:54.96"/>So what are we trying to do<br/>
with microbicides?<br/>
<time begin="00:27:00.57"/>This is an example of<br/>
HIV.<br/>
<time begin="00:27:02.52"/>This is a virus.<br/>
<time begin="00:27:03.81"/>It has lots of different structures<br/>
that you want to try to interact with.<br/>
<time begin="00:27:08.00"/>It then moves through the<br/>
vaginal tissue either<br/>
it's a cut or an abrasion or it's in the cervix<br/>
<time begin="00:27:16.24"/>and it's just making its way<br/>
through the single cell layer. And then it gets below the surface of the vagina and there are target cells that reside in the tissue, and that's where infection takes place. And then it gets below the surface of the vagina and there are target cells that reside in the tissue, and that's where infection takes place. And they are normal immune cells whose function is to go and circulate around the vagina and migrate into the tissue to test for all these other pathogens that existed way before HIV. And what HIV has done is high jack the immune system. So, the immune system comes to fight off other infections and HIV high jacks it and infects it. So, what we need to do is develop drugs that will stop the virus either from getting in or prevent it, if it does get through, from attaching to its target cell. If it does get into the target cell, there are other compounds that can be onboard the target cell and prevent it from multiplying. So, there's a whole gradation of approaches to try to figure out how we can block HIV from getting in. And the most effective microbicide would be a combination of these. Just the way HIV treatment is a cocktail, it's a number of different drugs that each work at a different part of the lifecycle. It would be the for same prevention.
We're going to ultimately need a combination of the most highly efficacious one. For the next generation of microbicides, the first generation microbicides were just acting on the virus. They were nonspecific. And in fact, the first study that was done was of the spermicide that's currently on the market called Nonoxynol-9. And Nonoxynol-9 is not a terrific spermicide, it's not a terrific contraceptive. Most people, if you really don't want to get pregnant, don't rely on a spermicide. But it's better than nothing. And everyone thought it's on the market, it's on the market in most parts of the world. Why don't we test it against HIV? And, it killed HIV. It kills sperm, it kills HIV. They thought, alright this will make a great microbicide. Let's put it in a clinical trial because it's already on the market and we'll see what happens. And what happened was that women who used the product multiple times a day, because there were many commercial sex workers who were in the trial, had such high degrees of irritation because it's a detergent.
basically, it's kind of like putting soap or washing your hands five times a day or ten times a day. It caused such irritation that the women in the Nonoxynol-9 group had an increased risk of infection. So that killed Nonoxynol-9. And an important lesson was learned, which was don't do anything to disrupt normal vaginal tissue, do no harm. So then the next generation of products that were developed and are currently in trial are those that are, we call them large sticky molecules. They're not specific against HIV, but they're large polymers that just get in the way of HIV from attaching to its target cell. So it's not likely they're going to be highly effective but they're at least going to have some kind of affect we hoped. And I said that in past tense and I'll explain that why. The next generation of microbicides which is something that I created the International Partnership for Microbicides to develop are based on what we learned in the last 15 years on how to effectively treat HIV. So, if you take the really good
antiretrovirals that we know in people with HIV rapidly reduces the amount of virus in their blood, and formulate them so that they become prophylactic rather than therapeutic. And we did this a lot in treatment. So, there are antimalarials that are used to treat malaria, that we all take when we go to Africa, so that we don't get malaria. So we take it as prophylaxis. And there are a lot of examples of that. So, what we're trying to do is take the antiretrovirals and get them from the big pharmaceutical companies and then formulate them into topical formulations. So they're antiretroviral based. We're trying to get products in each different class so we can mix and match them into great combinations. And then, we're looking at what we call non-coitally dependant application. The spermicides are meant to be used every time you have sex. So every time you have, you're going to have sex you're supposed to put this in an hour before. What we think is not, that is not going work in the lives of most women around the world. It doesn't work in the lives of most women in the US or Europe. But, you want something that women don't have to think about at the time of sex.
don't have to try to negotiate with partners in many parts of the world who don't want women to have any power in their relationship. So, you want something that they can put in, or like a ring and be active all month. And also have other benefits so that when the partners who may not want them to be using this question it, know, oh well it has this lubricating effect. Isn't sex better, hon? You know, and so those kinds of negotiations and they do occur in the bedrooms or huts all over the world. So, we have to kind of think this through. And we have lots of focus groups of many, many women all over the world to figure out what are the realities of their lives and how are we going to fit this in. There are a lot of different ways to deliver these drugs and all of them will have an impact on how often you use it, what the cost is. How easy is it to manufacture? Because again, we want these products out there in large numbers around the world. It would be nice in some cases if it was spermicidal if it had lubricating ability if it worked against other sexually transmitted diseases.
It has to feel good.
It has to taste good.
It has to smell good.
It has to be highly stable under high temperatures, which is no small feat.

