

Microbicides 2006: Plenary Sessions April 25, 2006

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ANATOLI KAMALI: I'm going to introduce our first speaker this morning, Mike Chirenje, who is an associate professor of obstetrics and gynecology at the University of Zimbabwe College of Earth Science, Harare, Zimbabwe. Mike is a gynecological oncologist whose special interest in cervical cancer screening and treatments and strategies in [inaudible] settings. He was the PI of one of the largest cancer screenings by Vision [inaudible] with ascetic acid, and that is now a program available in most resource [inaudible]. Interesting HIV research has forecasted on evaluating several [inaudible] HIV prevention trials including microbicides clinical trials. He is the investigator in the ongoing HPTN-035 which we heard yesterday. Dr. Chirenje is the co-founder and [inaudible] director of [inaudible] University of California [inaudible] Research Program.

He is going to talk to us this morning on an important topic, assessing microbicide safety.

DR. ZVAVAHERA MIKE CHIRENJE: Thank you for those kind words. And good morning, everybody. As my colleague has just said, I'm going to focus my talk on [inaudible] assessment for microbicide clinical research. And as a clinician you have to bear with me that my talk is more bias for clinical assessments. But before I do so, just as a background to the talk, maybe I should recognize that I think

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this was covered quite well yesterday. On a daily basis, you had an estimate 15,000 infections and the appalling rates are recognized in Sub-Saharan Africa. And for Zimbabwe, where I come from almost 65-percent of the new infections are among women between 15 and 45. And what's more worrying in this trend is that the younger women below 25, 26 are perhaps the highest target in our thought process. We really need to target our research interventions to those young groups.

So I've also listed the prerequisites for a good microbicide is [inaudible], effective, affordable and acceptable. So the first bullet of [inaudible] is what I'm covering in my talk. And just as a background, the main objective for [inaudible] microbicide clinical trials is really to identify compounds that may induce epithelial toxicity. And epithelial for the general talk is really the skin lining. And I'll just show you in upcoming pictures, skin lining of the genital track. Most of my talk is focused on vagina microbicides. So we are trying to identify compounds which may damage the lining and cause epithelial disruption and potentially this damage may actually invite portals of entry for HIV and other sexually transmitted infections.

The picture here from [inaudible] are greatly let's stress that because on my talk - this is the skin of the vagina wall I'm talking about. This is an annotated picture.

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The vagina is actually very thick. It has got several layers of what we call squamous epithelium. They start from the bottom here. This is called the germinal layer. And you go up. They actually mature. As you can see the bottom picture is very different from the top picture. And inside this very nice annotation, you've got viruses which are lying up here. So this would be the canal of the vagina, and this is now the wall of the vagina. And what you are avoiding is to create entry portals where cells like this called Langerhan cells will bind to the virus and then enter - the vessels are down here, the lymphatics are down here.

But if you note on this other side, the more worrisome is that the vagina wall itself is thick and robust. The entry of the uterus called [inaudible] is only one layer. So the cells which bind HIV are quite close onto the cervix compared to the vagina wall. And I may have to give reference to this very nice picture in my talk.

So now in terms of cervical assessment, [inaudible] microbicide must there have [inaudible] properties. And one of the most important properties is preservation of the natural anatomy of the female genital tract. And this is biological. Women are born with it. And this intact epithelium surface must be maintained from external genitalia, intraosseous, that's the entry of the vagina, the vagina wall itself, and the cervix. And in here I have a

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small little picture. This is a cervix. I hope you can see. One of the things I really want to demonstrate is this particular cervix has got a thick mucous in it. And this is a natural barrier. This is the cervix. This is the entry of the womb. This is where babies are born through. And the reason why it's called the birth canal, you can see, this woman has got thick vaginal walls which are quite robust, similar to the picture I showed you before. And all we're saying in terms of clinical assessment, we really want to make sure that our participants are coming to clinical cervix demonstrating an intact cervix [inaudible] and an intact vagina wall.

And as you can see, the complexity of the vagina - Sharon Hillier gave the talk yesterday and keeps on saying each time we have a talk together, our men do not understand the vagina. I frankly underscore that. The vagina is very complex. It's got a huge surface area. In this picture here we took about two weeks ago at the colposcopy clinic, you can see this the trunk of the cervix. This is the trunk here. And this is the lateral wall of the vagina down here. So the complexity is that it's almost like a tube; and when you're examining, you have to make sure that you orient your pictures through that tube.

And now the second level property that has been covered by a lot of speakers in this conference is something

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that has come through scientific development. This is evidence based, is the fact that if a microbicide we're assessing causes inflammatory response, the short of is that it will produce these things called cytokines; and these are essentially going to accelerate acquisition of HIV. This is the scientific evidence which came through that the [inaudible] care firstly accelerate a replication of HIV. This is another picture again to demonstrate the same effect. This is a picture again showing the vagina wall and the cervix, which I showed you before. And the important thing about the cervix is that the current scientific tells us that there are target cells on the cervix than on the vagina wall, which is fairly quite robust. It has to have tears in it for the virus to penetrate.

And then the other important thing as you can see in my talk, I will talk about the positive attributes of how the genital track inhibits acquisition of virus, compared to the detrimental effect which may occur when that environment changes. So the vagina itself maintains acidic environment, pH less than 4.5, which effectively controls survival of HIV and STD pathogens. This acidic environment may not be toxic. As you know, this 4.5 you compare with gastric mucosa where you have cells called parietal cells. The gastric mucosa will produce a pH of 1, very acidic. And the vagina itself then maintains a 4.5 pH, again, naturally very protective. But

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what is the problem? The problem is that we are also testing these microbicides and what we need to be sure is that they are maintaining the balance of [inaudible] species, which produce the lactic acid to making the HIV virus die in the vagina compartment.

In several cross-sectional studies, including the one by Agnes [inaudible] from Zimbabwe showed however that intra-vagina practices we do in Northern and Sub-Saharan Africa, women douche and much their detriment they'll destroy their [inaudible] and this is postulated to result in [inaudible] HIV. So [inaudible] microbicides during clinical trials requires us to come up with effective methods that will identify the important signals arising from exposure [inaudible] to study participants. We really wish to identify this early, as covered earlier. Those of you who were in the session yesterday, there were three studies. It does take a considerable amount of time for a product to move from pre-clinical testing into clinical science. So I thought for a few minutes I should talk about the pathway for microbicide testing.

Initially, the first level is in vitro testing where potential compound is demonstrated to have an effect on HIV isolates and other STD's. And the next level is what is the pre-clinical phase, what is commonly called the rapid vagina irritation model. And this is a copycat from the 1960's

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where they were looking [inaudible] formulations. And the problem with it that has been recognized with scientific work is that the endpoint that is looked at in this model is looking a cervical vagina epithelial toxicity; and when that is passed however, we then move on to Phase I clinical trials. But as we know, I think the South Africa Minister of Health yesterday spoke [inaudible]. So within the next few slides I'll show you that there is some evidence to suggest that the classical rapid vagina model is perhaps insufficient for [inaudible] exposure of cervical vagina compartment. And that we do know now. And this already has been through [inaudible] study. And as you know, [inaudible] is a microbicide that went through clinical evaluation and it is a non-ionic [inaudible] that has been used a spermicide contraceptive for over 30 years. Its chemical effects of disrupting spermatozoa and HSV and other isolates like HIV were well demonstrated in the test tube as it were. That moved on with very good publications from Lut Van Damme, who is in the conference.

Earlier studies however showed that they were safe, but the mouse study by Lut and group demonstrate, which is a Phase III study. It observed increased HIV acquisition among female [inaudible] following frequent [inaudible] more than three times a day relative to placebo. Really, that mouse study allowed us to look backwards. All of the studies we

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have now, people are robust; we have more vigilant, and what we know from that study is that the changes in the pro-inflammatory cytokines may have triggered the cervical vagina secretions to accelerate HIV acquisition. The challenge we have however is it is difficult to extrapolate data from animal model into human biological models.

