Official Press Conference: Newsmakers of the Day
Kaiser Family Foundation
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WARD CATES: — the press conference after this wonderful occasion. My name is Ward Cates I'm President of Research of FHI in North Carolina. We were one of the partners in the consortium that you just heard the results of the trial beginning with CAPRISA and having Conrad. And funded by USAID and then to my far left is NIH.

Let me just quickly let you know how we're going to organize this press conference. It will begin with the study PI's, co-PIs; Slim and Korisha Abdul Kareem [misspelled?] showing a film that will then have a statement by Robert Clay of USAID, Executive Director of the office of HIV/AIDS on that role in funding the trial. Brief remarks by Henry Gabelnick [misspelled] on the role of product supply. Remarks by Tony Fauci on implications of the trial and then we'll open it up for questions. So before I begin, let's turn it over to Slim.

SLIM ABDUL KAREEM: Instead of presenting any data, you're going to see a video.

[VIDEO PLAYED]

SLIM ABDUL KAREEM: Thank you.

WARD CATES: Thank you Slim. This is a remarkable finding. I've been to HIV conferences since 1985 in Atlanta, as has Tony I'm sure. For a scientific finding to receive three standing ovations from a chock full audience is a first.

It was just thrilling to see for all of us who were involved in the trial. Robert, your views as a funder.

Robert Clay: Sure. Thank you Ward and congratulations to Korisha and Slim and all your team. It really is a historical time and I was just noting the comments and adjectives that were used in the previous session. They range from fantastic to landmark to land breaking and to hot flush. So we will look forward to your adjectives in the press. I'm sure you'll have many headlines that will come from this study, but at USAID we're very pleased to be supporting this important work.

I'd like to take an opportunity to thank the leaders of the U.S. Congress. Especially Senator Patrick Leahy and representative Nita Lowey who have really been championing USAID's microbicides program from the beginning and has enabled for this work to continue over time. Health research is based on the best innovative science, is integral to the USAID's ability to achieve its development objectives world wide. For more then a decade USAID has been at the forefront of microbicides research and development.

Globally the greatest impact in mitigating and eventually reversing the HIV/AIDS pandemic will be through the development and the introduction of new preventive technologies. An effective microbicide will help fill the scientific and the critical need and as the Minister of Health

in South Africa mentioned, the missing link for the new prevention options for women and to compliment other existing or new prevention approaches.

If we're going to reverse the tide of this epidemic, we need to take calculated risk to push our knowledge and understand this disease. In USAID, and we provided about 90-percent of the funding to the research, we saw this trial as really a critical step to address this major gap and therefore we felt it was warranted for our support of looking at a female control method to prevent HIV/AIDS.

As Slim and Korisha mentioned earlier, our strong partnership with other governments, scientists and communities and also involving NIH who built the foundation for the research platform in South Africa led to a truly extraordinary discovery. The first ever proof of concept that a microbicide could effectively and safely reduce the transmission of HIV/AIDS from men to women.

This could not have been done without the dedication of those involved in the study, including the principal investigators and all the study staff at CAPRISA. The partners in South Africa Conrad Program, Family Health International, and most importunately the 889 courageous women in South Africa who volunteered for this clinical trial.

CAPRISA 004 illustrates how USAID intends future research and development programs under President Obama's

Global Health Initiative to progress. Many of the core principals of GHI were represented within this study. This trial focused on research, development and innovation. It exemplifies the U.S. government's commitment to advancing the health of women and children.

It supports country ownership. It's strategically coordinated with many different partners in the field. It promoted sustainability and health system strengthening and uphold the importance of monitoring and evaluation.

Before I conclude, I would like to just acknowledge the work of Jeff Speiler [misspelled?] and his team at USAID who were involved at the very beginning of this program and saw it through. Many times the donor is just thought of as their money and the funds that they bring but we also have technical expertise and Jeff and his team has provided a key technical input with the team on the ground. So we want to acknowledge that.

Finally, yesterday the USAID administrator Rod Shaw [misspelled?] applauded the CAPRISA 004 collaborative effort led by in-country investigators as a model for future research studies. He said, these results are the first step towards establishing the effectiveness of antiretroviral drugs for HIV/AIDS prevention.

