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**4th IAS Conference on HIV Pathogenesis, Treatment and
Prevention
Microbicides and Mucosal Immunity
International AIDS Society
and Australasian Society for HIV Medicine
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ROBERTA BLACK, PH.D.: Good afternoon. I think we'll start the session. My name is Roberta Black. I work at the National Institute of Allergy and Infectious Diseases at NIH in the United States, and I have the honor of the co-chairing this session with Bridget Haire of the Australian Federation of AIDS Organizations. This is a bridging session entitled "Microbicides and Mucosal Immunity." And I'm just incredibly honored to be the co-chair of the panel with this prestigious group of speakers who I've known for quite some time now.

So I think what we're going to do is they all have full 20-minute talks. We're going to hold the questions to the end of the session so that they can give us as much information as they have prepared. And just to give you a little bit of an overview, what we're going to do is kind of walk through microbicide development, starting with basis science and then the role of mucosal immunity in microbicides and prevention. Then learn about new products and strategies in the microbicide pipeline and then talk about clinical evaluation of microbicides. Those first three talks are really, I believe, focused on vaginal microbicides, and then finally, we'll have a talk on development of rectal microbicides.

So to begin the session, we have Dr. Robin Shattock, who is a professor in molecular infection at the Center for

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Infection, Department of Cellular and Molecular Medicine at Saint George's University of London, who will be speaking on the role of mucosal immunity and microbicides in prevention. Robin?

[APPLAUSE]

ROBIN SHATTOCK, M.D.: Good afternoon. It's a great privilege to be invited to speak at this excellent meeting. Because this is a bridging session, I'm going to do exactly that. I'm going to talk about mucosal immunity but also with reference as to how it impacts potential microbicide use. And I think this is an area really that the microbicide field but also the field of mucosal immunity is really only just starting to consider in any detail. But it may be really very relevant to the success of developing an effective microbicide that's used for prolonged periods of time, and also has potential synergy with vaccine approaches.

So what about HIV transmission across mucosal surfaces? Our understanding of the initial events of infection are rapidly becoming greater, but there's still a lot to be learned. We know that with stratified epithelium, the virus needs some strategy to go across that intact multilayer surface. And some very nice imaging work from Tom Hope funded through the [inaudible] Initiative, is starting to demonstrate that at least in the upper layers of the epithelium, virus can

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gain access to some of the Langerhans cells. Whether this is a fully productive process or not still needs to be clarified.

They may have a role in transferring virus across this type of epithelium to the underlying susceptible cells, or potentially it may require actual direct access across some sort of microtrauma in order to establish infection. And we know from a number of studies that in 60-percent of female adults having consensual intercourse, if you look carefully enough, you can see a demonstration that there are microtrauma that would potentially allow virus access to susceptible target cells.

Also what is becoming quite interesting and a new area that we're getting very interested in, is that the virus seems to have a non-specific affinity for damaged tissue areas. So if there is any tissue damage, the virus seems to stick more readily. If we think about columnar epithelium, the type of epithelium that lines either the colorectum or the endocervix, transmission may be easier because it again is only a single cellular barrier, and there may be other mechanisms involved.

Now, we're still in our infancy in terms of understanding what type of immune response would be best at blocking these types of events and how microbicides might interact with those pathways. If we think about what a microbicide needs to do or an immune response to prevent

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localized mucosal infection, it needs to act very fast. We know from animal models that an exposure models that an exposure time of 30 to 60 minutes is all that's required for infection to take place. The DC to T cell transfer which is very efficient for establishing infection can occur within a 1 to four-hour period, and localized infection is established within 16 to 72 hours. What also is quite dramatic is that the virus can be captured and taken to draining lymph nodes within a 24 to 72 hour period. Now if you think of that in context of a memory immune response, then a memory immune response would take three to five days to kick in. So in order to have mucosal protection from an adaptive immune response at a mucosal surface, we will need to design vaccines that can maintain effector cells in a way that no current vaccine can work.

So we started thinking about innate immunity and whether that would have beneficial effects in terms of transmission but also microbicide development. And our own lab worked by Maddie Hayes in my group looked at CPG triggering of mucosal tissue explants, and you can see from this experiment that we could get a two- to threefold increase in the replication rate if we treat these with TLR9 ligands. Now one of the interesting things to note is that in this experiment, it's a static system, so there's no influx of cells into the

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model. And in fact, in a real life situation, not only would you get enhancement of replication in cells already within the tissue, you would get influx of additional susceptible targets.

And this was exactly what was seen by Chris Miller in his group when they looked at CPG and [inaudible] treatment of macaques prior to SIV challenge, and so again, this enhanced viral replication and transmission. Does that mean that innate immunity is always bad in terms of prevention? Not necessarily, but one thing that now all microbicide development pathways are doing are at least screening their products to ensure that they are not inducing harmful pro-inflammatory cytokines. Now, that is always a fine line to investigate, because if you give me any product that's being developed for a microbicide, you will see if you look at enough cytokines, some modulation of the cytokine pattern. So we're starting to try and determine what level of cytokine is potentially harmful and what type of cytokine profile is harmful. So just seeing cytokines or not doesn't necessarily mean it's good to go.

But we're also interested to see if innate immunity could be triggered in a different way, to actually provide protection. The wonderful thing about innate immunity is it's quick. It can be engaged very rapidly. So we screened a wide number of different TLR ligands, and what we saw fairly early on was that if you stimulate again with CPG B and C prior to

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exposure of tissue explants, you can reduce quite dramatically the amount of infection. Now what was surprising is that if we took control oligonucleotides that have the CPG motifs reversed, you still have the same effect. And further work has shown that this is not a TLR9-driven phenomena, that in fact it is that the certain types of oligonucleotides can stimulate the epithelial cells to produce antiviral factors. And in this panel here, you can see that, in fact, if we transfer [inaudible], it's a soluble factor that is inducing resistance.

Now more recently, this work was initially started under the European Microbe Science Project, but we've picked it up under the CHAVI consortium to try and now elucidate using both proteomics and genomics, exactly what the factors are that are being released that cause innate protection to viral challenge. But you can see that we are already picking out some products that if you add before infection, block infection, but if you add after do not have any enhancing potential. So we're starting to be able to pull apart those beneficial innate signals from the potential harmful ones.

So in triggering of innate immunity as it relates to microbicides, we know that topically applied products are highly likely to modulate localized innate responses. Whether that's directly by triggering innate sensors or whether that's just by modifying either the microflora or the integrity of the

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mucosal environment. They are all likely to have some impact on innate signaling. These responses may enhance or reduce transmission, and understanding that delicate balance will be critical to success, as will understanding how that relates to either coitally dependent use, or sustained chronic use, which may provide very different pictures. But the other critical thing is because innate immunity is so intimately involved in priming and activating mucosal adaptive immune responses, if it's perturbed in the wrong way, we may actually be harming the ability to see adaptive responses to challenge when it's protected by a microbicide.

So microbicides able to stimulate innate immune responses may reduce transmission and also may have an important role in priming immune responses. So if you think about immune responses and what might be required for protection, particularly with antibodies, everybody is very much focused on neutralizing antibodies, although non-neutralizing antibodies seem to be coming back into fashion. Whether they will be important or not is still very much hotly debated. But what we still don't really understand clearly is what type of antibody, even if it's neutralizing, is best configured to give mucosal protection. Is it IgA with its role to trap viral particles in cervical mucus? Is it antibodies

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that can block transcytosis? Or is it antibodies that also have activity through different types of FC receptors?

Now initially in John Moore's group, an NIAID funded [inaudible] program, we looked at b12 and topical applications saw that at least with topical application of antibodies, you can get mucosal protection. More recently, Denis Burton has shown that with passive infusion, again the b12 will protect, but that protection is most robust if it's a full IgG molecule with its FC receptors, again demonstrating that perhaps just engagement of the neutralizing epitopes by the antibody is not sufficient to provide optimal protection.