So moving with that background, I just want to concentrate on the clinical [inaudible] assessment, knowing very well that all of the compounds that are on testing will have gone through a robust test tube testing, pre-clinical testing before we take them through Phase I. So in these few slides I have the take-home message I have is that we have the strongest [inaudible] among the participants is for us to assess through a comprehensive medical history to illicit symptoms of genital itching discharge, because these vagina products will be used [inaudible]. These interviews by the way have to be highly confidential. In the unit I work with all research nurses are female nurses. We think that's a good model, because when you do sexual history, it is quite tricky in terms of getting the participants to be on the same page as you.

Then after you do a comprehensive medical history, it must be followed by clinical examination to look for the signs. Then you have to collect correlates of biological specimens if there are any symptoms. Then there is also a

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role for colposcopy assessment. Colposcopy is a microscopic examination of the vagina and cervix with small magnification. And usually colposcopy - I mean, its role is really for now confined to Phase I studies [inaudible] colposcopy in these assessments.

Tissue biopsy is done by other groups, but [inaudible] again creating [inaudible] for HIV entry. Others have got facilities to cervical vagina [inaudible] major cytokines and the challenges we face in cervix assessment. Some of the endpoints we look for in the genital tract are basically the [inaudible] from the trial participants. What we notice is that there is definitely underreporting in those participants. And then the other issue is that interpretation of genital tract bleeding it really needs a carefully taken history. Many participants on progesterone implants have rectal bleeding. HPTN-035 [inaudible] time in this meeting for us to come together and advise our research science out to look into this issue of genital tract bleeding.

And the elicited symptoms must be followed by objective assessment of presence of science clinical manifestations. And the challenge here is that science may be present without the symptoms. In other words, a lesion may be noticed on that cervix or a purulent discharge may come from that cervix when the woman in fact is saying I

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don't have a discharge. And then most of these examinations are done for most of the studies, as you heard yesterday, through speculum examination. We try very hard to train our research nurses to use atraumatic insertion speculums to avoid injury done by the insertion themselves.

Now, going back to the colposcopy, colposcopy itself was originally designed for cervical biopsy of the woman [inaudible] Pap smear; and what we look for is something called cervical [inaudible] in which a change is occurring before cancer arises. And colposcopy has been around for probably the past 50 to 60 years. The problem with it however is in research participants for microbicides, the majority of them are HIV negative and do not have pre-cancer cells; and colposcope through publications scored very good concordance. In other words, if you put two experienced colposcopies one in one room, we'll call it x, one in the other room call it y, and the participant has a lesion, in other words, has a change on their cervix which is pre-cancer cells, if that pre-cancer cell is [inaudible] which is close to cancer, the concordance, the agreements between the colposcopies is going to be high. And I'll show it in a picture just now. However, if the same woman has a lower lesion called CIN-1 which the changes are just confined to the bottom epithelium, they are going to be arguing the whole day to say, I think she has no disease; compared to I think

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she has got disease. So that's the difficulty of colposcopy, because it's good when there is evidence of disease on that cervix.

As you can see on this demonstration here, it doesn't really take much training for my junior doctor or my fifth year medical student to say this woman's cervix has got abnormal cells on that anterior trunk of the cervix. But if you look at the same cervix, I may argue with lots of colleagues to say is this a lesion here, because she has also got a very early lesion. So what I'm trying to say, there is high concordance here, low concordance there. And also, in the same slide I showed you before from two weeks ago in our colposcopy clinic where [inaudible] was already in the audience or in the conference, this woman also had a small lesion here on the anterior lip of the cervix, and we spent time to convince ourselves that she needed treatment. And again, as I said before, you really need to look very closely to the vaginal walls around there if you are assessing.

So now, in terms of the challenges we meet in colposcopy, the other thing to observe - Ian Frazier [misspelled?] from Australia published in '99 that when you do colposcopies on HIV negative women, because of sexual intercourse, because of tampon use, you're going to find what you call [inaudible]. So it is very critical that when you do [inaudible] in Phase I studies, we must record baseline

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findings so that we can demonstrate that there is no incremental findings. I must acknowledge the work done by [inaudible] and they have published a colposcopy manual 204 which has improved terminology and standardized procedures as we do our [inaudible] across science.

I won't speak much about [inaudible] transcriptase inhibitors. This was covered very well in the talk yesterday. But my point here in terms of [inaudible] is the vigilance shown by Ken Maer [misspelled?] group in a recent publication to look for absorption points and correlate it with systemic tests so that the virological cervix testing is done on those participants who may show absorption from the genital tract. I think this was covered quite well yesterday.

So ladies and gentlemen, protocol chairs - not protocol chairs [inaudible] chairs, I basically am concluding this talk by saying that we've come through a very interesting pathway. Lots of us have had to learn the physiology of the vagina, the anatomy of the vagina in a very interesting way, because the standard teaching in medical school did not emphasize a natural defense mechanism as the most important weapon we have against HIV acquisition. And through [inaudible] research we have realized that [inaudible] models have to go through natural anatomy and natural physiology. I would like to point to a meeting held [inaudible] in Maryland by the HBTM group. And Ian McGowan

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and Sharon Hillier who spoke yesterday is compiling a publication which will be posted on the HBTM website. I thought I'd bring it to your attention. Also [inaudible] Harrison, who is in the conference, has got a summary of the meeting, microbicides [inaudible] meeting and the letters Microbicide Quarterly, which is available in the alliance of microbicide booth outside.

And [inaudible] remains a pivotal process at worst stages of microbicide development both in the pre-clinical and clinical science. And as you know, I only really softly touched on the pre-clinical component, but it it's extremely crucial, and we do know that lots of products do not make it to clinical development because they would have shown some untoward effects.

Ongoing research to assess reliable [inaudible] that are reproducible and clinically relevant remains a challenge. And the [inaudible] monitoring will also continue, of course marketing, and as we heard yesterday, we'll be looking forward for the meeting in 2008 which we hope will show an effective microbicide. And being an African, I cannot finish the talk by recognizing that I do come from Zimbabwe, which is the North of South Africa. But I must apologize, I did not find the General this morning. I wanted to ask the General if I'm allowed in this meeting to tell people that there is something called Victoria [inaudible] and I do not work for

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Zimbabwe [tape blank] tourism ministry. But I do encourage those of our friends from other countries to go see Victoria [inaudible]. And lastly, I would like to thank particularly resilient African women who are availing themselves to our research and who have carried the largest burden of disease and all of my colleagues I've worked with over the years. Thank you very much for listening.

[APPLAUSE]

HELEN REES: I would just like to acknowledge and thank Dr. Chirenje very much for that talk and just to say that I think it demonstrates well how important it is to have African scientists working in this region who really are on top of their subject. And we're very proud that you are a colleague working in this region. Thank you very much.

It gives me great pleasure then to introduce the next speaker, Julie Overbaugh. Dr. Overbaugh is a member and associate program head at the Fred Hutchinson Cancer Research Center in Seattle. Her work focuses on various aspects of HIV-1 transmission and pathogenesis, and is noticed for its emphasis on translational research. She has worked closely with the Kenya Seattle collaborative groups for the past 12 years, including on a number of studies of mother to child transmission of HIV-1.

She has served as the chair of the NIH Grant Review Panel on the molecular biology of HIV-1; as editor for the

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Journal of Virology; as organizer of several international meetings; and as a member of the Office of AIDS Research Advisory Committee. Her work has been recognized by an Elizabeth Glaser Scientist Award and by a Merit Award from the NIH.

So we are delighted to have such a well respected scientist to address us this morning. But I also want to note once more that many of our colleagues from the developed world are in strong partnership with the African region. And I note [inaudible]. So, please, you're most welcome.

[APPLAUSE]

JULIE OVERBAUGH, PHD: Good morning. I'd like to thank the organizers for the opportunity to speak with you this morning about mechanisms of HIV transmission. I'd like to focus today on studies of infection that are more considering the perspective of the virus. First, I'll talk about some recent data that eliminates some features of the viruses that seems to make them successful for transmission from host to host. I'd like to turn then in the second half of the talk to consider whether people who are already infected with HIV remain at high risk for re-infection. And I hope in addition during the course of this talk to bring my perspective on how these basic science findings might impact microbicide research.