Ongoing and similar studies supported by the National Institutes of Health and other organizations will confirm these

results. USAID will continue to work with PEPFAR multilateral organizations and partner countries to insure the full impact of this advance can be offered to women and girls worldwide and especially in low resource settings.

He concludes by saying with the support of President Obama and Secretary Clinton, we will continue to put science, technology and innovation at the forefront of our development work at USAID. So we are eager to follow up on the hills of these findings and confirm the results in ongoing and future studies, and USAID is committed to working with partners to make microbicides available to women and girls worldwide. Thank you very much.

WARD CATES: Thank you Robert. Indeed exciting opportunities. Henry Gabelnick, Executive Director of Conrad.

HENRY GABELNICK: Thank you. Having worked in microbicide development for over 20 years it is absolutely thrilling to have played a roll – even a lesser roll in this development. Conrad did provide the gel. We have it licensed from Gilead along with IPM and we are very much looking forward to the next steps.

We have established a relationship with the technology innovation agency of the South African government to license in the drug there and they're there form a public/private partnership to make the drug available when it is proved. The root to approval is going to be at least two pronged.

In the U.S. we will be approaching the FDA to ask them what studies they believe in addition to the voice study that's ongoing, which also has tenofovir gel arm used daily, might be necessary. The South Africans will be working with the regulatory agencies in South Africa, the NCC, to see what would be appropriate in their minds for approval.

The field in general is going to be trying to coalesce around a plan of how to deal with this very positive result. What would be the best route to move it forward and then to start to plan ahead for implementation and access. I'd like to say one other thing that Conrad is not just an organization which works on production of tenofovir gel.

We're a research organization. We look at things from discovery through product development. One of the aspects that we're going to be emphasizing even more in the future of using the grants that we have from USAID and the Gates Foundation, is combination products. We've been working on the for several years already.

To increase the intrinsic efficacy and therefore raise the effectiveness in the field. We also will be adding other antiretrovirals to further reduce – although it hasn't been seen – the possibility of resistance. Thank you.

WARD CATES: Thank you Henry. And I was so glad that Robert mentioned the really collaboration of building of the USAID funded CAPRISA 004 study on the NIH base because in many

ways FHI's roll in this trial is akin to a science facilitation roll we play in supporting many of the NIAID networks.

Whether it's the HIV prevention trials network or the microbicide trials network, our role in this particular trial was one of helping in protocol development, assisting in statistical analysis, doing the study monitoring, preparing, helping and designing the behavioral intervention, conducting an ancillary study within the trial and also the whole communications roll out according to the principals in a communications handbook for clinical trials that FHI has written.

This is very much linked to that sort of funding background of NIH and USAID and because of that I'd like to ask Tony Fauci to give the Director of the National Institute of Allergy and Infectious diseases to give his perspective on this trial.

TONI FAUCI: Thank you very much Ward. It's a pleasure to be here with you and to share with you the excitement about this extraordinary study. Ward asked me to spend a minute or two just talking about the implications of that. I'll be very brief in my remarks but to tell you that the implications of this are really enormous.

Congratulations to the implementers and designers of the trial. Congratulations to USAID for funding it and for Gilead for providing the drug for this. The reason why I say

with confidence that the implications of this are going to be enormous is that not only is it clear from the data and I know many of you, if not all of you in the room looked at the data.

There was a certain feeling of ease and pleasure as a scientist for me to look at data. That no matter how you slice it, it's statistically significant. Intent to treat, per protocol, modified intent to treat; the data are significant. That's important.

Number two. It fulfills an extraordinary need that we have that you've already heard described, and I don't need to repeat it for you. A need in the sense of science and public health and prevention, but also a need from a sociological standpoint for a group of people who for so long have had really very little opportunity to determine their own fate; namely women – particularly women in the developing world.

The first thing I'm going to do when I go home, when I talk about prevention I have slides that say these are proven prevention measures that have a concept that we feel comfortable about, and then the next slide is a bunch of prevention measures like a vaccine or what have you, that the data are accumulating but we don't really have a proof of concept.