So more recently, we've been very interested to start to try and take apart what role these different isotypes might play in mucosal protection, and again this is a study that's been initiated under the CHAVI consortium where we've taken the neutralizing monoclonal antibody 2f5 and have genetically modified different versions in an IgG, a dimeric IgA or a pentameric IgM version. You can see here on this graph looking at binding affinity, the IgM, as you would expect, binds the best, and the IgEs the least well. But if you look at their ability to neutralize virus, you see quite a different picture, that the IgG is definitely the most potent neutralizing antibody. Now, that may well have something to do with access of the larger antibodies to the neutralizing sites. But what

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is quite surprising and is really very early work in our group is that if you look at mucosal explants, it's the IgA version that really gives you enhanced protection, and not the IgG, even though in a conventional neutralization assay, it's the IgG that works the best. So really, it kind of highlights the point that antibody isotype may influence the degree of mucosal protection. Again, this is an area that really needs to be explored further.

So we're also interested in terms of both vaccines and microbicide use to start to understand whether vaginal exposure to HIV immunogens can induce an immune response. And this is the early data from a grant that we have under the Grand Challenges in Global Health funded by the Gates Foundation and the [inaudible] Trust looking at vaginal application of a trimeric clade C gp140 construct in a vaginal formulated gel which is very similar to the placebo gels we used in clinical trials. And what we could see with repeat application that we get both systemic responses and mucosal responses. And we've used that study now to transition into a clinical trial for safety and immunogenicity and also a macaque immunogenicity trial that we're just starting. And it would be interesting to see whether we can also in the context of perhaps more relevant systems, see that mucosal immunization can modulate mucosal immunity.

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We also know in terms of microbicide development that we're increasingly looking at the development of highly active molecules that interact with different steps in the viral life cycle. Now we're starting to wonder whether different approaches may have different impact on the induction of mucosal immune responses. And just to give you a few examples in a kind of whistle-stop tour, this is compound 167 again being developed under John Moore's U19 program. It's a CCR5 antagonist. You can see that there is difference if you look at infection of localized tissue between a short-term pulse with the drug and sustained use. Sustained use is obviously better, but we can get protection with just a short exposure. It's more complex if you look at this pathway of cells that migrate out of the tissue. Again, you can see sustained use is better. But we know from macaque challenge studies that with this compound, we can gain protection for up to a four-hour window.

If you look at another molecule, a gp41 fusion inhibitor, here 1249, what you can see is that the picture is slightly less promising in terms of the migratory cells, because here it's only the sustained use that gives you protection. Now, although we haven't got data for this molecule in macaque challenge studies, with a similar peptide,

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c52, we know that this does still give protection, but its window of protection is much smaller.

If you look further down the line in terms of the life cycle looking at PMPA we can see that we get very good protection of tissue and this dissemination pathway, and then looking at a range of other inhibitors that we started to explore some candidate PI inhibitors or integrase inhibitors. Again we can see that they all have a role with different potency depending on the type of drug at blocking tissue and migratory cell transmission. And what's interesting is that in this particular series, you can see that TMC120 here is clearly the most potent of those compounds. But quite interestingly also, we can see activity with Zinc finger inhibitors, which have been yet to be fully developed into the microbicide pipeline.

With TMC120 what is quite exciting is that if you pulse tissue with the drug, you can come back after washing it out and still see protection up to six days after [inaudible] drug. And that really is a testament to the long tissue retention of this class of inhibitors. I could show you a similar graph for UC781 and it probably has quite a lot to do with the fact of their very hydrophobic nature and strong tissue binding potential.

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Now, if you think about these in terms of what's known in animal models, the picture's fairly poor in that you will notice some big exceptions here already in that there is no data here for any of the current compounds in phase III clinical trials demonstrating efficacy against R5 virus. There are, however, some inhibitors now that are showing really very good promise, but again this is all with transmission events or challenge events associated very closely with the time of administration. So as a field, we're looking to try and develop the model to see if we can start to see products that give evidence based data for either daily or longer use in order to enhance the potential for compliance.

Now the thing that I'd really like to end on is the flip side of using some of these inhibitors that allow at least viral entry into target cells is that that may also allow immune responses to evolve, and this is a study led by Martin Kranich [misspelled?] but part of the rectal microbicide U19 program driven by Ian McGowan and Peter Anton. You will hear more about this study later. But what this slide demonstrates is that in animals that were protected and exposed rectally to drug, we could detect both blood and local T cell responses. This is to a single viral challenge, again suggesting that microbicides that allow safe exposure to virus may either prime

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immune responses or augment existing immune responses that may have been induced by partially protective vaccines.

So in summary, triggering of innate immunity may enhance or reduce HIV transmission. Its modulation by microbicide candidates really needs to be understood in the context of acute and sustained use. This itself may impact on priming or maintenance of adaptive mucosal immune responses. This is important for microbicides but is also a very important focus for development of mucosal vaccines and developing adjuvants that may prime in a safe way in an environment where there is potential exposure to infectious virus. That mucosal antibodies can provide protection if applied topically or through passive infusion. Whether this can be realized in a timely fashion through current vaccine strategies is an item for debate.

We also are starting to accrue data that intervaginal exposure or interrectal exposure either to infectious virus in the context of a protective microbicide or as a direct vaccine strategy may prime or maintain specific antibody or T cell responses. And so perhaps a goal may be in the longer term to develop microbicides to not only provide protection but maintain mucosal immune responses so that we can deliver both chemical protection from the microbicide but a degree of immunological protection, that may either combat breakthrough

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virus, potential resistant virus to some of these highly active molecules, or where compliance is patchy.

And where is the field currently looking to go? Well, it's moving now from really everybody developing their own inhibitors to trying to establish rational drug development strategies, product selection and rationalization. This is something that frightens many of the developers but really is essential for us as a field to move the best products into clinical trials. We also need to access more animal models to really be able to assess the strategies that provide sustained delivery, because this most likely has the best chance of demonstrating efficacy in a clinical trial where compliance of coitally dependent products is somewhat patchy.

We need to again enhance the development of potent combinations, something that we've been saying for a number of years, and perhaps explore more fully the strategies that get the best out of innate immunity. And then finally, the field will need to keep itself abreast of other prevention strategies in order to see how best it can integrate with different approaches. Thank you for your attention.

[APPLAUSE]

ROBERTA BLACK, PH.D.: Thank you, Robin. We're now going to move on to the next talk by Dr. Zeda Rosenberg, who is the CEO of the International Partnership for Microbicides, and

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she will be speaking on the topic of new products and strategies in the microbicide development pipeline.

ZEDA ROSENBERG, SC.D., PH.D.: Thanks, Bobbi.

Actually, Robin and I did not coordinate our talks, but it is a perfect segueway, because I'm going to talk about all the products in the pipeline, rationalization and combinations. So this works well.

I will begin by first of all just talking a little bit about the rationale for vaginal dosing, and one of the first things I started to put on the slide, well that's where the virus comes in, so that's where you ought to attack it. But it just seemed a little obvious. But part of the rationale for vaginal dosing includes that you can deliver very high levels of drugs vaginally, and that systemic exposure is much lower and can be lower. A lot of these drugs are absorbed systemically, but the degree to which they're absorbed is much much lower. So you can actually have a maximum drug to virus level locally in vaginal tissue, there's a lower chance for systemic related side effects, and there's of course a precedent in contraception for lots of different approaches for contraception, from oral contraceptives, injectables, vaginal rings, et cetera.

It's clear that no one prevention option will satisfy everyone. We're going to need multiple approaches that will be

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available to address women's preferences throughout the world, and as importantly for a rationale for vaginal dosing, these are women initiated, and it is clear that women are bearing the brunt of the epidemic, as we hear over and over again.