Everything that we deal with, and whenever you get a prescription or something over the counter if you read the package label know between 50 degrees and 80 degrees, okay. 80 degrees, doesn't, you know, isn't the lowest temperature we're going to hit in many parts of the world. And in fact when things are shipped and they're sitting in these metal containers on tarmacs in airports, the temperature can go up to 120, 140 degrees. So we have to make sure these things are stable at high temperatures for long periods of time, because people aren't going to throw them out and get new ones.

We spend a lot of time on formulation. Again, how does it feel? Will women like it? We have a formulation laboratory in Bethlehem Pennsylvania that has the most amazing machines all of which are trying to figure out the feel, the drip; you don't want anything dripping out. It has to be something that women will use for most of their lives. And if they have to use it everyday, it's one thing if a woman has a yeast infection.
and uses something that is messy and drippy for three days. You have symptoms, you feel miserable, you use it because you're going to get better. It is very different when you have to use something for most of your life that is supposed to be during times of pleasure. And so it has to really be right. And so there are all the kinds of measuring, how far will it drip, how do you characterize it, its tackiness. Will it dry to a powdery finish? In some ways it very much like the way the cosmetic industry develops all the cosmetics that we use, and all the lotions. And in fact, the lab that we have contracted with or we've literally high jacked used to do sunscreens. And again, high end sunscreens, you know for the places when you go into the department stores and pay 30 dollars for a little bottle. They've figured out what women want. I mean they know, and the marketers have figured out that even if women don't want it, they're going to make them want it. So, we've actually met with L'Oreal, and Estee Lauder and said, when we have a microbicide we're...
coming to you for marketing because you have done a phenomenal job in getting all of us to believe that we have to use makeup or lotions in order to be presentable in the world. I imagine what you can do if there's something that would actually be life saving. You know at first they were a little pissed when I said it, but then they got over it. And so we do have to come to agreements that we will be working in partnership with the big companies who are, by the way, making their money from women all over the world. It's actually in their financial best interest to keep women alive. So, we're trying to kind of have them see it their way as well as a business model. But, to get them to figure that they really have to also give back. And when we've met with the scientists at the science level, the business development people are a whole breed in and of themselves. When you meet with the scientists they are so thrilled to be able to actually be working on something that they think is meaningful, and I mean it really helps a lot and I'll tell you a little bit about our interactions with the pharmaceutical companies where it really means a lot for moral, for the scientists to be working on something
that can help. And, investors are starting to change their tune as well. You know, they want to see a return on their investments but they also want to see some ethical work going on. So, it's working in our favor. So, another technology that we're really are looking at very carefully is the intravaginal ring, because at a certain level it seems very attractive. It would be something that women wouldn't have to negotiate on a daily basis even and it would be especially useful in areas where rape is astronomically high in many parts of the world, especially Africa. And it's relatively easy to use and it's per sex act very low cost, because it can be used for a 30 day period. And they're on the market now as birth control and also as hormone replacement during menopause. But there are a lot of challenges. Rings have never been used in Africa. So, we're doing our very first acceptability study in four countries in 200 women, just to see if anyone will like this.
whether they’ll use it.

There are some real challenges when people aren’t familiar with the technology.

gels and creams they understand but rings is a new thing.

And how do you scale up manufacturing?

Currently only about a half a million rings are made in one particular manufacturer.

We’re going to need, you know, tens and 20 million rings a year.

So how would we scale that up?

How would we put in different drugs into the ring because they have to kind of come out slowly?

And the environmental impact, these are silicon and silicon doesn’t go away.

So we’ve contracted with people to come up with biodegradable rings and also to come up with rings that will secrete drug upon contact with semen, because if it’s something that needs to work in the vagina you would really like it for a woman not to have to be exposed to a drug when she’s not having sex.

So, the ideal would be something that triggers the release of the drug.

Well, the virus comes in with the semen, so why don’t we have something that is triggered by the enzymes in semen?