So as soon as I get off that plane, if I'm still awake I'm going to start changing those slides around and take microbicides out of the non-concept proven to the concept

proven slide. I've gotta tell you for many, many years following and being involved in this field, that's going to make me feel really good. So that's the second thing.

The third thing and I'll close on this, is really the importance of what was mentioned by several of the commenters and that is, we still have work ahead. This is an extraordinarily important proof of concept. But just the nature of what we saw tells us and begs for the fact that we can do better. We haven't hit a wall on this; there's adherence issues. There's issues of application.

We have an ongoing trial that was mentioned. The voice trial that has 1-percent tenofovir gel as one of the limbs but it's given every day. It's not given at the time of sexual contact before and after. It's going to be compared with oral formulations of tenofovir or Travata compared to placebo. So we're going to get data that not only will hopefully confirm, and I truly believe it will, but will actually push the field forward. So this is a very important day in the whole arena of prevention research.

WARD CATES: Thank you Toni, and just to emphasize that, the team that you see here representing the CAPRISA 004 team are also partners with the microbicide trials network-sponsored voice trial in terms of both sites and the types of study activities described to you earlier. So there really is a wonderful leveraging of all of our efforts.

Okay, we are now available for questions from you guys. Yes?

MICHAEL SMITH: Michael Smith, *Medpage Today*. This is a question which I guess the either of the professors Abdul Kareem can answer – choose among yourselves – and it's actually the HSV-2 piece. If you prevent HSV-2 does that give you an additional HIV prevention, sort of benefit on top of the direct benefit with the tenofovir?

SLIM ABDUL KAREEM: We know from several studies including our own, that women who have HSV-2 infection are at twice the risk of acquiring HIV. Whether that is biological or behavioral, or a combination of those two we have not been able to decipher. But it's clear that HSV-2 positive women carry this additional risk of HIV.

Therefore, it is reasonable to hypothesize that if we lower the overall prevalence of HSV-2, that we would have a long term impact on HIV. We don't have data to show that at this point from our study. Our study was not designed to do that. But it something that is biologically plausible and I would hope would be one of the lines of investigation we have stimulation.

JOHN COMB: John Comb with *Science*. Are the women in the trial going to be offered the gel still if they want to use it, and secondly if the regulatory agencies in South Africa or

the United States only require a single trial, could it possibly go to approval without the validating trial?

KORISHA ABDUL KAREEM: Thanks for the Chris and John. At this point in time the tenofovir gel is not easily available. It's produced in batches sufficient for the trials that are underway. We are very keen to look at and start discussions with the regulatory authority about doing subsequent studies that include the women who were part of the study in terms of making this available still within an experimental condition. In other words, an unlicensed, investigational product and that will require all the regulatory and ethics oversight to test that in the women who participate in the trial.

WARD CATES: Cindy go ahead. Second question John? Henry?

HENRY GABELNICK: I think that if they were to say it, that it was provable based on this trial, I'd be extremely surprised because the FDA has always had a requirement for having two trials with sufficient power, or one trial that had a much greater significance level than was seen in this study.

But again, there are risk/benefit ratio in various places, and it might be that instead of having a full-fledged randomized clinical trial that lasts five years, that there will be alternative designs and alternative studies that can be

worked out that would satisfy the needs for making the product available sooner.

We are going to try to explore all of the paths, but the reason why I emphasize that we're setting up capacity to manufacture in parallel is that as soon as we do have permission to go forward, most likely it will be the South African private partnership that will achieve that, then we'll be in a position to provide access.

JIMMY BENNETT: Jimmy Bennett from Bloomburg. John kind of asked my questions. As usual he's several steps ahead of me. But just to follow up on his first question, Korisha can you just clarify that women on the trial are not being offered the gel on an ongoing basis just because it's not available? Is that correct?

KORISHA ABDUL KAREEM: That's correct. When we enroll them into the study, we explained this is a randomized control trial, often experimental product. This will be made available to you for the duration of the study. You have an equal chance of getting the placebo or the tenofovir. At the end of the study, this study is about safety and effectiveness, that this product will still need to go through several steps before it will be available for use.