So one of the questions I get asked a lot, and I think most of us at this podium get asked is will microbicides work. And the question is it depends, and it really depends on getting the right drug at the right levels in the right place at the right time. And so there are lot of rights in here that have to be met.

First of all, right drugs and right levels. I agree with Robin that the highly potent ARVs that are acting early in the HIV life cycle stand a better chance of being effective microbicides. The right levels is you can actually get very high levels of these drugs vaginally. But the right place in the right time - the time to act is short, Robin already has said that. We need formulations that are able to keep the drugs either in the vaginal lumen or in the tissue which will depend on the drugs' mechanism of action. So all of this is drug-specific and the formulations need to be made drug-specific. And the long-acting sustained release approaches probably stand some of the best chance of working, because it will cover the right place at the right time.

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So these are some of the microbicides that are in product development, and I have a slide up here which goes by the HIV life cycle, and I think we've already said that something that works earlier in the life cycle will probably be more effective than drugs that work later in the life cycle. And part of that is because these cells, the infected cells in the vagina, will migrate away from vaginal tissue. So if you have a vaginal drug in vaginal tissue, you want that drug to be acting where it is. If the cell is going to migrate away, then the virus will replicate where the cell is not and drug will not be on board.

So I think that if we first look here at some of the products that are looking still at attacking free virus, there are several products that are still in development in phase II studies. These are some of the phase III products that will be talked about more extensively next by Lut Van Damme, buffer gel, cariguard [misspelled?], Pro 2000. Viva gel is a drug that's actually being developed here in Australia and is looking at a SV as well as HIV indication.

These are all non-specific HIV microbicides. When we start moving down, we start looking at those compounds that are specific for HIV, either monoclonal antibodies, as Robin already mentioned, there are entry inhibitors from Bristol Myers Squibb. There are CCR5 blockers that are being looked at

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by both Merck and Pfizer. There are products that contain both NNRTI activity as well as entry inhibitor activity that are being developed by a company called Inquest that has licensed these products from Samgen. There are products that are being developed again as fusion inhibitors, small molecules, by a company called Locus.

For replication inhibitors, there are NNRTIs and NRTIs and the NNRTIs are Dabo [misspelled?], dipiverine [misspelled?], which is TMC120 and UC781 as well as PC815 which is being developed by the Population Council within the Caraguard [misspelled?] base, and tenofovir gel. And the areas where we do not have products yet, which will be for future directions, include integrase inhibitors, because what you want to really do, and I know the jury is out on this, is get at the virus prior to integration, although I think there is some data, especially coming from Robin's lab and others that protease inhibitors and Zinc finger inhibitors may actually play a role as well.

But part of the microbicide development strategies that all of us have is to expand the pipeline as much as possible so that we have many different products from which to choose. And in addition to the kinds of drugs that are there, we also need multiple delivery types. There are gels, there are intravaginal rings, films, tablets and suppositories,

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diaphragms, sponges. Ideally these products need to be long acting, safe, effective, low-cost and user-friendly - high orders. And then what the ARVs allow you also is the potential for combinations of drugs to increase effectiveness.

Just one note about vaginal rings. It is quite an attractive technology. A ring would allow for 30 or more days of drug delivery. They are easy to use. They are self-inserted by women. They can be removed by women, low cost. Some of the unknowns with this technology is the acceptability in relevant populations, the feasibility of multi-drug combinations within a ring and the environmental impact of these rings, especially those that are silicone based.

So some of the early generation microbicides, and Lut Van Damme will speak a lot more about these in terms of the phase III trials, they are compounds that non-specifically block HIV from interacting with the target. They are the polyamines that recently are currently in HIV efficacy trials include Caraguard, cellulose sulfate, Pro 2000 and buffer gel and buffer gel also works by a pH lowering mechanism. Depending on the trials that have stopped or continuing, they are thought to have partial, low or no effectiveness, and they are short-acting. That means they need to be used at or near the time of sex.

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The next generation of products are being based on antivirals used to treat HIV. These are highly potent and HIV specific and they are small molecules which allow for sustained protection delivery mechanisms. So you can get them in rings and you can get them out of rings. They can be configured in gels that are once a day or used less frequently and in intervaginal rings, vaginal tablets, et cetera. They can be developed, as I already said, in single drugs and in combinations. There is currently a phase IIB trial of tenofovir gel which was begun in South Africa. It was initiated a few months ago by Caprisa [misspelled?] and Conrad, and funded by USAID.

The timeline for product development is estimated to be the following. Tenofovir gel is currently in phase IIB trials. Dipiverine or TMC120 gel and ring is currently in phase I and II safety studies and is anticipated to be in efficacy trials by the end of 2008, early 2009. UC781 gel is also being developed as a microbicide and is in early safety studies. Caraguard along with MIV150 has just started, I believe this month, a safety study. Monoclonal antibodies are being now tested for safety through Empro, and then the other products are currently in preclinical development, either alone or in combination or in different formulations. But these are two to three years away from efficacy trials.

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So the future pipeline. We clearly still need new mechanisms of action. Looking at integrase inhibitors I think would be an important next step, as well as small molecule fusion inhibitors, and there were some posters here at this conference on the development of small molecule fusion inhibitors as therapeutics. These need to also be considered as microbicides. We clearly need to add backup drugs to hedge against dropout. Drug development is risky. Drugs will come and they will show. They will show toxicity in early tests. We need to have backups in all the mechanism of action classes.

And we also need to add better options. Those products that have extensive safety shown already in their use as therapeutics will make very good microbicides because we will already have an extensive safety database on which to build. And I think that is very important. PMPA tenofovir has such a database, maraviroc is a therapeutic that will hopefully be licensed by the end of this year. So there are late-stage development of some of these marketed therapeutics that would be very important.

Now for combination microbicides, there are advantages and there are disadvantages into putting two or more of these drugs together in a single formulation. First of all, the advantages are that there could be a potential increased efficacy against resistant virus that is circulating in the

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environment. There could be coverage of multiple transmission pathways and therefore you could increase the efficacy of a microbicide over a single agent alone. And there could be potential synergy so that there would be need for less drug in the combination and potential lower cost. However, the disadvantages are the flip side of some of these. First of all, there are unclear regulatory pathways for such combination products, and it will make it more difficult, although if they are already two marketed therapeutics, that should make life a little easier. There will be difficulties in co-formulation. Some of these drugs are hydrophilic, some of these drugs are hydrophobic. You need to get them into the same formulation and being released, and that can be very complex. There could be a possible increased cost if you need to add two drugs to a formulation. There's the increased potential for toxicity. And remember these products are to be used in healthy women. And there's the issue of cross-company and institutional agreements that need to be worked out when combinations are in play.

Another part of microbicide development which I think all of us have been a little slow on the uptake is in product acceptability. And there has been a lot of work that has been done within the context of clinical trials about acceptability, but very rarely are market research studies done to see what

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kinds of products women would like to use the most. And there has been a study done of placebo gel formulations in three countries to assess women's preferences, which did support the acceptability and use of a daily product. There is currently a placebo vaginal ring going on in four sites in three countries in Africa to get some handle on women's acceptance and preference for a ring in high-risk populations. And there are studies planned for both a vaginal tablet and the film.

In terms of prioritization, if we have all of these different products and different mechanisms of action, how do we determine which products move forward, and especially into the large-scale efficacy trials? And there are a lot of different ways that we can look at criteria for moving forward, and preclinically - first of all, for mechanisms of action the notion that earlier in the life cycle is better. And that may or may not be true but you need to start somewhere. That new mechanisms of action are important, that if new products come along, the ones that you would choose would be those that could expand your coverage of the life cycle. Doing a comparison with other candidates with the same mechanism of action. And this is all *in vitro*. You can basically tell a lot in laboratory studies also looking at the toxicity and potency, ability to preformulate and the stability of the molecule. Can it be formulated for sustained release? And as important is

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the business case. Is there intellectual property access to the compound? Is there freedom to operate in developing countries where these products need to be used the most? What's the cost? What's the process for synthesizing the drug? Is it easy? Can it be done anywhere? Can you make it in developing countries? And the ease of manufacture of the product. So these are all considerations that should go into the initial selection of a candidate drug even to move through preclinical development.