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We know that the HIV variants that are transmitted from host to host appear to be a subset of those present in the index cases illustrated in this first slide. HIV is genetically variable, so that when a person is infected for a period of time, they have a population of viruses, not just one viruses, not just one virus, and diverse variants exist in these individuals. Interestingly, when they transmit the virus to another person, there is a bottleneck at transmission that often results in just one or a few of these viruses being transmitted to the new host and seeding the next infection.

There are some gender differences in this transition bottleneck. For example, women who have an STD or use hormonal contraceptives are at increased risk at being infected by multiple variants. So in this case, we see more diverse virus population in these women. But as illustrated in this schematic, we don't see the amount of viral diversity that was present in the index case, again suggesting that there is a bottleneck during transmission for the types of viruses that are successful.

So we wonder do these transmitted variants have specific properties that can be exploited to design interventions to prevent HIV transmission. We can't really ever sample or look at the initial virus host cell interactions that occurring at the very earliest stages of

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infection. It's simply not possible to define these early target cells in HIV infected humans because you can't sample them. Thus, a lot of what we think happens comes from analysis of the viruses that are found at these early stages. We know these viruses typically use CCR5 as the co-receptor for entry into cells, suggesting that the early target cells express CCR5, and of course the primary receptor for HIV-1, CD4.

So as discussed in the previous talk, these cells are likely to be CD4 positive T-cells, at least a subset of them, macrophages for subset of dendritic cells or Langerhan cells. And in fact, as discussed, these cells are the cells that are found to be infected in animal model studies where they can look at the earliest target cells for infection. But given the fact that we can't really look at these interactions in humans, we wondered whether the study of transmitted viruses themselves might give us clues as to what the dynamic is between the virus and the host that allows the virus to successfully penetrate the cell and begin infection.

We've known for many years that if you look at viruses present in the later stages of HIV infection during chronic infection or during later stages when there are symptoms, that these viruses tend to be those that are heavily glycosylated, and that is partly to shield the virus from antibodies and to allow them to escape immune pressure.

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More recent studies have suggested that the early viruses, those that are present in the first few weeks post-infection, tend to be among those with the fewest glycosylation sites in their envelope protein, and I'd like to share with you some of that data. But I am aware that perhaps there are people in this audience that don't think about glycosylation of the envelope protein on a daily basis. So I'd like to just step back and review this concept.

The HIV envelop protein is on the outside of the virus particle. It's present as a trimer. And it's the molecule that binds to the CD4 receptor and then binds to the CCR5 or CXCR4 co-receptor. I've taken this envelope protein from the virus and laid it out in a two-dimensional structure in sort of a ball and chain alignment where we're looking at the amino acids coming along in a two-dimensional manner. What I've highlighted in yellow is the core of this protein. This is the part of the protein that forms the structure that allows this protein to fold in a three dimensional structure in a way that allows it to carry out its function. This part of the protein is relatively conserved, compared to the variable regions. There are five variable regions, variable regions 1 through 5; and these sequences are highly diverse both within the sequences of an individual and between individuals.

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Within these variable loop domains are glycosylation sites. These potential N-linked glycosylation sites - you'll hear me call them PNGS - what they are there for is to allow the protein to add carbohydrates or sugars to the outside of the protein. These sugars create bulk; they create charge changes; and they eventually shield the protein in a way that allows variable access to this core structure. So when I'm talking about glycosylation sites, I'm talking about glycosylation sites on these variable loops; and I'm going to focus primarily on variable loops 1 and 2.

The first study that addressed whether early viruses or viruses that are transmitted differed in their sequences in terms of glycosylation or other features was a study of discordant couples in Zambia that involved a study of eight initially discordant couples, seven of whom were infected with subtype C, and all cases where virus transmission was through heterosexual spread.

In this figure that I've taken from the paper by [inaudible] Hunter and Science in 2004, I'm illustrating some of that data. Each of these sub-figures illustrates the results from one discordant couple. It shows the number of potential N-linked glycosylation sites in relation to the fraction of sequences for the index case, in green or the recently individual, in blue. And I think this case up here best illustrates the point that was made in this paper. You

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can see in the chronically infected index case that this individual has a variety of different viruses with different numbers of potential N-linked glycosylation sites ranging from 19 to 25. The virus that was transmitted to their partner is the one that is the least glycosylated and 100-percent of the sequences were of this type. When they looked at this data in aggregate they found that the viruses that were transmitted in these eight transmission pairs were those that were among the least glycosylated proteins.

So we asked in our studies in Kenya whether this was true for other HIV subtypes and other risk groups besides discordant couples. And for that purpose we examined the number of glycosylation sites and the envelope V1/V2 loop which I showed you in the early viruses from a 12-year perspective cohort study in Mombasa, Kenya. This first study involved 27 women and eight men, all of whom were presumably infected through heterosexual contact.

I just want to tell you a little bit about the Mombasa cohort. This is a prospective HIV negative cohort that was started in 1993 and continues to the present. High risk women are enrolled when they're HIV negative. They are provided as many mechanisms to limit their risk of HIV acquisition. Because they are high risk women, a number of them have become infected, and we continue to follow them if they decide to maintain in the cohort.

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We assess the time of HIV infection by serology and also by retrospective HIV RNA testing so that we can fairly precisely decide the time of their infection, especially given that these women come to the clinic about every one to two months. From this cohort we examined sequences at 70 days post-infection. We compared these early sequences to all subtype A sequences in the Los Alamos database, which is just a repository of all of the sequences that have been published in the field. And we excluded in this analysis those sequences that were from persons less than one year post-infection. This was a collaboration with Dorothy Lang and Better Corper [misspelled?] at Los Alamos Labs.

This shows you the data from that analysis. This is a box plot comparing the 35 early cases that we looked at with the 51 database cases that we looked at in relation to the number of potential N-linked glycosylation sites. And I should point out that in these analyses and the future analysis I'm only looking at V1 through V2, whereas in the Zambia study they looked at the whole length of the envelope V1 through V5.

But what you can see is that there is a statistically significant difference between these groups, and the early viruses tend to have fewer N-linked glycosylation sites. We also found that they tend to have significantly shorter V1/V2 loop sequences.

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So what about subtype B transmitted variants? For this study we examined V1/V2 sequences from women and men in the U.S. who are part of the hinet [misspelled?] cohort. This was a cohort study conducted by Connie Kellum [misspelled?] and Susan Buckbinder [misspelled?]. And these were primarily persons infected with subtype B HIV-1 who indicated their major risk factor was IDU. It was 10 women and three men, and we compared these individuals, the sequences from these individuals early in infection to the database sequences of subtype B cases greater than one year post-infection. And this data is shown in the same format here. And in this case, in the subtype B study, we do not find that the variants that are transmitted have fewer glycosylation sites than the variants present in the chronically infected index case.

So given the data that I've shown you so far which suggested that in subtype A and subtype C cases the viruses that were transmitted heterosexually tended to be less glycosylated, we wondered is there a selection for viruses with less glycosylated envelope proteins in the setting of mother to child transmission. Here we examine sequences in 12 mother-infant transmission pairs, most of whom were infected with sub-type A. This was a study that was part of a larger study that was led by Ruth Nduati, Grace John-Stewart, Dorothy Mbori-Ngacha at the University of Nairobi, and Joan Kreiss at the University of Washington. We looked at an

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average of eight sequences for each mother-infant pair. In total, we looked at 96 sequences. Most of these infections were presumably in the early breastfeeding period, as the infants were HIV DNA negative at birth but positive at six weeks.

The data here is shown in a slightly different format because we used a different analysis to account for the fact that we had multiple sequences from the same individuals. Nonetheless, we see again that when you look at the viruses that were transmitted, in this case to the infant, they had significantly fewer glycosylation sites than the viruses present in the mothers in this analysis.

So these studies I think show that there is selection for variants with less glycosylated and also shorter V1/V2 loop sequences in some settings, particularly, heterosexual and vertical transmission of subtypes A and C, but not in other cases. And I showed you this was true for subtype B IDU. But another study by Simon Frost and Doug Richmond's lab also showed that there was no apparent selection for differences in glycosylation in transmission of subtype B in the setting of MSM.