This is the first step, and because it is not a licensed product, we cannot make this available to the women who participated in the study at this point in time.

JIMMY BENNETT: Is there not a case to be made that with the efficacy you saw even among low-adheres and with the safety profile you saw that it's going to be at least three years before a confirmatory trial comes back with a result. Is there not a case to be made that this should be approved right now? And/or as soon as possible on the basis of this trial?

SLIM ABDUL KAREEM: Thanks very much for that. So I think what Korisha was explaining is that we cannot simply put it on a shelf and say to women, you're welcomed to have it because it's not a licensed medicine.

What we would like to do, given that these women have been part of the risks and benefits involved in the trial, we would like to continue to have product available to them should they wish to continue to use it. It will have to be in the context of a study; something like a long-term safety study where there's no placebo gel, but just tenofovir gel.

It's under the context of a study that we can offer long-term access to the study participants, but that requires we have to make gel, we have to raise the funding, we have to get approval from regulatory authorities. That will be a few months of a gap between there.

The women however, continue to attend both of our clinics. We provide the most comprehensive services both for antiretroviral therapy and for prevention. Those services continue to be offered to the women.

LAURIE GARRETT: Thank you, Laurie Garrett. Since tenofovir is everybody's favorite drug of choice now for first line therapy for treatment, before Gilead's stock jumps any further, the 3-percent plus so far today, is there any reason inherently, that this proof of principal is going to end up being a tenofovir gel product?

And might there not be time Tony, to consider some sort of international discussion about how to prioritize which of the ARV's should be available exclusively for treatment purposes, and which might be for prevention purposes to mitigate against the possibility of resistance that eliminates the utility of the drugs for treatment?

TONY FAUCI: I can partially answer that question and I think Slim also showed some, I think interesting data. The answer to the first part of your question Laurie is that there will be, I can assure you, trials using other drugs besides tenofovir. In fact, if you look at the Voice Study, one of the limbs is tenofovir gel compared to oral tenofovir and oral Travata.

So there will be, and I'm sure with the excitement that's generated by these data, they'll be other interest in other types of trials. I was very struck by the lack of any degree of resistance that was noted from the application topically of this particular drug. That was really quiet encouraging.

There are a lot of important things about that, namely the concentrations that you can get in the vagina compared to the concentrations you get in the plasma, really tell you that you're getting a real whopper of an effect locally, but you're not getting any problem of resistance systemically which is sort of the best of all possible worlds.

I would hope that that applies continually to the use of tenofovir, but also for any of the other drugs that are going to go into clinical trial. There were a lot of good things about the presentation that you guys did, but the resistance one ranks up there.

WARD CATES: It sure does. Henry how about combinations?

HENRY GABELNICK: Exactly. As I mentioned, we are working on combinations and have been for some time, using other antiretrovirals so that we can further reduce the likelihood of resistance. I'm confident that this will end up not being a problem.

I do want to add one thing however, before you all go running out and buying more Gilead stock, I mentioned that they have licensed the tenofovir gel for developing world, which is where the HIV is the problem, to the international partnership for microbicides and the Conrad. So they're not going to get any royalties from the sale of tenofovir gel to the people who

need it, and I guess maybe it's just coincidental their stock jumped three points today.

DAN KELLER: Dan Keller, *Medscape*. Two questions. Did you do studies on serum PK's based on frequency of use of the gel – sort of intracortical sorts of things to see if there is accumulation. And second, as I understand it, in this trial these women received monthly intensive counseling and I assume that it included safe sex practices.

From other trials, once techniques moved into the real world situation, are you willing to extrapolate what may be happening in the real world once this does become wide spread? If it becomes wide spread?

SLIM ABDUL KAREEM: So I'll leave Angela to answer the question about steady state after multiple use versus single use because she's the expert in that area. I'll answer your second question in the meantime while she gets up to the microphone.

In a study of this nature, it is a fundamental challenge that you have a women coming into the clinic every month. One of the things that you have to continually emphasize to her is that we do not know if this gel works. We do not know if this gel is safe. That is why we're doing the study. We do not know the answers to those questions, that is why this study is being conducted.