Early clinical trials - these candidates are then assessed in small numbers of volunteers and then there's information that you can glean from these studies that again can help you prioritize the compounds. For example, we need to know that the drug gets in the right place at the right time. So PK studies - where the drug goes in the body, what the concentration of the drug is in tissue, what the duration of the drug is in tissue. Do you want a wide distribution in the genital tract? Does the drug get out of your formulation and distribute widely through the genital tract, since we still do not know where the point of HIV infection occurs vaginally. Is it there for a long duration, and again at a sufficient concentration? Acceptability is part of the assessment and prioritization of these formulations. And the safety, looking at the drug, the formulation and the delivery over prolonged

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use, the product safety evaluated in diverse populations, and it is really important to note here that while all of us gives us points of information, early preclinical trials cannot fully predict the risk of enhancing HIV transmission. And that is a factor that is a fact of life for most of us in the microbicide field, and we need to be able to do these trials carefully, ethically, and be able to stop them as soon as any point of harm. And that I'm sure will be discussed later.

So which candidates should then move forward into efficacy trials? What is this notion of best in class? How can you decide? And again, it is based on the information that has been gleaned preclinically and in early safety studies. And I would argue that the essential criteria need to be the potency of the compound, its safety, its pharmacokinetics, and whether or not it's in an acceptable formulation. And the secondary criteria should be focused on mechanism of action, cost, ease of manufacture and access concerns, once the product is shown to work. And I think that these products can be looked at in a blinded fashion, preclinically and there can be a lot of information gleaned as to prioritization.

So what's the critical path then to phase III? Again, some of this a little repetitious, but in product development, you want evidence that there's sufficient drug in appropriate compartments relative to the dosing regimen. You want evidence

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that the product is safe, evidence that the product is stable, and Nancy [inaudible] had mentioned this earlier today in her plenary, having an objective compliance measure would be a really good thing in order to be able to categorize these phase III's and conduct them.

In the developing world, the notion of sufficient clinical side infrastructure has been a concern. There's been a lot of work done, and many of these trials have gone off beautifully within the clinical sites. Regulatory and ethics committee approvals is part of the critical path to phase III and also has been a factor that has resulted in significant delays often, but is a crucial part of the approvals at these trials. The notion of the trial design, what the incidence rates are in these sites, whether or not there is a stopping rule that can set to look for futility early, to be able to move on to other products as quickly as possible, and clearly to secure sufficient funding for initiation of the study.

I want to end this with two slides. One is the notion of the risk of drug development, and we all know that drug development doesn't occur perfectly all the time. And it is very rare that compounds that go into phase III trials actually show efficacy. And even in the area of therapeutics, where there are surrogate markers at every step of the way, and you have a pretty good idea before entering phase III that an

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outcome should be positive, only one in five compounds actually gets to the end of the clinical development pathway. And with prevention technologies without the existence of surrogate markers, these numbers are going to be much lower. So we need many drugs in the pipeline, we need to be moving many products along, but there needs to be balanced expectations of the level of efficacy that we're going to see at the end of the day. And there's a lot of lessons that have been learned from HIV and AIDS treatment where we now have highly effective and successful therapeutics. It took a long time to get there. There was, in '87, a single agent approved for use, and it wasn't until '97 that three-drug therapy was available. So that was 10 years with good clinical trials with the existence of to be validated surrogate markers. But they were clearly working on viral load and CD4 counts. And I think that we just need to be practical and realistic that it will take a while to get an effective microbicide, but the issue of a raging epidemic in the developing work is such that there can be no other option but to continue this effort. Thank you.

[APPLAUSE]

BRIDGET HAIRE: Thank you, Zeda. Our next presenter here today is Dr. Lut Van Damme, and she's an international clinical research manager at CONRAD in Virginia in the U.S.

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And Lut's going to be speaking to us on an update on the phase III trials.

LUT VAN DAMME, M.D., M.SC., PH.D.: Thank you. Good afternoon. I would like to thank the organizers, especially John Kaldor, for inviting me to give this talk.

I will only focus on the phase III trials with microbicides, so not on safety trials. That would lead us too far. And I will also not talk about the diaphragm trial, since it's not a microbicide in itself. The diaphragm trial has been covered in many sessions and there's a late-breaker later this afternoon.

Just as reminder, the phase III trials all have a primary objective the effectiveness of the product against a male-to-female transmission of HIV. I stress effectiveness because I think today, as we hear about the problems with adherence, we can't assess efficacy. Secondary objectives in most trials is the effectiveness in preventing other STIs. I say most. There are some trials which do not have secondary objectives.

As you all know, we had some early closing trials. The first ones were with product [inaudible]. Both trials were implemented by Family Health International and sponsored by USAID. The Nigeria trial was stopped due to futility. This means that the study team had a very low chance to be able to

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detect that there will be an effect if the trial continued in the way that it was going on at the time of the interim analysis. And the Ghana trial was stopped due to a lower than expected HIV incidence. I will not be presenting results of these trials.

And then as you also know, the cellulose sulfate trials both were stopped early. The CONRAD trial which was done in multi-countries and of which I was the PI. Sponsored by USAID and the Bill and Melinda Gates Foundation, it was closed at the end of January 2007 because of a potential harm that we observed in the interim analysis. As a consequence of that, the Nigeria trial, done by FHI and also sponsored by USAID was also closed. They did not see the effect, but based on our data, they also recommended to close the study. You will have to wait for the results because they will be presented in a late breaker later this afternoon.

So completed and ongoing trial, and I call the Population Council trial completed because they saw the last participant on the 31st of March of this year. This is a trial sponsored by USAID and the Bill and Melinda Gates Foundation with a compound called Carraguard, an entry inhibitor. It's only implemented in South Africa in three sites, and they had enrolled 6203 women. Those women were between 16 and 40 years of age, so it's one of the few trials where minor women are

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enrolled. And the sexual criteria to be in the trial was that the woman had had at least one vaginal act of intercourse in the last three months. The trial had three DSMB reviews by the end of the study. The results are expected by the end of this year, [inaudible] November of this year.

An ongoing trial is the Microbicide Development Program. This is funded through the UK Department for International Development. And this trial assesses two concentrations of PRO 2000, .5-percent and 2-percent. The trial is implemented in multiple countries, South Africa, Tanzania, Uganda and Zambia. Their sample size is 9673, and they started enrollment on the 25th of October of 2005. In June they had enrolled over 5,000 women in the trial, and the team thinks they will have complete enrollment by March of 2008. also, here in some countries women can be 16 years old to be in the trial, except in South Africa and Zambia where's it's 18 years or older. The sole criteria with regard to sexual activity is that the woman is likely to be sexually active. Also this trial had had multiple IDMC reviews, with the last one on the 18th of June 2007. And the recommendation was to move on as planned, no changes.

Another ongoing trial is implemented by the Microbicide Trial Network, the MTN, funded through the National Institutes of Health. And they have four arms in their trial, it's the

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HPTN 035 protocol, so the team has PRO 2000 in a .5-percent, BufferGel, a placebo gel, and a no gel arm. It's a phase IIB trial implemented in different countries, Malawi, Zimbabwe, South Africa, Zambia, and also a site within the United States. The planned sample size is 3,100 women and the team is close to full enrollment which is already completed in some sites. The women in this trial are all 18 years or older. The sexual criteria to be in the trial is at least one vaginal intercourse in the three months prior to screening. Also, this team has had multiple IDMC meetings with the last one on the 15th of June of this year and could proceed as planned.