So, of course, the important question in all of this sequence gazing is does it mean anything. And to think about that and to try to start considering that - and I should say we don't really know the answer to that. I want to know take

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you to the three dimensional structure of the envelope protein. So if you remember that yellow part of the two-dimensional structure, I'm now showing you in detail a schematic of the three-dimensional part of that protein. So we're just looking at the core of the envelope protein here.

What you see in red are the positions in the envelope protein where CD4 binds, and what you see in green are the positions where CCR5 binds. Now, I've been talking about specifically the V1/V2 loop, its size, which I didn't refer to in much detail; but its extent of glycosylation, which I told you impacts the size of the protein. So you can imagine if we consider that V1/V2 probably lays right about here on the protein, if you have a relatively small unencumbered V1/V2 with less glycosylation, you might have pretty good access to these binding sites. In contrast to this situation, if you have a larger, more heavily glycosylated V1/V2 sequence, where the access to CD4 and CCR5 binding may be occluded, this could impact the affinity of the envelope protein for the CC35 receptor or the CD4 receptor, which in turn could impact the susceptibility of these different proteins to CCR5 inhibitors such as those being considered as microbicides.

It's also been speculated that the size of the V1/V2 loop could impact the access of antibodies to the protein, because sitting on this face of the protein is also where

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neutralizing antibody binds. So again, the bigger the V1/V2 loop, the harder the access may be to neutralizing antibody. And again, I think this has been suggested in studies but remains to be seen. So it may in fact be advantageous in thinking about how we can get at this virus if the envelope protein has a smaller V1/V2 loop, because less of this region of the protein would be occluded.

So I think when we think candidate inhibitors that could be used as microbicides for testing we'd need to use relevant stains. The important characteristics of these virus include that they be envelope variants that were recently transmitted ideally by sexual transmission, and that they be representative of different subtypes, particularly given the differences that we see between subtypes A, C and B in terms of the features of these viruses.

To that end, we've been developing a subtype A panel of viruses. This panel to date includes 14 envelop variants for five women at one to two months post-infection in multiple viruses per woman. Don Mosier has examined the sensitivity of this panel of viruses to PSC-RANTES, which is an inhibitor of CCR5 that is being considered as a microbicide, and the data from his lab is shown here. What I'm showing you is each virus along this axis; and in blue are the viruses from our subtype A panel, and in gray are the

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viruses that are commonly studied subtype B strains that a lot of laboratories use for screening.

On this axis is shown an increasing dose of the inhibitor showing the amount of inhibitor that's required to neutralize the virus 50-percent of the time. And I think what you can probably appreciate is that the viruses in the early subtype A panel are actually more sensitive to this inhibitor than some of the commonly studied viruses like BAL or ADA [misspelled?]. So this is actually potentially good news if these envelope proteins are indeed more sensitive to inhibitors than what we think based on screening some of these subtype B viruses.

We've also looked at the sensitivity of these subtype A viruses to the commonly studied monoclonal antibodies. Here I'm showing you the different viruses along this part of the table, and different monoclonal antibodies that have been of interest for blocking HIV infection. And I would say these are of higher interest potentially in passive immunization in infants, but also have been examined in some settings as consideration for microbicides, probably not quite so practical due to expense at the moment.

But you don't need to look at the numbers in this table. The table is color-coded. So gray means that the virus was not neutralized at the highest dose tested by that particular antibody. An increasing blue color means the

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potency of neutralization was high. So I think what you can appreciate by all of the gray in this table is that most of these early subtype A viruses are poorly neutralized by these monoclonal antibodies which all happen to come from subtype B infected individuals.

For example, 2G12 did not neutralize any of these viruses, and that in fact is directly due to the fact that these viruses are less glycosylated, because this is an antibody that recognizes sugars. But these other antibodies also did not neutralize with high potency, suggesting that these antibodies may not be all that effective against recently transmitted subtype A viruses.

I think there are important lessons for pre-clinical screening that we can take from the vaccine field, and I'd like to just touch on that for a moment. Many years ago in the vaccine field when people were screening for vaccine efficacy, the initial studies of antibody sensitivity focused on lab adapted isolates of HIV. These were isolates that were grown in an artificial setting and ended up being viruses, we learned later, that mostly used the co-receptor CXCR4 and not CCR5. And I told you earlier that CCR5 viruses are the ones that appear to be transmitted. And it turned out that these viruses that people studied were ones that were very easy to neutralize by antibodies.

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And what's the field transition to starting looking at more relevant viruses, and that was primary isolates of HIV or isolates that were grown in primary cells for short periods of time. They actually realized that the primary isolates were much harder to neutralize. And this created a low point in terms of developing vaccines that could elicit potent enough neutralizing antibody, because people became discouraged thinking that the bar that they had to achieve was much higher than they had previously appreciated.

I think recently the field has finally recognized that screening vaccine immunogens for neutralizing antibody efficacy require testing against early virus variants. So I think the message here for the microbicide field is to bypass these first few events and go straight to testing compounds of interest against early virus variants. And in that regard, I think the field can take advantage of panels being developed by the vaccine field. I've touched on our subtype A panel which is still a bit small. There's a much more comprehensive subtype B panel that was developed by David Montefiore's lab. We're working on a subtype D panel, and I think there are others working on subtype C panels. So these viruses could be useful reagents to the field.

I'd like to also comment briefly on how this may impact - how we see pre-clinical testing that's in animal models such as the [inaudible] model. And the question is, do

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these animal models model transmitted strains, which I've showed you have different features. And in fact, the SIV's and the CHIV's/NU's [misspelled?] were specifically developed to cause high viral loads in rapid disease. They were meant to be pathogenesis models. And thus their relevance to transmission is a little bit unclear and variable.

For example, many of the CHIV's, the chimeric SIV/HIV's that are in common use actually enter cells using CXCR4 as a co-receptor. And I've told you that these types of viruses are rarely transmitted or establish infection. There is one model that focuses on CCR5, and that is CHIV-162 P3 and P4 that was developed by Cecelia [misspelled?] Changmire [misspelled?]. This model allows testing of interactions with relevant cell targets in the model. And I was delighted at the recent keystone meeting to see that Ruth Ruprecht has a new CCR5 CHIV that was developed with a subtype C envelope protein from an infected infant.

But I think in general, it is my view that we need better CHIV models, designed with relevant envelopes to improve pre-clinical screening of candidate microbicides and vaccines. It's an enormous undertaking to develop these CHIV's and it takes quite a long time, but I think we're in this for the long haul, and it would be a useful reagent to the field.

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For the last five minutes, I just want to turn the second question I posed, and that is whether pre-existing HIV infection is enough to block re-infection by another HIV variant. That is to say, are people still at risk for HIV infection when they are sero-positive? I'm going to return to the Mombasa cohort initially for this study, because we've looked now at women in this cohort; 57 cases over three to five years of follow-up after their first infection; analyzing sequences at early time points, one to six months post-infection, and then again three to five years later. For cases where we see discrepancies in these sequences that suggest re-infection, we analyze sequences in between by a variety of methods to more precisely pinpoint the time of re-infection.

An example of that is shown here. This is an individual that was initially infected with subtype D. I'm showing the viral load versus the day's post-infection. At the first three time points we analyzed, we detected subtype D viruses by all three methods we used, up through 264 days post-infection. And then starting at 385 days post-infection, we began detecting a sub-type A virus. We continued to detect both the sub-type A and subtype D virus throughout the rest of the infection in this individual. We assumed that the timing of transmission of the second virus is somewhere

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between 264 and 385 days post-infection. So this is our window where we first detected the second virus.

This is a schematic of that kind of analysis of the eight cases we've examined so far where each of these bars represents a case, and the length of the bar represents the window from the time we didn't detect the second virus until the time we did. And the windows longer simply because of the time points that we had available.