We also spend a lot of time, and we have a separated team doing the HIV risk reduction that is promoting condoms and safer sex. In the midst of all of that we're also telling them, also use the gel. Now you can only give that message so many times before it sinks in. Why am I using this gel when these guys don't even know if it works or if it's safe. I think that's part of the challenge that we see. I think we will see very different behavior and very different gel use outside of the trial setting.

When the message is one that's positive; here's a product that protects at this level. You are now invited to come and use it and acquire it at the local clinic, I think we will see a very different kind of picture and a different kind of effectiveness.

I believe that going forward, research needs to continue to look at proof of – at doing a study that replicates our findings, extends our findings through placebo control trials but in addition we need to be thinking about what are the challenges in implementation. We need to think about those now so that in three or four years, however long it takes to get this product license that we have those answers.

KORISHA ABDUL KAREEM: Can I just add a 30 second editorial to Slim's comment? Which is in thinking about behavioral disinhibition in women, for women where abstinence is not an option, where they are faithful but their partner may

or may not be, and they cannot get their partner to use agree to female condom use or use a male condom, we have nothing else to offer them. So there's no behavioral disinhibition in terms of protecting themselves. I think that's a big difference. This product gives them something versus nothing.

WARD CATES: Thank you. Angela Kashuba [misspelled?] is Director of the pharmacology part of both this project and at UNC Chapel Hill. Angela?

ANGELA KASHUBA: So the answer to the question about whether tenofovir accumulates in plasma with multiple doses can be answered from the Conrad Phase I study that has been presented at a few different meetings in 2008 and 2009 by Jill Schwartz [misspelled?]. In that study the evaluated a single dose of tenofovir and what the plasma concentrations were. Then they compared it to daily dosing for two weeks or twice daily dosing for two weeks.

The concentrations at the end of that two week interval in plasma were really no different then the concentrations after a single dose. The half-life in plasma is relatively short. It's about six hours or so when the gel is used intravaginally. So you would have to use an extensive amount of gel dosed multiple times in a day, likely to see any accumulation. But up to twice a day for two weeks there's no accumulation compared to a single dose.

WARD CATES: For those of you who are wondering, the term tenofovir, is actually southern – southern Canadian because Angela's from Canada for tenofovir. Yes?

HILLARY BEARD: Hi, I'm Hillary Beard representing the media delegation from the Black AIDS Institute and I have a question about your genital herpes result, which I don't know if you'll be able to answer since the results were somewhat unexpected. But we know that genital herpes can also be transmitted externally and so I'm wondering if there's any thought or any hope that it could be applied topically in addition to vaginally to provide additional protection against herpes moving forward.

MALE SPEAKER: I think your opening comment was accurate; I can't answer the question.

WARD CATES: But the good question is the extent to which the finding of protection against genital herpes, or at least HSV-2 infection is something that can be built on a whole different development profile; whether through Gilead or NIH funding or through other mechanisms. Tony, actually when you first heard those results you had certain hypothesis of what might be in fact happening. Do you want to go into those?

TONY FAUCI: It's not going to answer your question but as you know from Slim's results, they were measuring serological conversion to herpes. There are some very interesting data from Larry Corey's [misspelled?] laboratory in

Seattle that even when you treat herpes, once you get it, so you don't have an ulcer, the very fact that you have herpes in a non-ulcerative way actually is associated with an increase of activated T-cells in the submucosal area.

I think that the benefit is even going to be better than what we're hoping it's going to be because you don't necessarily have to have a genital ulcer to have the infection herpes give you an increase in susceptibility to HIV. You just need to have activated T-cells that are hanging around the submucosal area. So I wouldn't – Slim presented that in my conference room before the meeting and I stood up in my chair when he said that; among other things.

WARD CATES: Everybody gives Slim a standing ovation at this. Even Tony in his conference room! Okay, Gus?

GUS: Yes. Two questions, one's just very short. Just to hammer down the herpes thing. So you're saying there was no statistical correlation independent of adherence between the women who were infected with HSV and the women who were infected with HIV? It's not a cause and effect thing, is that right?

SLIM ABDUL KAREEM: I'm trying to understand your question?