Then we also have further a very recently started trial is CAPRISA 004, sponsored by USAID and LIFE Lab, which is part of the South African government. This team has the first ARV in microbicide, a tenofovir 1-percent gel. It's also proof of concept or a phase IIB trial solely implemented in South Africa, with a sample size of 918 women who are all 18 years or older. Women in the trial will be either family planning attendees, attendees to STI clinics or sex workers in a ratio of 3:1, and all women in the trial are required to use contraception. Enrollment started at the end of May of this year. Twenty-six women were enrolled by the end of June, and the team hopes to be fully enrolled by September 2008. This team has a little bit of a novel way of applying the gel than

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all of the other trials I presented. First, you have to apply the gel within one hour of sexual intercourse. Here, the first application should be done within 12 hours of intercourse, second application within 12 hours after intercourse, with a maximum of two applications per day. So although greatly dependent, an easy regimen in theory to handle.

Then some planned trials by Zeda and her team, the International Partnership for Microbicides. They will be trying dapiverene, also known as TMC120, and the team is building on our experiences of the country's three trials, but they will try to really improve adherence and also the measurement of adherence. And so if they decide to go with the gel, it will be once daily use, and it may be done under directly observed treatment. If it's a ring, of course it will be another way of monitoring. Statistical designs are still in discussion. It will be a [inaudible] trials, but no formal sample size calculations have been done yet. The team does plan to have futility and safety stopping rules as they go on with the trials. And I thought they were going to start at the end of 2008, but as Zeda said, maybe it's early 2009.

This slide had been brought to me by [inaudible] from the MTN, so they planned the VOICE study. This is a five-armed trial where the team will compare the potential oral prevention treatment versus the vaginal. It will not be powered to do

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read of oral versus topical but it will be in one trial. So women will be randomized either to oral or topical vagina microbicide, and then within that arm they will, for the oral, be randomized either to Truvada, tenofovir oral or a placebo and within topical either to the tenofovir gel or the placebo gel. It's also a phase IIB and will be done in multiple sites. And Ian can give more information required. Of course, also here, drug resistance will be monitored in the women who acquire HIV during the study, especially with the oral treatments.

What are some of the common challenges and issues that we face in the phase III trials, and I also would like to draw the attention that we have [inaudible] some responses, because you often hear only the problems that we face. As was mentioned by Nancy [inaudible] this is a short summary and I've just picked up certain subjects that I would like to briefly talk about is what we hear about the lower than expected HIV incident, high pregnancy rates, a low adherence to product use, and linked to that, we don't have an objective measurement. Retention problems are challenges and staff fatigue.

HIV incidence - some trials, and I would like to stress that most of the trials did not have to change their plan when the IDMC reviewed the data. So there are only a few trials who indeed had either to be stopped or change the sample size

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because of too-low HIV incidence. And it is difficult for us to predict how high the incidence in a certain study will be when we move in with a trial, as very clearly described by Nancy this morning where we do everything we can to give the standard of care for prevention and do a very intensive preventive method.

So what can be done with incidence studies, based on the last, but there is no gold standard yet for doing that. And I think a very nice approach has been done by the NDP. It's the pilot studies in which you do a study with the same procedure because that's important to try and have a real idea about incidence, that you will do in your trial. If possible, you can already introduce a placebo gel to try and start working on adherence and counseling messages in the study population. Of course, the drawback with that is - it's costly, it's probably a costly with moving in with the real trial. So there is a little bit of a bargain. Do you move in with the real trial, and if it works, have a reapply, or do you first do a pilot study with an inactive product and then decide do you want to continue, yes or no?

And also being done by multiple groups, including CONRAD is adaptive recruitment strategies in the trial so the incidence is closely monitored, and when you notice that incidence is not as you want, where you start working with the

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behavioral and social scientists to try and identify within the community that you work women who may be at higher risk than who you are currently enrolling. And another tactic which is also now called an adaptive strategy, is where you monitor again incidence very closely within the trial, and you do closed sites, or do not start up the trial with those sites if there is an indication that the incidence is low, and so that you move into new sites where the incidence is estimated to be higher. Again, this was going to be done by CONRAD, but we had to close the study unexpectedly.

Another issue is the pregnancies. The data that I have presented in the following slides are all given by the trialists themselves. So if you see blanks, it means that people are not willing to share or the data were not available. It's not only the rate of the pregnancy that's important. What is much more important is, what is the time of product? Later in my presentation, I will show a slide from Doug Taylor in which you can see the impact on the power of a study of women who were not using product. So the pregnancy rates vary wildly amongst studies, and the time off product is less variability, between 5- and 10-percent in most studies.

So as I just said, we worry about it because except in the Population Council trial where women were discontinued when they became pregnant, all of the other trials keep the women in

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the trial but off product. And this has a huge impact on the power. Most currently, ongoing trials have [inaudible] or immediately had it in the protocol that women have to use effective contraception all have amended their protocol to make effective contraception available at the study clinics. Another issue is that maybe if we had seg III data for the product, we would be allowed to keep women on the product while being pregnant. This being said, definitely if you work with ARVs it would require a very intensive follow up of pregnant women.

Adherence - the next two slides is condom use independent of gel use, gel use independent of condom use, and then the third line in every trial, which is the most important in a way. It's dose [inaudible] in which women report not to use condom, however to use gel, and that is - although we want to assess the effect of the gel, the microbicides above and beyond condom, it is in fact the acts where the gel has the most chance to work or to show its efficacy. Condom use, gel use very high in the trials. Condoms not used and gel use varied from 45-percent up to almost 80-percent in some trials.

So we have heard a lot about adherence in the trials, and Nancy has very broadly addressed the fact that we miss an objective measurement, and I absolutely subscribe that it's very important that we try and come up with tools which will

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give us a better idea of what is going on in the trial and can we or can we not rely on self-reported data? I think - and that's thing I put here on the slide - we also have to work on the other side of the equation, and that is let us try to do whatever we can to make women and participants in the trial use the product. Even with the best tool to measure, if we cannot make participants use the product, we are still where are today.

So it is a very difficult message we have to give - like what I was showing that gel use with no condom use, in fact we kind of ask that women do an inconsistent behavior. Where they cannot be compliant with one prevention tool, the condom use, male dependent, but we do ask them to be compliant with another prevention tool, the gel use. And I forgot which speaker showed that there is a very strong correlation between both women who use condoms or with gel users. Women who do not use condoms it's more difficult to make them use the gel. So what many trials did is to really retrain and repeat training to the staff to try and explain why do we ask such [inaudible], why do we think it's so important, and of course to support participants also. But it is extremely challenging.

And here you see the slide courtesy of Doug Taylor of FHI the impact of no product use on power. You see women - this is like less than 80-percent of the acts are covered by

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the gel, the power goes down, and the power is where we can demonstrate the effect. So this is why it's so important that we get people to use the products.

Retention in the trials also varied widely between 77-percent up to 90-percent in some of the trials. How do we deal with that? And I think there is a lot of sharing of ideas of how to do it. We should not forget that the high medical care in the trials is for many women an incentive to be and stay in the trial. Not to use the products but at least to come to the visits. Every team, I think, tries to build a really good rapport with the study participants so that the participants feel at home and at ease in coming to the clinic and with dealing with the staff. Several trials do count on the need to come back for the visits every time that they are asked for. Most trials have flexible hours for the clinics, with opening hours in the evenings and on weekends so that women who have other jobs can come in without having to take vacation. Some trials not mentioned here do provide childcare at the clinic.

All the trials have intensive tracing of participants as soon as they do not come for a given visit, and often does those attempts are documented in the notes. Some trials make calls to remind people of their appointments. Most trials have the help of behavior and social scientists to work with the team on is there a rumor of or something that goes through the

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trial which has an impact on retention on which we can work. And of course in those [inaudible] there is a lot of sharing of the experience between the different sites and what works in a given setting. Most of us, in one way or another, make a provision of meals and drinks to deal with the long waiting periods.