I show you here the month's post-infection up through a year, because a lot of the infections occurred in the first year I've drawn that out; and then a more compressed version of the next several years in infection. But I want to highlight a few things. The first is while we do see a number of cases where infection occurs early, re-infection, and a case that a showed you where it's occurring about one year post-infection, we also see cases where people are being re-infected after one year after their first infection. And on average what we see is that the re-infection is occurring about one year after the first infection in our cohort.

Now, this is actually somewhat in contrast to the findings from Caroline Williamson's lab who also looked at this type of question in the South African cohort and showed, interestingly, that in these women, in six of the 31 women she examined, by three months she could already find evidence of two different viruses in these women. She couldn't tell

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the order of these viruses and when they infected the individual because it happened so quickly. But what was interesting about her study is she didn't see any evidence for re-infection at any time points later in these women up through two years; and this was 25 women that she analyzed with an average of 15 exposures per week. So I'm not sure why we see a slightly different outcome than Caroline did. One possibility is that the women in the South African cohort have probably 10 to 20 times more exposures than the women in the Mombasa cohort, so perhaps that could contribute to why there are so many early what are called dual infections, potential cases of re-infection.

So one possibility is that we're actually missing the virus; and the virus was present prior to when we detected it, but at low levels that we missed in the assays. We think that's unlikely in the Mombasa cohort for the following reason. During about a one year period we would estimate that these women have about 50 exposures. So this two-percent transmission risk is much more consistent with the estimates of transmission risk in HIV naive women exposed through heterosexual contact. So it seems unlikely that they would be re-infected here when they have so few exposures. But I think the most compelling evidence that re-infection occurs later after the first infection comes from a published study in 2002 by Stephanie Jost who is following an individual who was

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infected with a subtype AE virus. This was a person who was infected for about two and a half years with that virus; participated in a number of clinical trials; and then decided it was time for a holiday and went off to Brazil. When he went off to Brazil, he admitted to several high risk exposures, and lo and behold, he came back with a second virus that had all of the signature sequences of a subtype B virus from Brazil. So I think this is a fairly clear case of re-infection occurring after several years.

So we know that re-infection can occur up to several years after the first infection. We're not quite sure what the clinical consequences of this might be. Although one study that looked at three cases of intra-subtype super-infection with subtype B reported that these individuals had increased viral load after they got the second virus.

The two studies, including the study that I alluded to from the South African cohort where they looked at dual infections, that is infections that were present at the very early time points that they examined, these individuals also had higher viral set point. So the jury may still be out on whether super-infection, that is sequential infections leads to faster disease progression, because only a few cases have been studied. But the evidence suggests super-infection may accelerate disease. So this is of concern in terms of the clinical outcome.

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People have argued that re-infection is mostly occurring early after the first infections. I hope I've shown you from some of our data and there is other data in the field to suggest that re-infection can occur at different times after the first infection. There haven't been large studies with longitudinal cohorts to know if the risk is higher at certain times than at other times. And people may continue to be at risk of HIV infection after sero-conversion. This could have consequences for clinical outcome. Again, we don't know that for sure, but I think there's a lot of hints that this might be true.

Finally, I'd like to acknowledge the team of people that have been involved in this research. A lot of the projects that I talked about from my group were based in Mombasa, led by our field director Luto [misspelled?] Lavrise [misspelled?], Keyshur [misspelled?] Magdalia [misspelled?], and this program was started by Joan Kreiss. I mentioned the group at the University of Nairobi in the MTCT study. I'd like to specifically acknowledge the women in the Ganjoni clinic who participated in our cohort study and provided the opportunity for us to understand a little bit more about HIV transmission.

This work was done in my lab at the Fred Hutchinson Cancer Research Center, and I'd particularly like to highlight a talented graduate student, [inaudible] Nachohan

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[misspelled?] who is in my lab visiting from Kenya and getting her Ph.D and will be returning to Kenya to lead a laboratory there in the next year or two. Thank you for your attention.

[APPLAUSE]

ANATOLI KAMALI: Julie, on behalf of I think of everyone here, I'd like to express a special thanks for tackling a very important topic that really touches on the design of the microbicide trial. Thank you very much.

Ladies and gentlemen, it is my pleasure to introduce our third speaker this morning, Dr. Morenike Ukpong, a peridontist by training. She is a [inaudible] with the University in Nigeria, Obafemi Awolowo. She is a member of the National Ethics Board and coordinator of the Nigeria HIV vaccine and microbicide [inaudible]. The coordinated effort of her organization has resulted in [inaudible] changes on the national and community level since with respect to issues and policies related to the new HIV prevention technology research and [inaudible].

She has kind of accepted to tackle an important aspect within the microbicide research, which is the law of community and advocacy in defining the microbicide research agenda.

[APPLAUSE]

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DR. MORENIKE UKPONG: Thank you very much. I'd like to thank the organizers for giving me an opportunity to share my thoughts on the subject that is of importance to me. I'd like to start by acknowledging the contributions of a number of people to this presentation. I'm standing here to share the views and our perspectives as [inaudible] advocates. I'd like to thank [inaudible] for contributing to this presentation; [inaudible], as well as Rhonda White of HPTN. And I'd also like to appreciate a presentation of Justice Cameron during the opening ceremony on the [inaudible] importance of community participation in microbicide research, and that has set the tone for this presentation.

I'm showing the slide with respect to [inaudible] make my presentation today. I'm going to start by defining the research agenda, and then go on to define community and community advocates, as well as discuss on the why and how the community wants to [inaudible] in the research agenda, and then finally discuss recommendations and conclusions.

First of all, the research agenda. In 2005, the International Working Group on Microbicide Research and Development [inaudible] eight month period and [inaudible] with respect microbicide research and development. The first [inaudible] area they defined was that of basic sciences and pre-clinical trials which would inform product development. The second, clinical trials processes which encompasses

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logistics, ethics, as well as design. And doing the deliberations they did acknowledge the place and role for community with respect to facilities in clinical trial processes. The third area identified was that about understanding manufacturing, as well as foundation need, which would ensure user [inaudible], and they did acknowledge that there was very little progress in this area. With [inaudible] issues which would eventually address delivery systems and strategy, and they did note that it was important to start addressing this issue right now because a lot of products have [inaudible] completion of effectiveness studies, and a number of them we need to move on to commercialization.

Some background questions. [inaudible] importance of developing the microbicide as a complimentary tool to [inaudible] prevention tools. We know that the main challenge still exists is the lack of the scientific proof of concept. The biggest challenge right now with respect to [inaudible] microbicide therefore seems to be scientific. And I'm show there are people who wonder why and what's the importance of community involvement and [inaudible]. And others would wonder why the noise about community involvement in research, when all the research efforts is actually towards ensuring that a product is developed and made available for the community to use.

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[Inaudible] most specific questions with respect to a product. We do know that for a product to be developed that a lot of complex issues are involved. And therefore, in trying to answer that question, it becomes very pertinent of a question as a community oriented answer so as to ensure that that product is eventually used when produced. And in giving a community oriented answer to a question, community input is needed to answer that question. And for me I think this is very important, because a number of studies tend to show the community perspectives to an issue often [inaudible] to a not necessarily [inaudible] with a science perspective on the same issue. This was brought to light by the presentation made by [inaudible] on community perspectives on safety monitoring and microbicide trial in a recently organized consultative meeting in New York. And she presented that very beautifully.

We [inaudible] find [inaudible] concerns on issue in terms of mild, moderate, severe, life threatening or death. The community defines the [inaudible] issues in terms associated with problems with friends, peers, spouses, families and partners. This does not translate to the fact that communities cannot in totality comprehend or related to simplified scientific details. But then when scientific data is [inaudible] to answer a research question, that data would

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most likely have meaning and relevance to the community when the answer is people or community oriented.

The community [inaudible] that such scientific data has a human face and usually advocates [inaudible] get to understand the science and trust they got science to comprehensible community language, as well as translate the community language to the science world.

Who then is a community? A broad definition of the community sees the community as one or many groups of people who share common identity on the basis of location, ethnicity, occupation, sexual orientation or behavior or common interest or activity. From the researcher's perspective, a community is a group of people who will participate in or likely to be affected by or have an influence on the conduct of the research. This main group, is the group from which the trial participants are drawn. The [inaudible] with the trials will be conducted are often persons like families or friends. This definition was gotten from the HTBN site.