GUS: In other words, are we possibly seeing the fate because the gel protects women against HSV; than they don't catch HIV.

SLIM ABDUL KAREEM: Oh okay, that's easy to answer. If you look at the study, 454 women have HSV-2 infection at baseline, so they already have HSV-2. There is protective effect of HSV-2 in that group.

Tenofovir gel protects those women against HIV to a similar extent that it does in those who are HSV-2 negative because any effect on HSV-2 only impacts on half the study and in that half only in half of them because half of the half are getting placebo; the other half are getting tenofovir.

Any impact – and that's one of the problems – well not problem, but one of the challenges in the study I would have liked to have seen some kind of secondary effect of HSV-2 reduction spilling over to HIV reduction. I don't think that it's feasible in the study in the way in which we conducted it.

Now I think a study needs to be designed to answer that question because I can only – I think the potential of tenofovir gel for HIV prevention would not be 39-percent. That's what we just showed. I think there's a whole independent mechanism that is possible that would help boost that.

GUS: That wasn't the question I was actually going to ask. I think – Tony no it was you who said, I think these things will be used very differently in the real world. It's a question about how we should be aiming to regulate, approve and market microbicides.

Should we be going down the route of regulating them as medicines? Or should we be looking at regulating them as soon as possible as things that are at least additionally available as over the counter products. Should we be hastening that in a sense?

One of the reasons I'm asking is because the rectal microbicides people have done studies finding that certain gels have toxicity in themselves and it becomes clear that a lot of gels fall into a kind of regulatory black hole between medicines and the consumer products. So the regulatory landscape is not clear. On the other hand it would be a shame if you could only get these things in the clinic. You'd have doctors deciding whether you could have them or not?

SLIM ABDUL KAREEM: Again I have no understanding of regulatory issues so I can't comment. I'm just intrigued by your options that you're putting on the table.

WARD CATES: Anyone care to comment further? Or just let Gus's comment stand as is? Okay. Next question.

NATIONAL DEBT RADIO: Thank you. National Debt Radio. I understand the gel was applied before and after sex within a time frame of 12 hours or something like that. Now we hear a lot about rape. Would this also work as it is only applied after sex and not before?

KORISHA ABDUL KAREEM: This study tested the dosing regimen and the 39-percent efficacy that we saw was on the back

24 adherence which is before or after. Slim mentioned, and others, that there's room for other dosing strategies.

At the moment, in South Africa for example, for survivors of rape these post-exposure prophylaxis, the one month course that's available, and this could be part of that broader agenda in terms of stratifying the population, in terms of needs, and looking at what niche population needs are and then balancing formulation and doing in relation to those needs.

SLIM ABDUL KAREEM: Perhaps just to add that in the study we did not ask the question if you used it only after would it be as good or better or worse than if you used it both before and after. So we cannot answer your question; but it's an important question and it needs to be addressed.

I think that's part and parcel of the kinds of questions we have to ask going forward. When we first saw these drafts, within the first week I must have written down something like 160 questions because that's what good data do. They make you ask a whole lot of new questions and these are among those that we have to prioritize which are worth answering.

WARD CATES: Thank you. Next question.

JOHN FONGUA: Thank you. I'm John Fongua [misspelled?] a Mexico social counselor in the area of HIV/AIDS prevention among immigrant population in France. I have two short

questions. The first one is what is the difference between the nonoxynol-9 project, which we [inaudible] in Cameroon and tenofovir project. And as a researcher, what kind of communication can we use presently for the women? Thank you.

SLIM ABDUL KAREEM: There's a very big difference between studies done on nonoxynol-9 and studies done on tenofovir. Nonoxynol-9 works on the basis that it was already a licensed product that was available and it was being tested for a new indication.

It was being tested on the basis that it would act by disrupting the viruses. I think it was a bit of a surprise to everybody that it also not only disrupted the virus, but it also had some effect on the vaginal mucosa.

This product has a different mechanism of action. It doesn't work by disrupting cell membranes. We didn't share any of those concerns that we witnessed in the nonoxynol-9 research. Instead, this product has been shown to be safe. Indeed it's being used by hundreds of thousands of patients every day as part of their treatment. We know very well its safety profile. This is a new application of that drug. The second question was what are the communications.