And then the last issue I'm going to talk about is staff fatigue which has come up in the recent working group meeting by most of the trials. We should not forget these are very long-term studies which in the peak of the studies some have up to 100 or more visits a day of people coming into the clinic. Very important is also that most trials screen out a lot of women at screening because they are already HIV positive, and that brings a huge burden, and it becomes routine.

So what do the teams do? In some way or another give incentives, that can be by extra training of the staff in a specific issue, or by giving extra opportunities, for instance after the trial to be able to do some extra education. And then there is also some trials who work staff rotation so that the procedure that that particular staff is doing is not the same for years and years.

So to conclude, what do we know? Effectiveness trials are difficult, and I can subscribe to that, but we can do them.

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And every current trial has been flexible in trying to adapt protocols and procedures to deal with the challenges that we are facing and the new trials, the planned trials, share and try to make it better.

So where do we go now? As has been said many times, there will not be the magic bullet for HIV prevention, we need a range of methods, because no women in the world will all use the same product. So we need to continue the research on the coitally dependent topical products, so the vaginal/rectal microbicides, topical products which are not coitally dependent, the rings that Zeda was talking about, or another dosing regimen, and also the oral prophylaxis.

I would like to thank all of you, all the study participants, collaborators and donors.

[APPLAUSE]

BRIDGET HAIRE: Thank you, Lut, for that very interesting and informative talk. Our final speaker this afternoon is Dr. Ian McGowan. Ian's a professor of medicine at the Center for Prevention Research, David Geffen School of Medicine. And Ian is going to be talking to us today on rectal microbicides.

IAN MCGOWAN, M.D., PH.D.: Well, good afternoon, everyone. It's a pleasure to be here and to give you an update in the evolving field of rectal microbicides.

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In contrast to the very comprehensive and detailed overview provided by Zeda and Lut, which really tells you how in a way crystallized the approach to the execution of vaginal microbicide trials is, rectal microbicides are really in their infancy. And so what I'm going to do is give you an overview of the field of the science, and the way in which we're trying to move ahead in developing strategies for evaluation of these products.

So I'll touch briefly on the epidemiology of anal intercourse and why we need rectal microbicides, just highlight why this site is so particularly vulnerable, and then move onto the current state of the design of phase I safety studies for these products. And then perhaps move into slight more, if not contentious, exciting potential directions, and that is well what about developing a rectal microbicide that might be effective against HIV, just not one that is safe to use in the context of anal intercourse. And then finally just to give you an update on some of the real vigorous growth within the advocacy community and their involvement in rectal microbicide development.

So to begin with epidemiology, it's not just gay men who practice receptive anal intercourse. It's very clear that men and women, both gay and heterosexual, are doing just that. Here's a couple of epidemiological studies, and I'd ask you

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just to focus particularly on the U.S. National Survey for Family Growth. You'll see here this was a study which enrolled almost 12,500 men and women and conducted face-to-face interviews in their home, and actually used a [inaudible] assisted computer questionnaires for sexual behavior. And what we see here in this study is that this generally selected, generalizable U.S. population, 40-percent of the men had had experience in receptive anal intercourse, and 35-percent of the women. This is not an MSM only activity. Nor is it actually confined to North America. These are some data from other, admittedly much smaller, epidemiological studies, but they clearly show that women in low- to middle-income countries are actually having experience of receptive anal intercourse, and there's more literature indeed being presented at this conference which tells us that women in the developing world need protection too.

So why is it that the rectal mucosa is so vulnerable? Well, here's a couple of pictures that illustrate it. You can see that the - well, it's self-evident - the colorectum is a large organ. It's a large surface area, and it's primarily vulnerable to infection because it's actually, as you can see, highly vascularized and a very delicate mucosa. You can actually see the blood vessels just glistening here. But when we look under the microscope you really see the problem at

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hand, and that is that what we have is a columnar epithelium which is only one cell thick. So this if you like is the virus, and this is the sub-epithelial [inaudible], and this is where the virological synapses that Robin told you about earlier are going to happen.

Because of this anatomical histopathological situation, unprotected receptive anal intercourse is by far and away the highest risk factor for HIV transmission. This is a variant of Robin's slide, just to show that we have two areas to worry about in the context of rectal microbicides, the columnar epithelium I've just shown you, but also I'm going to show you some data which suggests that the anal canal, which is analogous to the cervix, it's a stratified squamous epithelium, is another area of concern. Many physicians have a very shaky knowledge of where the rectum ends and the anus begins. It's quite astonishing when you go to meetings. But that's the anus and that's the rectum, and when you do high-resolution endoscopy, you actually see this region, which is the anorectal junction. This is a [inaudible] line which separates the white anal epithelium from the rectal epithelium. So this is columnar, this is squamous.

So my colleague, Wes Cranston at UCLA, has been doing some work on looking at this as an additional target to worry about, and here is some data from patients with chronic

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infection, who we stratified by the viral load. But if you look at those with quite high viral load, and green is anal viral load, red is rectal viral load. What you're seeing is that in patients with chronic disease, there's plenty of virus in the mucosa.

Well, okay, that's chronic infection, but is the anal canal really a potential portal? Well, here's some data where we took biopsies from both sites. And on the left we have rectal tissue, we gated on CD4, and we looked at the HIV co-receptors, and as reported in many of our publications and others, there's plenty of target cells. But if you look on the right, this is anal epithelium, you can see almost an identical picture. A little lower, but nevertheless plenty of cells which are actually supporting or capable in theory of supporting infection.

And the last thing to add to this, then, is if we used a colorectal explant challenge system, which Robin has used and we've used. On the left over here we have an R5 virus, and here an X4 virus, anal rectal tissue - what you're seeing is that both tissues will actually support viable replicating infection. So I think in the context of developing rectal microbicides, because I suspect the formulations required to protect the rectal mucosa may be quite different than the anal

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mucosa, I think we have to take on board this as another target area.

So then moving to the process of drug development, it usually begins at preclinical studies. This is a slide just showing some of the modalities that are in use in the context of rectal microbicide evaluation. We have Murine models, non-human primates, explants and human studies. And I've lined up some of the candidates you already heard about earlier in the symposium. I just wanted to focus your attention on two really - let's look at N-9. And it's very clear that there's been a comprehensive assessment in the literature. It's clear that N-9 is cytotoxic and not probably very safe in all of those models. If we look in contrast at the bottom at something like the NNRTI UC781, you can see fairly comprehensive assessment and no signals and in fact a phase I human study's just begun. But in the middle, what you see is some rather patchy landscape, where we either don't know because those studies haven't been done, then maybe some very mild signal, plus or minus, or in some cases it's negative. But it's clear we haven't got all the data we need.

This is just another approach to the situation. This is some data from David Phillips' group, and here they're looking at the HSV enhancement model, some cytotoxicity assays and rectal sloughing. And you can see that the top of the list

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N-9, lighting up, there are other candidates with varying degrees of capacity to induce injurious effects on the mucosa, and also some appear quite safe.

This is just one picture that says it all. This is from David's other paper in which they put N-9 into human volunteers, and what it's really telling you is that you get a very early mucosal lesion up here, 15 minutes you see destruction of all the goblet cells in the epithelium, but by 8 hours you've got reconstitution. The implication of that is you need to look very quickly for a safety signal.

A variant of this approach is some work pioneered by Craig Hendricks and Ed Fuchs at Johns Hopkins. They were interested in looking at the effects of common, let's just say, fluids that will end up in the rectal cavity. On the one hand, if you're douching with tap water, that has a very low osmolar challenge. Whereas if you use this over-the-counter sexual lubricant, you incur an extremely high osmolality. Well, why are we concerned about that? Well, we're concerned because if you put an iso-osmolar product rectally, you can see the mucosa is preserved. On the right you can actually see that the epithelium is sheared off, it's no longer there. So probably putting a high-powered osmolar and actually possibly [inaudible] osmolar products not a good idea. And the organization I'll mention later in my talk, the International

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Rectal Microbicide Group have actually put out a survey on the web. I encourage you to fill it out if you haven't, because it's actually asking consumers within the broad community what are they using and how are they using it? And to date I think they've accumulated about 6,000 questionnaires, which is really quite a body of information to process.