So, there are a whole bunch
of people actually at the University of Utah who are working on that.

So, some of it is a little Star Wars yet, but it's this notion of, if you decide and you get the money and you apply the money to the problem there are really smart people out there who will figure it out. So, it's just a matter of defining the problem and saying it's important. So, after you figure out what your product is going to look like, what the drug is, in there, and you've done all of the animal testing, which, you know, for safety it has to occur. And I am probably one of the world's most proponents of not using animals in testing. In many cases they have to be used. And so, in this case we need to make sure that these products are not gonna cause harm in women before we put them into clinical testing, which is in different phases. Phase one, phase two, phase three which is also called efficacy. And then once you've got it on the market you have to do all of these post licensure studies, which is where we found Vioxx was a problem. You really have to continue the studies even after something is marketed. So in phase one, we're really working with very small numbers of women.
Usually these studies are done in the US or Europe, because we are very sensitive to the notion of experimenting on women, vulnerable women in resource-poor settings. If the product was made in the US or Europe, I think the ethics require that you do those studies first in the country of origin of the drug. And so, that is kind of something that the HIV prevention field has become comfortable with. It's very interesting that sometimes when I meet with my African colleagues they get upset with this. And they say why are you being so maternalistic about this? We can make decisions over what drugs can be tested here and at what stages. So, you're trying to do a nice thing. But that's not actually what you should be doing. So, many of us now have come, okay, we'll do them in parallel and so, we have usually a sight in a developing country and then in Europe or the US. And we first test these products in low numbers of women and, you know, sometimes they're sexually abstinent and we ask them to be sexually active. And safety we're looking at the damage to the vaginal lining. We look through the a
microscope<br/>
called the colposcope<br/>
which many women here may have<br/>
had colposcopic procedures.<br/>
And we look as hard as we can.<br/>
And then obviously we look for any evidence of any systemic toxicity as well as acceptability.<br/>
But, in general the women who are in these trials, they may find it acceptable or not<br/>
but they're really not the target population that we're interested in.<br/>
And so, and lessons from these trials, we learned the hard way with Nonoxynol-9 that the more something is used, the more irritating it is.<br/>
So ergo, let's try to find something that only has to be put in once a day at most or even once a month and that would be better.<br/>
And that, sometimes symptoms that a woman feels doesn't correlate with what you see.<br/>
And, you can see perfectly normal intact vaginal epithelium and the woman says it feels horrible.<br/>
And there are different processes.<br/>
There are a lot of nerve endings obviously, and you can have something that causes a burning stinging sensation that looks perfectly safe.<br/>
But it doesn't matter, it's going to have to go because women won't use
So we need something that women say feels good and actually by clinical findings looks good. And then you move into the next stage of trials and this is generally in higher risk people, and it's usually in developing countries and it's more women because you really want to get a better sense of the safety. And again you look exactly for the same things. And in this case most often we have a placebo control, so that you're randomizing women into two groups, and you're blinded everyone is blinded, the women, the investigators the sponsors so that you don't know until the end of the day when the study code is broken, who was in what group and so that you're not biased. And then come the phase three trials, which are the big studies. And they're randomized placebo controlled trials and in large, large numbers of people. Because the end point that you're looking for is HIV infection, you want to see whether or not this product prevents HIV infection. That means the study has to be done in women who would normally be at high risk of HIV infection. Otherwise, you can't do the study. Ethically, you are also required to make sure that women have access.
to every known HIV prevention strategy, because it would be unethical to not provide them with condoms, male condoms, female condoms. You treat all their sexually transmitted infections, they are counseled extensively. And in general, the risk of infection for a woman is reduced just by enrolling in a clinical trial, regardless if she gets placebo or active. Because it's women who are receiving healthcare for the first time, many of them in their lives. They're getting access to information that they didn't have before and they're being treated with a lot of respect. And they're being able to take these messages home to their partners, oftentimes, and so we often find that HIV infection goes down by a factor of two, just by being a part of a clinical trial, which is a very nice kind of benefit if the product doesn't work. And so we need to make sure that these women can be followed over time, so they can't be moving around, they can't go back from the city to the village, because if there's an adverse event that occurs, any kind of toxicity, they have to be around the clinic to be able to measure it.