So if you go to any of our three websites; FHI.org, CAPRISA.org, or Conrad, you can download a series of information fact sheets and documentation that provides you with information about all aspects of the study, and you can

use that to make your own materials or you can even use those directly.

WARD CATES: Yes?

DAN KELLER: Dan Keller, *Medscape*. Dr. Kashuba, are there data on absorption into the blood of other drugs applied vaginally? Or do they all behave like this? Second of all, for one of the trialists in this, of the women that did become infected, were they infected with a strain of HIV that was resistant to tenofovir? Or was it mainly based on behavior that you saw these failures?

D**R. KASHUBA:** To address the pharmacology question, yes there are data on other drugs that are applied vaginally. In fact, there are pharmacies that will make vaginal suppositories out of other drugs to try and achieve efficacy. There is a significant degree of variability, however, in which drugs achieve high concentrations in plasma and which drugs don't and it really depends on its structure so it's not easily predicted.

WARD CATES: Question?

SLIM ABDUL KAREEM: Sorry can I can I just answer the resistance question? Within the study we looked at resistance mutations that are known related to tenofovir and we found none. None in the 38 women who used tenofovir but we also found none in the women who were on the placebo gel. We have at this point, just very reassuring information that we do not

have circulating strains of resistant virus that were causing these infections. We now need to understand, so why did they get infected while using tenofovir and that's a whole set of new questions that we need to ask.

WARD CATES: Question? Okay.

BACHA RATA: I'm Bacha Rata from [inaudible] It's maybe a silly question but i want to know what's the difference between the HIV virus for third world country and first world country? Because here it's the same, sex is sex if you are not using the protection, you can get AIDS. Here for example in Austria, there is not too much awareness for sex.

Many people even they don't know whether HIV exists or not. In Africa there are millions; people are infected every day and dying every day. What's the difference between that? And the second things, the researcher, when they find the vaccination or the medicine will they discover also for third world country a vaccination in here? Or the same medicine will protect the HIV? Thank you very much.

WARD CATES: Tony how about viral strains and when we're going to have a vaccine? Viral strains and anything else?

TONY FAUCI: Yes the predominant strain for example, in the United States is a group B and the predominant, particularly in Sub-Sahara in Africa is A and C. So there are different clades or strains if you want to say that. But there

really are no fundamental differences in the pathogenesis of the disease except for the associated diseases that are particularly relevant.

For example, in Africa; in South Africa with the extraordinary burden of tuberculosis; tuberculosis and HIV are really comorbidities of extraordinary correlation. But as a fundamental viral pathogenesis, there is not difference.

When you talk about a vaccine, when we test for vaccines we would hopefully and are, testing vaccines in countries and using the viral clayeds that are relevant to that country. So when we did the trial in Thailand, we had an E and a B and trials that will be done in Africa will almost certainly be C & A.

WARD CATES: Thank you. I have one question for Robert. In your description of the very appropriate pride you take in USAID funding of CAPRISA 004, what are the implications of further funding, not only at USAID for product development of this type, but possibly PEPFAR funds as well being kicked into development of products to at least the scale up implementation science or those types of activities?

ROBERT CLAY: Well as we've heard, this is a real winner in terms of a donor because we do have some very positive results. At USAID we are very committed to see this through. As we've heard, there's lots of questions that remain. There's a lot of data that needs to be analyzed.

There's additional issues in terms of how we roll this out; looking at marketing and the product development.

All of those are sort of next generation questions that come up and we're very committed to work with our partners to make sure that those are addressed. Because our real point in funding this study is not just to have a study that looks nice, but it's really to have the impact in the field.

There will be a meeting in the end of August that USAID will be funding through the WHO. It will bring together key experts to look at next steps. I think that will be very critical meeting of laying out the agenda of how we move forward and we're certainly going to be very active participants in that and we'll be looking at ways that we can help.

WARD CATES: Thank you. Question?