However, we the community have a significantly important group of people that we think need to be identified with respect to research. In identifying this group, we place an importance on research [inaudible] especially in developing countries; we therefore become elated. We advocate therefore define the community to include the other members

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of the general population at that time, not trial participants. They are not donors. They are not activists. They are not researchers, nor are they policymakers. But they are many people touched by the day to day issues of life and [inaudible] microbicide trials and research, except when they are [inaudible] about it's input in their routine day to day lives.

The community activists are often the ones who tend to allot the community of others. And so community advocates are often defined as representatives or consultative representatives of the community. They are the vocal, active members of the community who give a voice to the concerns of the community they represent.

This slide is a good representation of the community. This slide was borrowed from [inaudible], and it actually demonstrates the entire spectrum of the community that has a stake in the microbicide research at agenda. The trial [inaudible] community to the research seems to be the trial participant community. And we have the immediate community of the trial participants' family and friends. Oftentimes, many microbicide trial sites, many researchers have had to grapple with the need to relate to the participants' family and friends [inaudible] of the local cultural norms that govern gender relationships.

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Just as we research [inaudible] on how to effectively engage the community of [inaudible] families and friends, they equally have to grapple and think through on how to effectively engage this many layers of the community in a very simple research. However, we presently have models and practices that demonstrate the possibility and practicality of [inaudible]. The stories that [inaudible] from the various trial sites [inaudible] helps us to understand the possible consequences of not ensuring a broad [inaudible] in which the many communities are engaged. The ongoing [inaudible] in Botswana is an example of a trial that engages a wide range of communities that are directly and indirectly related to the trial.

The tragic part of the International Consultative Workshop and Informed Consent on HIV Prevention Trial convened in May, 2005 notes the concern of the research team which would expect to engage in a wide range of people in the research process. They note that the engagement of this wide range of communities may pose a challenge which with respect to how to preserve participants' confidentiality, as well as how to identify the needed information to share with various constituencies.

While their fears and concerns are real, the answer equally lies in consulting constructively with the community to identify how to address them. Oftentimes, the science

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committee consults among themselves to find answers to community related [inaudible]. Such answers often prove to be expensive in the long run. Constructive engagement with the community in the long run maybe longer but then it's often rewarding.

One thing we definitely note is that the community is far unlike a community of the trial participants. The research community needs to deal with this larger community in an effort to maximize the potential for benefit of such collaborative efforts. I want to refer to the U.N. report on Creating an Effective Partnership, which was published in the year 2006; it came in the Journal 8. And I quote, "As more groups and people define themselves as part of an interested community, both the concept of community and terminology needs to be broadened to [inaudible] or stakeholders." I find this definition more apt, and therefore, for the rest of my presentation, I will be referring to the broader community as the civil society. And when I use the word "community", I'm referring to specific community identified within that layer.

The following slides try to address the needs of the civil society engagement. The first two slides were provided by Mitchell Warren of AVAC and [inaudible] civil society engagement. We note that with civil society engagement or without civil society engagement research and development may

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not be prioritized; resources for microbicide trials and research may not be sufficient; trial approval may be slow; recruitment of [inaudible] and trial participants may also be slower; and also their retention may be compromised. We also know that trial conduct may be disrupted; [inaudible] may be delayed; procurements may be limited; demands and distributions may also be reduced; and people may end up not using the technology if and when developed.

A positive outcome of civil society engagement with respect to research agenda as been aptly demonstrated and documented from the experience of the treatment activists and the civil society involvement in facilitating [inaudible] job development and research. The same can happen with [inaudible] trials, especially with microbicide research.

While this is true that science remains the significant [inaudible] factor with the development of the microbicide, we also know and acknowledge that the civil society has a significant role to play. We know that [inaudible] for defining research endpoints are still yet to be defined. We know that animal models are still yet to be identified. [Inaudible] other science related questions are still yet to be answered. But then civil society involvement [inaudible] the issue also remain as challenging. A process for ensuring facilitated microbicide research and development [inaudible] continued engagement of the community and

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community members, to advocacy, to lobbying, to the use of pressure when necessary, to publicity, exchange of information or entailing planning, strategizing, follow-up and evaluation of processes.

Scientific rigor and [inaudible] must definitely [inaudible] on the student opposition. It is crucial to the success of HIV prevention research. [Inaudible] the researchers on the civil society should work for the single which respects the development of a microbicide which would enhance the health for the global good. Therefore, microbicide research, as well as [inaudible] research must be done with not for or on the community.

The civil society therefore advocates for partnership and not [inaudible]. We the civil society ask for a greater involvement in microbicide research and development efforts. We demand that we be included in defining research priorities, determine how our trials will be conducted, as well as monitor trial implementation. We must call on board the research platform as equal partners and not as underdogs. We look forward to seeing that the demonstrated evidence of partnership in active engagement of a civil society and the design implementation and monitoring of microbicide trial research is regarded as an ethical imperative in the future with respect to [inaudible] approval.

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I'm going to present some slides with respect to this caution facilitated by [inaudible] on the online discussions and ethical framework for HIV prevention trials. This discussion was facilitated in April last year, and the summary of that discussion is available at the [inaudible] booth for anybody interested.

A participant on the forum noted, and I quote, "Partnership means working out the relationship between two groups, one whose main characteristics is a desire for self-preservation and another whose main duty is to demand for accountability." Another made a point on the essence of partnership, and I quote, "Without partnership the [inaudible] of the civil society in biomedical research would be severely hampered, and that's an affect paralyzed medical advancements." On the other hand, the civil society needs the advancement to live a healthier and a happier life. Therefore, the civil society and scientific community need to exist [inaudible] in a [inaudible] atmosphere entailed with mutual care and [inaudible]. Partnership between the science and research community is therefore needed.

First partnership, however, needs to be built on the conception of model that recognizes the link between the various identified layers of the community and the individual, as well as the entire relationship among these layers and the individual who participates in that trial.

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In other words, or in the words of an advocate, there is no shortcut to this. We all have lessons to learn and apply [inaudible], as well as offer past and ongoing HIV related trials.

Building partnership or relationship is a tedious process that starts with a desire to. We all need to give the process a chance, as well as facilitate a conducive environment for the growth of this crucial relationship. Here is another quote from Karen Kaplan, who is from Thailand. And she notes that we the community want to be added value, not an extra burden, not something to shake off your feet. In essence, the present relationship that exists between the research and the civil society cannot be described as partnership. In the recent past, effort has been made at trying to involve or engage a civil society in research efforts. The process has not altogether been smooth. In some cases, it has been discouraging.

And I want to talk next on how we believe we can move this partnership forward. To move this partnership forward, effort therefore must be from us all, from the researchers, from the civil society, and from the advocates. We need to remove existing barriers such as miscommunication and mistrust. Openness and transparency also needs to be encouraged to help build this process. Because we've created such an anxiety with respect to openness and transparency is

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the need for openness as to clinical trial data, discussions that emphasize the need for interested stakeholders to have access to complete, accurate and unbiased medical information on drugs and medical devices. It is therefore paramount and pertinent that clinical data, whether they are positive, favorable, negative or neutral be made available to all stakeholders. However, the inevitable concern is that any move that increases transparency could have negative consequences for interested pharmacological industries, and this could lead to violation of [inaudible] property rights, the competitors gaining easier, deeper and any insight into competitor's activities; and this in essence may result in fewer new products entering development, especially with respect to [inaudible] and increased input by this [inaudible] industries.

Clinical trial transparency for what's better and more robust decision making, not just for the science world, but also for we the community. Mistrust has also been bred between the two communities, as highlighted in the [inaudible] of this advocate. This [inaudible] also, which I'm going to show next, was taken from the [inaudible] online discussion.

One of [inaudible] identified with militants' obtrusiveness, abrasiveness, noisiness and irrationality. In many circles the civil society is looked upon as an irritant

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that should only be tolerated. It is difficult to appreciate that militancy and aberrant obtrusiveness of the civil society is a reaction to the response of the science community in particular, and the rest of the society to their genuine demands for justice, equality and accountability.