otherwise you're going to miss critical events. So where these trials get set up is selected very, very carefully and the populations that get enrolled in these studies is selected very carefully. So what just happened? There was a trial that was of one of those large, sticky molecules, the polymers, that was stopped on January 31st, this year, and these are the headlines of the trial closure. It was stopped on safety concerns. And, in this case, much like the Nonoxynol-9 trial, the women in the treatment group showed a trend towards a higher risk of infection. The data haven't been finally analyzed yet, but all of these trials have what's called an independent data safety monitoring board, so a group of people not affiliated with the site, not affiliated with the sponsor of the drug, but who get access to the data and review it frequently. And when they reviewed it at this particular meeting, they found that the trend of infection was higher in the treatment group than it was in the placebo group and they stopped the study and they said this is unacceptable, which was the correct thing to do. And after the Nonoxynol-9 trials, the earlier trials, what we did was instituted as a field an early look at...
the data. It costs you, statistically, when you do that. It means you have to have larger studies because you're taking more frequent looks, but it was something that everyone thought was critical to guarantee and protect the safety and well being of women in these trials, and so it actually worked. The trial design worked. We found out that a product was ineffective and actually might cause harm. The study was stopped. That actually is, I mean, obviously we were all devastated. It wasn't IPM's product, but it doesn't matter. We were all devastated as a field, because we really wanted this thing to work. But I think that the systems that were put in place actually worked quite well to guarantee, as much as possible, the safety of the women. However, there was a lot of other media that came out, especially in South Africa, women used as AIDS guinea pigs. And this became on the billboards of all of the places in Johannesburg and Durbin where these trials were going on, and it has caused a huge backlash about microbicides in general. You know, South Africa orders...
And, in fact, they have ordered a probe, which is appropriate, but they are doing an ethical review to make sure that the women were truly informed about the risks of the study, which we've all looked at the informed consents. Every woman, before she comes into a study, has to be counseled about the risks of the trial. And the informed consent document is very long. It is read to her. It is translated in many different languages and it does say, obviously, that there could be, since we don't know, we as a field, whether there's an increased risk of infection, and this is part of the risk of being in this trial. There is an issue in South Africa. The government of South Africa requires that every woman get 150 rand per visit. That is a mandated amount of money that they get, which is actually a significant amount of money. So there could be this perception that women are coerced into the study because they are vulnerable, they may be drawn, ask any med student in this country who is poor and volunteered for all the clinical trials, they do it because they need money.
a fact and we have to figure out a way, with constant education, to say we either decide not to continue these trials at all, and then women will die of HIV infection, or we do appropriate and informed consent and appropriate ethical monitoring of these studies and try to find something that will work to prevent women from getting infected and save lives. So it's this constant controversy, which always happens, And what we do, we try to do, is first when we go into a country to say this is a place with high HIV incidence. The first people we meet with are women's groups, HIV AIDS groups, community groups and say these are the issues. Total transparency. These are the potential problems. There are ethical issues here, you need to work with us to figure out how to ethically conduct these trials. And if they are agreeable, then we go to the government and we say, okay, this is something we would like to do, and we meet with the ministries at all different levels, you know, up until the president in many places in these countries. And we get a whole commitment from the government.
that this is something that they think is needed. But it can't be what used to be and I guess it was the constant gardener that exemplified this, this parachute research of a company, a big pharma, you know, kind of parachuting into a country, testing their drug and then vanishing. Those days really should be gone. I'm sure certain places are still afflicted by this, but everything is being done with the highest degree of transparency because it requires that, because too often these trials will run into problems because that's the nature of drug development and we have to be able to continue the research in order to really find something that's going to work.