MITCHELL ZOLAR: Mitchell Zolar, *Internal Medicine News*, a two part question. First, Dr. Fauci in your talk this morning you were talking about the initial steps of infection and involving activated T-cells in the submucosal area. Am I correct in thinking that the presumed mechanism of the tenofovir prediction is penetration into that tissue and into those cells and that's what's going on?

TONI FAUCI: That is correct if you'll recall the model I put up. The point that I made, that's a very vulnerable point for the virus but a very important opportunity for

intervention, it that when the virus transcends and goes through the mucosal surface, either hitting a dendritic cell and then going to arresting or an activated T-cell, those cells need to get infected and then produce a virion that infects another cell and then affects another cell. And then when you get the momentum you develop an established infection.

The microbicide in the tenofovir in there is absorbed through the mucosal membrane of the vagina – the mucosal surface as it were, not membrane and when it gets through, I mean we're not there looking at what it's doing but I'm virtually certain that it's essentially putting out those little sparks before a fire gets started.

WARD CATES: What I was wondering is whether the gel vehicle had been selected, designed to optimize that penetration process or is there additional room for improvement there as well?

TONY FAUCI: I think you'd have to ask the people who designed the gel that.

ROBERT CLAY: Well, in actual fact we didn't design the gel; Gilead did but the fact of the matter is, based upon the data that Angela has assembled, it seems like there's not a problem at all petitioning into the epithelium.

WARD CATES: Okay last two questions now?

HUNGAI MACHUROVIA: My name is Hungai Machurovia [misspelled?]. I'd like to know in terms of adherence in the

study, what barriers – if there was a research into what the barriers were to women adhering to using the microbicide because we know full well that there are barriers to women using other devices such as condoms, which include gender-based violence and all sorts of other reasons. So was there a separate social survey to find out what barriers there were to adhering throughout the trials?

KORISHA ABDUL KAREEM: Adherence is really important in the context of antiretroviral pertaining to intervention trials. We knew that and we spent a lot of time as part of preparation for the study and during the study to support adherence, and in how we measured adherence during the study.

We used what was called motivational interviewing. There are two facets of adherence that we support. One is the mechanics of the gel use – unfortunately I didn't bring an applicator with me – but there are component pieces that you need to assemble and insert that into the vagina and dispel the contents in a particular way.

The second part is around the dosing and supporting women for the three components of the dosing. As we prepared women for this, at the pre-enrollment and post enrollment visit we went through very detailed support; at every study visit a different set of study staff worked with each woman to figure out what her obstacles weigh in terms of mechanics or particular components of Vat 24 [misspelled?].

A large number of the women, within a month or so were able to get all of these components right. Some of them had challenges around timing or particular aspects and we created – somebody just passed me a gel. So you see it comes in this wrapper; you've got to open it and all of this.

For each woman; for each study visit we asked her what the facilitators and the barriers to the Vat 24 was and we set goals incrementally where women were having challenges to meet it. So we don't expect women to do everything right away. A lot of the women were able to do that but then as things changed over time, during the study we were receptive, we heard we supported in different stages for women and as a cohort as a whole.

WARD CATES: And actually, there's been an additional ancillary study that my colleague down here in front is doing, a case control study of women who get infected a long with a series of matched controls to actually dig deeper into reasons and effects of what happened around the time of infection will be – provide some very rich data therein.

Last question; quick question, quick answer?

HILLARY BEARD: Yes can you characterize the nature of the gel for me please? What does it look like? What does it smell like? What's the touch, feel? How does it taste? Take me through the five senses.

KORISHA ABDUL KAREEM: Come right over.

WARD CATES: Uh oh.

KORISHA ABDUL KAREEM: It's right here.

SLIM ABDUL KAREEM: If you've ever seen KY jelly or Astro Glide. If you've seen those, it looks exactly. It's clear, it's colorless, it's odorless. It's almost tasteless and you can squirt some on your hand and look at it. It's mostly water.

WARD CATES: It's almost like a hand purifier, so it's getting to be a best seller right now [laughter]. Alright. Okay. Well let me just say thank you so much to the panelists. You guys were great and really answered a lot of questions. The questions themselves covered the spectrum of issues regarding this remarkable trial and we'll plow on. Thanks again [applause].

[END RECORDING]