The next two slides points to the feel of power and balance in the existent civil society research relationship. [inaudible] civil society and having a sense of oppressive control of our relationship by the researchers. As this post noted, [inaudible] within the scientific community do not believe the members of the civil society are [inaudible] understanding the intricacies involved in science research. Many also feel that engaging the civil society is a time wasted effort.

The next slide also shares the concern of a civil society that feels that science is indeed a cult of the learned that have the answers which we the community must receive.

This last slide comments on the need for us to walk with and not for or on the community. [Inaudible] discuss the need for true partnership and not just talk as involvement. For years we have identified the need for civil society engagement and research process. In recent times, we have emphasized community involvement. Now we talk about partnership.

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For the next few minutes, I'd like the how's of facilitating with this partnership. First, it matters that we all share with common understanding and belief in the need to ensure partnership. While this does not exist, conflict - when partnership does not exist, conflict may keep [inaudible] at the trial sites, as we presently have with the PREP [misspelled?] trial that is ongoing in Thailand that involves injection drug users. Each party needs to be open to new ideas and concepts. The process is not about preventing conflicts that can disrupt a trial. Rather it means that we engage in meaningful, productive relationship, which will ensure that even when troubles are called of a trial, the troubles can be identified, solution can be developed in partnership with the local community and then the trial can continue.

Secondly, we need to learn from our collective pasts and current activity. The NI trial and the PREP trials are case studies very closely related in the microbicide experience that we can readily learn from. There is so much to learn from the ward of the treatment activists, as well as the HIV ward in general. These are lessons we can aptly adapt to our world. Many are new lessons that have to be learned and facilitated to open engagement of the civil society in an otherwise science dominated world. In [inaudible] civil society/researcher relationship or

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partnership during the microbicide trial and development efforts, it is equally important to identify the roles that the community can play within the signs of the research process.

I do appreciate the many [inaudible] that civil society can facilitate a supportive external environment that can help expedite research and develop improvements. I also believe that many acknowledge that civil society can advocate and ensure that microbicide research and development programs become national, regional and global priorities. They can mobilize resources throughout the process. They can help create a conducive environment that may ensure support for trial conducts. They can advocate for positive changes in policies that may expedite essentials and procurement, as well as help ensure prompt [inaudible] and sustained use of the product.

These are traditional areas within which the civil society operates and the researchers do not contend with them. What more then can the civil society give and why do we want to delve into the world of science? A civil society can do much more than I have enumerated. We have the enablement to ensure that the science process is community oriented and approached. We can help ensure that the entire process delivers an accepted product through an acceptable process. Because the research and development process is a

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co-owned process, that means it is owned by the researcher and the global community, successes are celebrated and failures are well managed. Conflicts and crises are more often internal, easily resolved and would not result in opposition.

To facilitate the civil society involvement in research processes, it is critical that we are involved at the inception of the research. It is important to start bringing on board the civil society at the point of conception of the trial before the development of the protocol. This helps to breed a sense of co-ownership of the project, with less tendency for anti [inaudible]. Most projects try to do this to formative research, if formative research helps to identify issues with respect to specific approaches to design a protocol, as well as to implement the trial. It also presents a formal opportunity to establish initial contact with community leaders and members.

However, I feel strongly that the focus of the formative research should be redefined. Formative research is [inaudible] for collecting data from the community to inform protocol development by the researchers. Rather that process should focus on facilitating active engagements of a civil society in the development of a protocol for the conduct of the research within their community. It should serve as an entry point of the community and civil society in making

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input to the design and implementation of the research protocol.

The formative research is often conducted concurrently with site preparedness activity by the research team. I have a reservation on this. I believe that site preparedness effort should be done by organizations or groups already working and well known within the target community. The lesson I learned from the [inaudible] trial conducted in Nigeria makes me appreciate this. I noticed I learned that the same team heading the formative research ends up handling site preparedness. This cannot be effective. Site preparedness is far much more than dishing out information.

A pilot program that was conducted by my organization, the Nigerian HIV [inaudible] and Microbicide Advocacy Group, which one of the microbicide trial sites in Nigeria further reinforces this - we noted that many of the research team members that were recruited as community outreach officers had very little skills with respect working with a community. I [inaudible] advocate that site preparedness efforts need to be contracted to a community based organization working within and well trusted by the community where the trial is be conducted. Such an organization or group can be identified during the formative research process.

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The involvement of the community and stakeholders in planning and carrying appropriate activity is one way of beginning a two way relationship. This is crucial as a well prepared community would also have some form literacy and power to effectively engage in the research process.

The International Workshop on Informed Consent in HIV Prevention Trials that was held in New York in May 2005 also discussed extensively on this. They noted that the civil society can play [inaudible] with respect to the informed consent process. The civil society can help formulate approaches to inform consent provision. It can help develop, and preview and test materials as well as alert researchers on their emerging community concerns.

The civil society consultative process can also help define appropriate tools for enhancing informed consent processes, including the right use of pictures, language and colors. The community can equally be engaged in the monitoring of trials. All clinical trials carry with it an obligation to ensure optimal conduct of research. Usually, for many clinical trials, the sponsor designates one or more properly trained and qualified individuals to monitor the progress of the clinical research.

The monitor often relates with the researcher and the data that the researchers provide. Hardly does this monitoring process obligatorily involve the participants.

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The monitoring or monitoring process only engages the research team. Here is my own recommendation. There is a need for a community monitoring officer for microbicide clinical trials. Community monitoring officers will take [inaudible] of trial participants' needs and would focus more on relating with trials participants. Community monitors officers would not be not be on the payroll of the trial team. They could be identified [inaudible] to perform monitoring roles. You then find that such efforts would help authenticate the scientific reports from the community perspective.

During the trial [inaudible] trial in Nigeria, one of the bane of contention was a trial was being implemented and monitored by the same trial sponsor. The trial sponsors paid the trial participants education; the paid the participant advocate; they support the trial monitor. The community therefore queries the possibility of sponsor allegiance by all of the parties, thereby compromising the authenticity of their reports.

The presence of the true independent community monitor on a trial may help address this lapse. It is equally important to discuss the process of facilitating civil society consultation. Civil society consultation should not be limited to the trial participant's community. As much as possible, members of all of the identified layers of the

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community should be consulted. Groups and individuals should be consulted [inaudible] the community can be identified during the formative research per stage.

Prospective trial participants can be identified through social groups they belong or identified with or who the few best to represent our interests. Researchers or the research team can also place an open individual to an invitation to the general public to identify interested organizations or persons who want to be involved in the consultative process.

I want to go on now to my recommendations, especially with respect sustaining community participation. The rule of [inaudible] in facilitating community consultation participation research, the microbicide research agenda has been excessively discussed in many foras. This structure provides a formal [inaudible] for ongoing education, communication, advocacy, as well as problem-solving among representatives of the community. It is also noted that [inaudible] could also facilitate on a proper timing and ethical research processes.

The place where [inaudible], which understands his role and responsibility and is empowered to [inaudible] where the needed skills and knowledge cannot be replace. This includes [inaudible] help member better understand research concepts. But then past dialogue such as that facilitated

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that the global campaign for microbicides have recognized that other models can play a similar role when properly constituted.

I have used the [inaudible] in this presentation to connote any model or structure that plays that rule. Equally, I refer to an empowered [inaudible], because in reality most inaugurated [inaudible] are structures put in place as funding requirements for most proposals. They are empowered to perform their roles. They are not properly constituted. And worse still, many are on the payroll of the trial sponsors.

I do [inaudible] may also be voluntary, but then such voluntary structures tend to give room for low active engagement of its member in the [inaudible] activities; therefore tending for low tendencies for collective learning in the process.

These are critical issues that needs to be addressed. There is also equal room to supplement the activities of [inaudible] to the use of other identified mediums. It is in the view of the fact that a [inaudible] can become entrenched or colonized by the trial as identified in the IC workshop reports. One of such structures that could possibly compliment a [inaudible] is what I call a community [inaudible] group, the CCP. The CCC for a microbicide trial is comprised of members from other local [inaudible] involved

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in relevant clinical trials, as well as interested advocates, relevant stakeholders, as well as HIV positive individuals.