Informed consent, women are counseled extensively for family planning methods and provided family planning, should they desire. Counseling them pre and post test for HIV. Referrals for women who become pregnant. Referrals for those who when they first appear in the door to volunteer for your trial are already infected and don't know it. And this is one of the
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horrific stories I was going to tell you.

Unfortunately, in South Africa now still has the highest risk of HIV infection, which is why most of the trials are done there. They also have the greatest concentration of highly educated researchers and they have the best infrastructure of most of Africa. So you can get clinics there that will actually be able to function. There is generally uninterrupted power, so that the machines will all keep working, the refrigeration.

It's a good place to work and it has a huge burden of disease, okay but when women come into the clinic they may already be infected and in one area outside of Durban, these are young women between the ages of 18 and 30, 50 percent of them presenting to the clinic were already infected and didn't know it. So that's the level of disease burden that exists in these relatively healthy, early in their disease, relatively healthy women and so whenever I get frustrated about can we really do these trials, I say how can we not do these trials? Because if you don't do them, all of these women are going to die.
kind of say it's too hard to do. You just have to figure out a way and keep talking to people and we'll talk tomorrow about the journalism role in this, the press role, because keeping people interested and informed in an appropriate way is critical to the ability to have a scientifically literate population.

So then we treat all the sexually transmitted infections and the most important part and also treatment of anything that happens to them as a result of your drug. Clearly you are ethically obligated to do that.