Okay, let's move to phase I rectal safety. As a prelude to this, I and other colleagues at UCLA conducted a study where we have 16 volunteers who underwent three sequential flexible sigmoidoscopies to try and define the landscape. What is the normal colorectum in the resting state before you put any products in which might cause damage? And this is coming out in Jades later in the year, but essentially we discovered that you could certainly do these types of studies. We showed that some markers of tissue damage are very stable, cytokine mRNA. But other things, like meticulously counting cells in the mucosa, is actually not very reliable.

Very modest differences between the two sites we sampled, and that's important because it means we can probably scale down the magnitude of the studies we do and just sample one site.

Here we have a summary of really what's been done to date, and you can see most of it refers to N-9, some Carraguard. And this was an important study here from David

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Phillips, because they actually looked very quickly after the N-9 was administered and were able to show the lesion. In studies which looked at a later time point, they couldn't see that the drug was actually noxious.

Now out in UCLA, my colleague Peter Anton is the PI in an NIH funded study we're doing. This is really the first phase I IND regulatory type safety study for a microbicide in the rectum. The primary objective is to look at safety and acceptability, and other endpoints are obviously the frequency of grade 2 adverse events and acceptability. These are generic things you measure in safety studies. We're looking at two doses of UC781 and placebo and the general design is to have a single dose and then seven days of repeated dosing.

This, to me as a mucosal immunologist, is a more interesting slide, because these are our secondary objectives. And what we're looking at in all of these endpoints is really whether or not the drug actually is associated with induction of mucosal damage. And so we've cast the net deliberately quite broadly. We're looking at things such as epithelial sloughing, which has been done in macaque studies by Dorothy Patton. We're also looking at histopathology, but as you can see, we're looking at various other things. And I would point to fecal calprotectin, which is a neutrophil release product in inflammatory conditions that is indicative. But also,

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excitingly, we're using this study to actually get a first read on efficacy. So individuals who come in will actually have tissue explants collected post-exposure to the drug which we'll then try to infect in the test tube. And we'll do it after the single-dose administration, but also after the week of daily dosing.

So as has been alluded to before, it is difficult in microbicide development to get a level of confidence and that the drug might work in this situation. But using this modality, I think we can at least add more data to the decision-making algorithm of the type Zeda alluded to.

So this is what it looks like for the patients. They screen, they come in, we always do a baseline endoscopy. They're then randomized to whatever drug they're going to get rectally. They have a single dose in the clinic, and then they have the first post-dose endoscopy within 15 to 30 minutes of all the other investigations, and then after a recovery period, they self dose at home over seven days and have a third endoscopy.

And the great news is whereas a couple of years ago there was a relative wilderness of this type of study, other studies are beginning to line up. We have our study, of course, at UCLA. There's another study I can't really tell you about except that it is probably going to happen later this

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year, [inaudible]. And the United Kingdom MRC are actually going to conduct a phase I rectal safety study of PRO 2000, the drug they're evaluating in their phase III study. And we're working in UCLA to actually develop a rectal specific formulation. I haven't perhaps emphasized is what we're doing until this point in my presentation is really trying to tell whether or not vaginal microbicides, if they're used rectally, which we all think will happen the day after they're licensed for the vagina, are actually safe or not. But downstream, we may want to actually develop a formulation which is specifically optimized for use in the rectum.

So that brings me to our next slide. Okay, well, why? Well, the answer, why is there a need? I've already shown you some epidemiological data saying this is not just MSMs, this is also heterosexuals too. But at the end of the day, within North America, Latin American, Western Europe, the MSM population is if not the most affected is very on par with other groups. In addition, there's mechanism here that to use these products, 88-percent of MSMs use lubricants for rectal intercourse, so this is an obvious approach that has applicability to their sexual lifestyle. A bit more worryingly, 26-percent are still using N-9 products.

Okay, this is our scientific rationale. If people are skeptical about vaginal microbicides, they usually collapse in

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a heap when you suggest you're trying to do a rectal effectiveness study. Well, here's some monkey data from a study that Robin mentioned earlier. Martin Kranich has been organizing this in London as part of our collaborative grant. Essentially it's sort of a conventional macaque model where we give the animals drug varying time points, 15 minutes prior to virus challenge or placebo or afterwards. And then we look to see whether the animals get infected. And I'm summarizing a lot of elegant data, but this is essentially telling you about the animals who got the drug and then were challenged, and we look for virus in a number of different ways, but you can see there's a lot of blanks and very few plusses. Which tells us we actually did indeed see a very significant level of protection in the rectal macaque challenge model.

This is just showing you the data in a different way, but just focus here - this is what happens when we give the product 15 minutes before a traumatic installation of the virus into the rectum, and you can see of all these animals, one looked similar to the no treatment, and the other looks a little odd, but these four animals were completely protected.

So I think we have a scientific rationale, so let's get on with it. Well what do we need to do? Well, again, Craig has led the field in terms of the imaging studies that are pertinent, but we really need to find where we need to protect,

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how we're going to measure this protection, how we get drug in the right place at the right time. This is from a presentation Craig gave last year, but it's just showing you some of the modalities he's working with where he's using radiolabeled semen surrogates and microbicide surrogates and creating these three dimensional plots of distance from the anorectum over time and drug concentration. But he's now gone further, and in addition to these imaging studies, and this is an imaging study showing you where the semen simulant goes to, he's also able now to endoscopically take brushings from the colon and show you concentrations of drug, which is a critical component in the modeling of how much drug we need and in the right place at the right time.

At the same time, the study we're doing in Los Angeles, we're using a vaginal applicator. And guess what? Most of the men and women, well certainly the men, aren't too keen about putting the vaginal applicator into the anus. It's not designed for that. So Alex Carballo-Diequez has been assembling a pretty scary collection of applicators. I just highlight some here. This is actually the vaginal applicator, which you can see is probably not much fun. I think these are particularly scary, and well I don't know. But anyway, he assures me in collaboration with an AMFAR grant, he's going to

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come up with something that will be very acceptable to the target audience.

So moving then towards the end of my talk, advocacy. I think this is an area that's been quite astonishing. Many of us have been working in the field of HIV gut stuff for a while and rectal microbicides have been about in theory for three or four years. But the huge body of advocacy has grown over this timeframe. And the International Rectal Microbicide working group, and we have Bridget Haire here, the vice chair of the steering committee, was founded in 2005, and I'm sure this is out of date, but we have about 360 advocates in 35 countries. That's a huge level of interest, and I recommend you visit the website and take a look at this investment in advocacy document, which really defines the field, says what might be needed to move towards an effective microbicide.

So to conclude in the last few minutes, I think we've now reached a point where most of the vaginal microbicide developers have accepted that really every vaginal microbicide development portfolio should include one phase I study, just to check that the product isn't going to be dangerous in the rectal compartment. And as a consequence, these studies have begun and they're going to increase in number. The design methodology for the UC781 is deliberately complex and comprehensive, but we need to have a step-down approach, and

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that's going to happen. And I think rectal microbicide advocacy is increasing, and it's going to include demands for rectal safety and effectiveness studies. At the end of the day, this isn't a gay issue. I think this is just an issue for adults who practice receptive anal intercourse and are in need of protection for the colorectum. This is just a rather beautiful 16th century sculpture from Florence, and you see both male and female posteriors. So that's just to remind you we need to look after both groups.