A CCP may not meet as regularly as the local [inaudible], but they can play a role in ensuring that community input into the scientific process and protocol reviews are insured. And the rapidly evolving world of research - and I'm trying to roundup now - we also need to think of other ways of ensuring sustainability of this community relationship. Equally important is the need for global investments in [inaudible] efforts. This is very important and should precede the influx of research into the community. It is also equally important for bi-directional communication, as well as for the research world to start linking prevention, testing, and treatments at trial sites.

Community advocates are already walking in this respect. We did a lot advocacy efforts towards microbicide treatment and [inaudible] efforts, and the science world can start thinking and referring to the civil society with respect to building these linkages.

Finally, I want to talk about crucial issues with respect to moving on. Like in the words of our advocates, we need dialogue. Dialogue is not simple, but then it is needed. We also need to see ourselves as a single community, not two communities of researchers and the civil society. We need democratize the research agenda.

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We need to drop the mistrust, and in truth, we need to start thinking of a new direction. Science can no longer conduct things in the same way. A new paradigm is imagined and we need to flow in the strength.

In conclusion, this present [inaudible] with respect to universal access to treatment, with respect to treatment as well as [inaudible] exercises the need to encourage quality accessibility and participation of affected groups with respect to delivery of products. We need to facilitate this process to [inaudible] and consultative process. [inaudible] universal access to the finally developed microbicide needs to start now. We need to start developing new models to ensure that sensitive data tools can analyze different community models with respect to different microbicide trials going on at different sites.

All stakeholders including researchers and civil society need to appreciate the need to walk together in partnership to help deliver the much needed prevention tools, and that hopefully can stop the progress and reverse the HIV epidemic in time.

Thank you and I acknowledge the following people.

[APPLAUSE]

FEMALE SPEAKER: I'd like to thank Morenike very much. I think speaking from the research side, I think that very

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often one does get slightly intimidated or you think you're following the recipe and you have your community advisory board, and you think that perhaps you've done it. And I think what you've actually managed to do is to set out an incredibly clear, one of the clearest presentations I've heard of what really is required to be thought about as we go forward.

We do have a few minutes before 10:00, and I suggest that if we got some runners and some microphones we could take some questions. We were meant to have some runners here. Would somebody like to come forward with a question for any of the speakers?

MAURA LIGANAR[misspelled?]: I'm Maura Liganar from Ocel [misspelled?], and we've been trying to express [inaudible], which is a sugar binding protein; and in light of your findings that some of the early infecting viruses have less glycosylation, have you looked at [inaudible] or the other sugar binding protein to see if their effect on the virus.

FEMALE SPEAKER: We have actually not specifically screened ourselves any of the compounds. But when I heard one of the talks yesterday, I was thinking exactly along these same lines. So we are happy to make our make panels

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available to people for that kind of screening, because I think it would be interesting to see if they're still sensitive to that compound.

MAURA LIGANAR: Yeah, that would be great you. Thank you.

FEMALE SPEAKER: Are there any other questions?

MALE SPEAKER: My question goes to the same speaker. We [inaudible]. And in Nigeria according to the [inaudible] research conducted we have [inaudible]. I just want to ask, has anything been done to develop [inaudible]

FEMALE SPEAKER: I'm not aware of anybody who is specifically developing a subtype G panel. I think maybe the critical piece of that first would be to ask you whether there might be cohorts of people where individuals have been identified early. Because I think to develop these panels and have recently transmitted viruses it would be important to have access to those kinds of samples. So that might be the first step. But I'm not specifically aware of individuals who are doing that.

We focus most our attention on the Kenya cohort for obvious reasons, but I'm not aware of that.

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FEMALE SPEAKER: Thank you. Question over here.

FEMALE SPEAKER: It's not so much a question. It's just an invitation that tonight we have at 4:30 a symposium on informed consent; and I'm just inviting everyone who would like to continue the discussion to come. Morenike will be speaking this evening, and we will talk more specifically about how to engage communities in the informed consent process.

FEMALE SPEAKER: Thank you very much. Was there another question here? Yes, please?

DR. SIVIRAH[misspelled?]: I'm Dr. Sivirah from India. My question to [inaudible], did you try [inaudible] in your studies, because [inaudible] is also common in most of Africa and India too. And what about subtype C trials, especially in Indian context.

FEMALE SPEAKER: Have we looked at HIV 2 specifically?

DR. SIVIRAH: Yes.

FEMALE SPEAKER: We have not, but I am kind of aware of the ongoing studies in the Gambia where I believe they're

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going to start looking at some of the HIV-2 sequences early in infection. I think they have a big study that's developing where they want to look at those issues.

DR. SIVIRAH: Another question to the [inaudible]. What have you experience, especially with HIV-2, especially in colposcopy studies?

MALE SPEAKER: You're saying HIV-2 in relation to colposcopy findings?

DR. SIVIRAH: Yes.

MALE SPEAKER: From a [inaudible] point of view, most of the clinical trials for microbicides are really looking at HIV negative women to start with. But there are smaller studies which have looked at colposcopic findings in HIV positives. But that's entirely not related to the relationship between persistent HPV and cervical pre-cancer cells, not from a microbicide perspective, but purely from disease [inaudible] from pre-cancer to cancer.

DR. SIVIRAH: Do you look for any pattern of virus findings in the colposcopy studies?

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MALE SPEAKER: For us from a study point of view, not from a [inaudible]. All our cohorts [inaudible] HPV screening. And we don't treat by HPV findings, we treat by colposcopic findings. [Inaudible]

FEMALE SPEAKER: Thank you very much. Question over here?

MALE SPEAKER: Yes. When I think of community participation in microbicides trials, one of the things I think about is actually seeing more African scientists in the leadership of these trials. And my question is, are there any plans to make that happen, and what are some of your ideas as how to bring that about?

DR. MORENIKE UKPONG: I'm sure the African Microbicide Advocacy Group this is one the lead agendas, and they're working actively with respect to [inaudible] scientists lead [inaudible] with respect to microbicide trials in Africa. Yes [inaudible] is working on that.

FEMALE SPEAKER: And just in support of that, if anyone is interested there is a booth in the reproductive health and HIV research. But we in partnership with a number of local academic institutions are on a four week research

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methods course, which is residential in Johannesburg specifically to train young scientists and African scientists. We've now trained several hundred from 17 different African countries. So if anyone here is interested, please take that. We try and raise funds, so we try and make [inaudible] available to facilitate participation of scientists.

I think at this point I can't see any other hands. So I would like to then bring these proceedings to an end. It's been a fascinating and wide ranging sent of plenary inputs, really fascinating. I've got a list of questions, but I'll go away with them. But thank you all very much.

Last comment and then we'll have to cut off.

FEMALE SPEAKER: I do have a question about community participation. One of the problems is the contradiction between science and community participation. And in my own work as an activist in the Caribbean, I have to say that one of the things we do in the community is to politicize women and politicize them about having control over the science that affects our bodies. And in trying to build up a constituency, what we try to do is to put pressure on organizations and institutions so that we can raise the necessary money that would develop technologies and science that would serve us.

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So I would like to add to the presenters comments about community participation is that we as women have to do a lot of important feminist work in raising the consciousness of women about their participation in microbicide work. Also, we need to do more work with the medical communities and medical institutions. As the doctor pointed out, the environment of the vagina which has its own beneficial features, has not been part of the medical training as well. So we need to do advocacy at every level.

Also I would like this conference to make its work more accessible to ordinary people, to activists and to have session in which a lot of the science is made accessible and translatable to us.

[APPLAUSE]

FEMALE SPEAKER: Thank you for those comments. I think in particular in the stores [inaudible] at the start of the meeting for a much stronger women's movement in this region, which I think is really called for. But then to wind up once more, I'd like to thank the three speakers. I'd like to thank my co-chair. I think as I said, very, very interesting individual presentations. I think there's a lot more discussion to be had on all three. But thank you all very much. And we'll now adjourn.

[APPLAUSE]

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