But one thing that is now happening and it clearly happens in our studies is that anybody who becomes infected during the course of the trial will be provided treatment, okay, and that means that you have to figure out a way to set up some kind of trust fund and ability to provide drugs for them even after your organization may no longer exist, because women may not become eligible for treatment for five, ten years. Treatment doesn't occur right away in HIV infection, and so you have to be able to set up some kind of structure in country that will survive the sponsor. And that's not easy. And many of them are going to like the medical research counsel in South Africa, they're going to local universities and setting...
up trust funds where there are two signatories and that women will be
guaranteed funds to pay for care and that of course assumes that say the government of
South Africa still allows treatment to occur. I mean what if the government of South Africa says nope, sorry, you can take all your ARV's out again because it took a long time for them to agree that antiretrovirals were important. So what if they say no we've changed our minds, then you have made this promise to a participant that you can't keep. Because you can't get drugs to her. So these are really difficult ethical questions, and they just need to be out on the table at all times, so that people don't think we are trying to pull a fast one because this is not easy. And realistic expectations, it's going to take a while even when we think of how good HIV treatment has gone. I mean it took a long time, the first case of AIDS reported in 81 and the virus identified in 83 and we had AZT, which was incredibly fast, by 87. And that's because it has already been developed as an anticancer drug so there was a lot done, so they were able to take advantage of that. Okay and then it took you know eight years before the second drug was available.
And AZT when you look back at it, is not a great drug. I mean but it kept people alive long enough, many of them to avail themselves of the next generation. But you know I know many people who didn't make it until 95 and then three drug therapy in 97 so it kind of got quicker and Brazil offered free access to treatment there, and then the global fund was established in 2002 and much more expansion to treatment in the developing world and then drug combinations are now there to reduce the pill burden. You can take one pill with three drugs, which is great, and you know by 2006 there are 26 FDA approved drugs, but research continues as the virus develops resistance. So, but this is a continuum from you know 87 to 2006 so to expect a microbicides to be developed very quickly and to be out there and work its magic as soon as possible, is just unrealistic. It's going to take a while. But it's a while that has to happen and has to happen as soon as possible, which is why we designed the International Partnership for Microbicides. We started with Rockefeller foundation money and Rockefeller foundation came to some of us working in the field.
and said, we think that there needs to be an International organization that could raise attention about microbicides and raise funds from donors who traditionally haven't given to microbicides and at that point in time, it was Rockefeller, The Gates foundation, and the UK, Great Britain. And so we formed this not for profit in 2002 and then I spent the next year and a half as they said as a traveling sales woman on the road, raising funds, and we now in 2007 have a number, we have 11 governments and the world bank and The Gates Foundation and Rockefeller, the European Commission and we raised nearly 220 million which is a lot of money, but when you see the quotes that the pharmaceutical companies make about how much it takes to develop a drug, it's not as much as they say it is because they're accounting for a huge infrastructure you know they say 800 million, but it's a whole lot more then 200 million. It's expensive to develop drugs, the cost of these large clinical trials is about 100 million dollars in and of themselves, and that's because we actually have to build the clinics. It's not like here where we can go to the medical center in Athens or in Atlanta and say we'd like you to enroll patients,
no we actually have to build the clinics<br/>
<time begin="00:55:54.91"/>and so I actually have some<br/>
pictures of that.<br/>
<time begin="00:55:57.94"/>There are a whole bunch of<br/>
different<br/>
places where it was critical<br/>
<time begin="00:56:01.19"/>that IPM take a leadership<br/>
role in<br/>
getting more products into the pipeline.<br/>
<time begin="00:56:06.05"/>more drugs that we can have<br/>
access to,<br/>
formulation capacity, regulatory manufacturing<br/>
<time begin="00:56:12.04"/>and optimizing a whole lot<br/>
of<br/>
<time begin="00:56:14.99"/>different places so that<br/>
things can move<br/>
much more quickly through the pipeline.<br/>
<time begin="00:56:19.42"/>And so what we have done, and<br/>
it really does help to have money because you can sit<br/>
<time begin="00:56:23.83"/>down at a negotiating table<br/>
and you can say,<br/>
we've got enough money to take your drug<br/>
<time begin="00:56:27.98"/>into clinical trial so give<br/>
us your drug and we<br/>
were able to negotiate agreements with Johnson<br/>
<time begin="00:56:33.74"/>and Johnson, Merck,<br/>
Bristol-Myers Squibb and<br/>
Gilead for their antiretroviral compounds,<br/>
<time begin="00:56:39.72"/>for the developing world and<br/>
these are royalty<br/>
free licenses, so we didn't have to pay for them.<br/>
<time begin="00:56:44.47"/>They gave us these drugs, we<br/>
american free to<br/>
manufacture them as microbicides alone<br/>
<time begin="00:56:50.12"/>or in combination with any<br/>
other drug,<br/>
for distribution in the developing world<br/>
<time begin="00:56:54.62"/>and the developing list, and<br/>
we negotiated<br/>
hard over the list of developing countries,<br/>
<time begin="00:56:59.03"/>and that includes Brazil,<br/>
Thailand, India,<br/>
you know we wanted to make sure that we had,<br/>
<time begin="00:57:04.04"/>and China, had access to<br/>
countries<br/>
where we knew women were not empowered,
and that it would be really critical to have access and so we've been able to do this, and I think I have another slide that we're a non, and we insisted that it be a nonexclusive license because if there's anybody else out there who can do it faster, we want them to do it faster, our goal is not to get an IPM product out there, our goal is to get a microbicide out there. So we actually fund other developers to do their work, because anyone who can do it and should do it as fast as possible and as correctly as possible should get the money to do it. And clearly because we have the license, and we have the intellectual property, we can set the cost. And since we're non profit, it's going to be as low as possible. Obviously people in the supply chain need to make some money, we're not going to get, you know, a company in South Africa to do it for free but they can do it at very low margin, high volume, low margin, and so the whole goal will be to have these products be as low cost as possible. But one thing that was interesting and only one or, actually I think three of the companies, have done this already.
They said do you really think there, we said we didn't think truly that there would be a market in the US or Europe, or at least as a market sufficient for a big company. But if you think there is a market in the US or Europe, by all means you should manufacture it. So we agreed to a license back provision to the company, should we develop a successful microbicide and they want to market it in the US or Europe, we'll give them back a license, and they agreed to pay us royalties, so that if they actually make money they will pay us a certain percentage and they will also pay us back for our development cost which we can then put back into the pipeline, so I thought it was a state of the art agreement and one of the companies, the first one that worked with us was Johnson and Johnson Tibo [assumed] tech and we were very honest with them, we said you're the first, we don't know what we're doing, we want you to give us what was for you a commercially insensitive agreement, you know that you will never do, because you are going to help us, you are going to be really nice people. So sorry I do talk too much so, we'll move a lot faster, I'm getting the five minutes sign.
So anyway, we have a manufacturing facility where we manufacture the gels for the phase one and phase two trials, small numbers. I think we've made 300 thousand applicators of different kinds of gels so far and this is just kind of pictures of the applicator filling line. We can do gels there and then we work with the rings with Queen's University in Northern Ireland and a company called Warner Chilcott, and we're working on different kinds of structures of rings that release drug at different rates. And so we're working on many of those, and then the development of sites. I touched on, for clinical trials, it's really critical, if we're going to do these trials that we have sites that are able to carry out these studies according to what's called GCP or good clinical practices and that requires an enormous amount of training.

So what we now are working in nine countries, eight countries outside of South Africa and South Africa, and a total of 23 different sites in various stages of development from full functioning clinics to holes in the ground, literally. So this is just an example in Kenya where we're still at the site assessment stage.