So finally, I just want thank some people. This has been a difficult field to get moving for all sorts of reasons, and I think I have to acknowledge that the NIH Division of AIDS and DMID have been incredibly supportive in funding many of us in this room and without their support, this field wouldn't be happening. Similarly, AMFAR has been very prominent in helping with initial funding and pilot funding for a lot of studies in this area. And then there are other colleagues we collaborate with to get access to the drugs we need to do these studies. So I'll finish there, and thank you very much for your time.

[APPLAUSE]

BRIDGET HAIRE: Thanks very much, Ian, and thank you for that marvelous plug for the work of the International Rectal Microbicides working group and for reminding us that everybody has a bottom.

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We're now open to take questions from the audience, please. So do make your way to the microphones. I'll ask you please to all introduce yourselves, and try to keep your questions brief if you can. Number two, down here, please.

MARK WAYNEBURG [misspelled?]: Mark Wayneburg from McGill University in Montreal. Excellent symposium and thanks to all of you. My question is for Lut, who spoke about pregnancy-related issues, and I'm wondering in the context of all the microbicide trials that have been carried out thus far that presumably must include by now some women becoming pregnant while taking certain microbicide products, whether we know anything at all about how well the offspring have done in the context of a woman who used a microbicide product while conceiving.

LUT VAN DAMME, M.D., M.SC., PH.D.: Yeah, as I showed, many women do become pregnant in the trials. I think every trial collects pregnancy outcomes, at least in the cellulose sulfate trial, and I'm almost sure we all do. So whatever the end of the pregnancy is, we collect it, also if it's miscarriage or abortion or full-term pregnancy. I don't think any of the trials have yet analyzed that.

Off the top of my head, I would say that cellulose sulfate we did not see any problem in that regard, but again, I don't think that anybody has really fully analyzed the data but

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they will be available in the future. We are all collecting that.

STAN VERMONT [misspelled?]: Stan Vermont from Vanderbilt University. One of the things that I had hoped to learn from the symposium is a little more on the background on the controversy around CAPRISA 004, and I don't know if Robin or Zeda might comment on some of the concerns and if Lut or Ian might comment on why those concerns perhaps shouldn't hold back the trial. I know there's diversity of opinion on the panel and if you could illuminate those of us in the field as to the origin of that controversy and where it might be going.

ROBIN SHATTOCK, M.D.: So to come back on that question, I think that this current session is not the right forum to debate that, because we haven't got presentation of the data, so it's hard to have an informed discussion. But I'm sure any of the speakers would be happy to talk about it afterwards. And the other point to make out is that there is a meeting happening next week with the principal investigators to at least discuss the scientific background of the trial.

WARD CASE [misspelled?]: Ward Case from FHI. I have probably gone to 100 overview lectures on microbicides and I am so glad that this is on the Kaiser listserv, because this was absolutely the best. All four presentations were like they were choreographed in the New York Ballet, there were wonderful

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slides, and I'm actually going to go back and watch it again, which I never do. And so, congratulations.

My question is for Z, and you know, when you were talking about acceptability and then looking at some of the trials that might be going on to look at some of the products for microbicides, a lot of those trials have been done for contraceptive products, again with N-9 for pregnancy prevention, but in the '80s and '90s. And the question is, how relevant - and I don't know myself on this - how relevant would the acceptability of the film or the gel or the tablet or the ring or the whatever to prevent pregnancy would that be for preventing HIV?

ZEDA ROSENBERG, SC.D., PH.D.: I think they're actually very relevant. The problem that we've come up with, especially for the intervaginal ring, is that some of that data exists from many many years ago, you know, from maybe 20, 30 years ago, and we can't get access to it. We've tried. I'm also not sure - it would be important to see it, but I would also like to get more current data on acceptability as well. The ring is currently marketed in the U.S. and Europe and there's a lot of acceptability data from those populations and we do have access to all of that from the companies that make Femring and Nuva Ring. And I think for contraception, some of the questions are different, and so I think we need to look at acceptability and

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market research within the context of high-risk populations in developing countries, at least for the products that we're trying to develop.

BRIDGET HAIRE: Microphone three.

AP SIEGEL [misspelled?]: I'm Ap Siegel from South Africa and Australia. I think it's fantastic to have the option of microbicides, particularly in the context of empowering women. I do have concerns, though, and I'd like the panel to comment on this. What do you think the impact will be on resistance and I guess limiting women's future options if they were to contract HIV if they are using antiretroviral containing microbicides? And the second question or comment is would be encouraging women to use microbicides that reflect the viruses that they partners may or may not be infected with? So if their partner had a tenofovir-resistant virus, and they were continuing to use a tenofovir-based microbicide, they would really be using that sort of under false pretenses or have a false sense of security.

ZEDA ROSENBERG, SC.D., PH.D.: I think the issue of resistance is something that we're paying a lot of attention to. I think that we don't have the answers currently. The answers about the emergence of resistance with the use of vaginal microbicides will really only be answered within the context of phase III trials when women are using the product

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and become infected with HIV, who may be not using the product and get infected and then using it later on to see if there is any issue. So all women enrolled in those studies will be followed very carefully, especially the women who become infected, will be followed in seroconverter protocols. Their virus will be genotyped and phenotyped, and I think ethically all women should get access to whatever appropriate therapy is relevant for their virus. Because I think we need to be able to look at these phase III trials, conduct them with very high ethical standards and then answer the question - what is the relative efficacy of these products and what is the issue, if any, of emergence of resistance in women who continue to use the product once they're infected? I think because such high concentrations of drugs can be available locally, it may actually overcome a lot of the issues of efficacy against incoming virus. Resistance is not an all-or-none phenomena, it just makes a virus less sensitive to drug. And in therapy there are limits to how much drug you can give systemically. But in the vaginal tract, it might be possible to put in enough drug to overcome resistance.

BRIDGET HAIRE: Microphone 2.

NANCY PEDIAN: I have a question. I'm Nancy Pedian from UCSF. I have a question for Doug Taylor, who's not on the panel. But this is the statistician that Lut showed that very

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nice with adherence in power and I just wondered if he might think about adding into that the erosion of power due to condom use. Because for example when you showed on the slide before, there was the percentage of people who used products without condom, you know it might be 48-percent. But when only a small percentage of the people aren't using condoms, you can see that it actually ends up being a small number. And so I think that again unless we have products that really have a strong measure of effect that to see the measure of effect over and above condom use is just yet another challenge and a challenge power.

LUT VAN DAMME, M.D., M.SC., PH.D.: I think none of us can really speak on behalf of Doug since he's so good and I don't think any of us is a statistician. Working very closely with him, yes, Nancy - you cannot imagine one thing that he doesn't think of with trying to help you through the design, not always making life easier, but at least trying to improve the quality of the trials. Part of the condom use, of course, we tried to deal with that and assuming the sample size and HIV incidence that we assume in our estimations, but it's a very challenging point and it's very well taken.

BRIDGET HAIRE: We are now out of time, but we could probably use a bit of buffer time to get that question from number two.

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MARK VOIGHT [misspelled?]: Okay I'll try and make it quick. Mark Voight, Australia. Zeda, you put up a good slide, I felt, about the essential and sort of important criteria about which you would take products through to phase II trials, and what I didn't see, and what perhaps is more controversial is who actually decides whether those criteria have been met? And by way of just a very quick background to the question - as part of the CAPRISA 004 controversy, I think that some people have said that maybe given all these products that are coming through the pipeline, maybe there needs to be a better coordinated body of people that can actually decide which of these products really deserves to go through to phase III, particularly on the background of the very high-profile failures.

ZEDA ROSENBERG, SC.D., PH.D.: It's an excellent question, and there are a lot of conversations going on amongst the developers in the field, and most importantly, the donors, because to some degree, we can't do these trials without funding and the donors have a great responsibility here in ensuring that the best products move forward and that we're all working strategically together. Because the goal is to get a microbicide that is safe and effective out there soon.

[END RECORDING]

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