Where we're working with the community groups to say is this something you really want to do and we're working in four...
different regions in Kenya with a local group called Urban Research and Development Center for Africa, so we work with local investigators, local community leaders, and the money goes to them to be able to kind of do the ground work necessary to say whether or not we need to do a trial. And in Rwanda we've been there much longer and in fact have a fully functioning clinic and this is what I call the extreme laboratory makeover. You know it had been much worse than this, this is halfway through, but we have a fully functioning lab there, it's a clinic with a lab, the offices and reception, and counseling rooms and every site has a community advisory group of people from the community that will read the studies, will read the informed consents, will let us know what we're doing right or wrong. And in Tanzania again we started with a hole in the ground and this is the end, this is the clinic, this is the big freezer being sent in, fully functioning lab. And what we did here, is we had land donated from the Kilimanjaro Christian Medical College, and they gave us some land and we said we would create a clinic that once the trial was over, it could be a wing of the hospital. And so every time we set up anything, it has to be owned by a local
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non for profit group,<br/>
<time begin="01:02:00.85"/>clear/>(either a hospital or a local NGO, non governmental<br/>
organization, so that it will become part<br/>
<time begin="01:02:06.26"/>clear/of the community, as capacity building,<br/>
<time begin="01:02:08.71"/>clear/>(Okay, obviously there is<br/>
a lot of urgency to this<br/>
<time begin="01:02:15.34"/>clear/>(and I mention how long it took for hepatitis B<br/>
vaccine to get from you know the US and Europe<br/>
<time begin="01:02:20.88"/>clear/to even China where, by the way HBV vaccine,<br/>
<time begin="01:02:23.76"/>clear/>(you know liver cancer, is one<br/>
of the leading causes of death.<br/>
<time begin="01:02:27.97"/>clear/>(That paradigm has to change,
I mean it<br/>
<time begin="01:02:33.11"/>clear/>(because people aren't use to rolling out<br/>
products first in developing countries.<br/>
<time begin="01:02:37.96"/>clear/>(There used to doing it in US and Europe<br/>
<time begin="01:02:43.02"/>clear/in the world, but the microbicide field as a<br/>
whole is committed to expediting this as quickly<br/>
<time begin="01:02:47.61"/>clear/>(as possible, and that means we<br/>
have discussions with the World Bank,<br/>
<time begin="01:02:50.98"/>clear/>(with the Global Fund, with groups that are doing<br/>
what is called advanced market commitments,<br/>
<time begin="01:02:56.31"/>clear/>(actually having governments pledge<br/>
to pay for products that don't exist,<br/>
<time begin="01:03:01.19"/>clear/>(so that they will stimulate the manufacture<br/>
and the development of these products<br/>
<time begin="01:03:05.00"/>clear/>(and guarantee a market).
Because people are too<br/>
afraid especially drug companies in vaccines<br/>
<time begin="01:03:10.45"/>clear/(to get into that race because they're<br/>
afraid that there won't be a market.<br/>
<time begin="01:03:13.94"/>clear/>(So access efforts, you know

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to be able to have these products out there for people. Start with our licensing agreements, everything we do in our license is about getting the product to as many woman as possible, manufacturing capacity, working with the community, asking women what they want, marketing research. If we were really to have done this right, before a company like L'Oreal decides there going to put out a new lotion, they don't decide they're going to put out a new lotion, they go and do all of this testing first, right? They do an incredible amount of marketing research. And it just makes good business sense, and from our prospective we just substitute the bottom line of money into lives saved. But at the end of the day, women have to be able to use the product, either they were going to make money off of it or it's going to prevent HIV infection. So we just kind of substituted different bottom lines and we're working on social and behavioral studies, what other vaginal practices, what other products will women use, vaginally that may interact with the product that we're developing. We have done these studies of successful introduction of reproductive health technologies.
in different countries, what's worked, what hasn't worked, what can we apply to microbicides. And profiling many different countries and asking people if a microbicide were available tomorrow would you get it at a pharmacy, would you want to get it at the family planning clinic, would you get it, you know, at a kiosk in town? Where would you feel comfortable accessing this? So a lot of work has to go into it. So actually I think I'm on time. With all of this, it's a huge amount of effort but it takes a lot of people working on this and people all over the world and there are many, many researchers and especially the participants who actually are the true heroes of all of this, because the women know that when they are coming into these trials that they are actually part of something historic and they, the one issue that has not plagued the microbicide field is lack of recruitment. Women are lining up to become part of this effort. And when you talk to women they have seen all of their friends and their mother, their parents, and they've seen people die of HIV. It's not something that is just kind of an abstract notion to them.
their kids, and so that's what they do, and that's what we do.

So thank you very much.

[Applause]