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**Safety and Effectiveness of 1% Tenofovir Vaginal Microbicide
Gel in South African Women: Results of the CAPRISA 004 Trial
Kaiser Family Foundation
July 20, 2010**

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GITA RAMJEE: Welcome to this very important session on the results of the CAPRISA 004 Trial. I would like to thank [inaudible] from WHO for putting this session together. I'm Gita Ramjee from the HIV Prevention Research Unit of the South African Medical Research Council and I'm absolutely delighted to co-chair this session with Tim Farley from WHO.

As someone who has been working on multiple clinical trials of microbicides in South Africa for over a decade, these ground breaking results from CAPRISA 004 means a lot to me personally and gives hope to thousands of women in South Africa and elsewhere who have committed to microbicide research in the past and continue to do in the future. Today, we celebrate the proof of concept of microbicides. [Applause]. Thank you.

Without further a due, I would like to introduce the first speaker, Professor Quarraisha Abdool Karim. Quarraisha is an infectious disease epidemiologist whose current research interests are in understanding the evolving HIV epidemic in South Africa. She's also an Associate Professor of Health and the Associate Scientific Director of CAPRISA. She is also the co-chair of the HIV Prevention Trials Network funded by the NIH. Quarraisha.

QUARRAISHA ABDOOL KARIM: Thank you very much, Gita, for that very warm introduction. Distinguished guests, in particular I'd like to recognize the honorable Minister of

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Health from South Africa Dr. Aaron Motsoaledi, [applause], the honorable Premier of the province of KwaZulu-Natal Dr. Zweli Mkhize, Dr. Zena Stein, [applause] and all of the gender activists and scientists that have been part of this process of trying to find a method to protect women. [Applause].

It is indeed a great honor and privilege on behalf of the CAPRISA 004 Team for Salim and myself to present the data from the effectiveness and safety of vaginal microbicide 1-percent Tenofovir Gel for the prevention of HIV infections in women. If any of you need reminding of the HIV epidemic particularly in Southern Africa, I'd like to share this slide from you from the prevalence of HIV infection in pregnant women in rural Venenschwela [misspelled?], which is one of the clinical sites for this particular trial.

By age 16, one in 10 women is already infected with HIV. By age 18, that's one in five. By age 20, that's one in three. By the time these young women are 24, it is one in two. By 1990, Dr. Zena Stein [applause] published this paper in the American Journal of Public Health drawing attention to the need for methods for women and it was an important catalyst to draw attention to the issue of the lack of protection for women and catalyzed a whole generation of studies around six candidate microbicide trials to date across 11 trials over a period of 15 years.

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I'm going to switch now to the CAPRISA 004 Trial and share with you why did we choose Tenofovir Gel and there were several reasons for that. We had extensive experience with use of Tenofovir as an effective therapeutic agent. In that context, it had a very good safety profile and that's important when we want to use a prophylaxis agent in uninfected agent. It had already been proven for preventing mother to child transmission of HIV.

The gel formulation is very rapidly absorbed and has a long half life. In addition, it has very low systemic absorption and therefore we expect fewer side effects, as evidence from monkey studies that it protects against transmission with Simian Immunodeficiency virus. The purpose of the CAPRISA 004 Trial was to assess the safety and effective of 1-percent Tenofovir gel.

The dosing regimen that was used the acronym for that is the BAC24 [misspelled?] regimen and it's sequentially related gel use dosing regimen. It comprises the insertion of one gel up to 12 hours before sex, a second gel as soon as possible but within 12 hours after sex and no more than two doses in a 24 hour period based on existing safety data at that point in time.

The inspiration for this scientific concept came from the proven HIVNET 012 Nevirapine Study where infected mothers were giving one dose of Nevirapine at onset of labor and the

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infant 72 hours postpartum and that demonstrated at 41-percent reduction in transmission from infected mothers to infants. In CAPRISA 004, the Tenofovir gel regiment, we advised women to use the gel 12 hours before sex and as soon as possible after sex, not more than 12 hours and not more than two gels in a 24 hour period.

It's a proof of concept, double blinded, randomized placebo control trial. We enrolled high-risk HIV infected women reporting two coital acts in the past 30 days and these are known high-risk populations from pretrial feasibility studies that we conducted at the two clinical sites. It's an endpoint trial with 92 HIV endpoints. HIV infections serve both as a primary safety and effectiveness endpoint.

HIV uninfected people were defined by two negative rapid HIV tests and the endpoint was determined by using polyamours [misspelled?] chain reaction positivity in two separate blood specimens. All HIV positive endpoints were confirmed using western blot and the analysis that I will present to you is based on an intent to treat analysis except for the adherence analysis.

Here's a visual of the rural and urban CAPRISA clinical sites where this trial was conducted and in terms of ethics and regulation approvals, informed consent, the process that we utilized for informed consent was informed by community consultation and engagement prior to trial initiation. The

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informed consent process involved multiple steps. Initially, volunteers were provided with a general information session where they were shown the gel, the applicator, they were reminded about key concepts in clinical trials and what obligations and rights of research participants are. If they decided to proceed with volunteering in the study, we assessed as part of the second step the language choice, literacy levels and cognitive ability for autonomous decision making.

On completion of the consent process, a comprehension quiz was administered that unscored knowledge of study goal, trial concepts, obligations and rights as research participants and if the participants or volunteers met those criteria we then proceeded with study procedures. The study was conducted under the ethics, guidance and oversight of the University of KwaZulu-Natal Biomedical Research Ethics Committee as well as the Protection for Human Subjects Committee of Family Health International. Regulatory oversight was by the South African Medicines Control Counsel and we had an internal protocol safety review meeting bi-monthly and an independent data safety and monitoring board that looked at the data independent of the study team.

Over the course of screening and we screened a total of 2,160 women and enrolled and randomized 1,085 women. The main reason why volunteers were excluded from the study was HIV positivity and other reasons included not meeting eligibility

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criteria in terms of inclusion and exclusion criteria set for the study. I want to highlight these 196 participants who have been excluded and I will talk more about these participants as I present the sensitivity analysis.

There were 135 corn rowed participants. There were 50 participants in another study less than one year ago. We had one participant who was less than 18 years of age making her ineligible. Then we had eight preexisting HIV infections and we had two participants we had no follow-up data following enrollment, so in total we had 889 legibly enrolled participants in the study and 611 at the rural site, 278 at the urban site.

Now, I will present data, not by sight, but in terms of the cohort of the study. Of the 889 enrolled participants, 445 were in the Tenofovir gel, 444 in the placebo, 15 we lost to follow-up in the Tenofovir AIDS were terminated early, 10 lost to follow up in the placebo, 12 terminated early, one died. For 422 women in the Tenofovir completed the trial and 421 in the placebo. We had an overall retention rate of 94.8-percent.

I'm just going to highlight a couple of characteristics in terms of the comparability of the study arms at baseline in relations to such selected sexual behavior characteristics. What you see is good balance in terms of mean age of sexual debut, number of sexual partners, frequency and practice of anal sex. I want to flag the practice of anal sex being very

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low and pretrial cohort data indentifying this particular characteristic and because we are testing vaginal use of 1-percent Tenofovir gel, it was one of the criteria we used in terms of site selection. Coital frequency in the past month was 8.6 and about the same reported condom use across both arms.

In terms of assessing the effectiveness of the gel in preventing HIV infection, we had a total of 98 HIV infections, 38 in the Tenofovir gel arm, 60 in the placebo arm translating to an HIV incidence of 5.6 in the Tenofovir per 100 women years and 9.1 in the placebo arm yielding an incidence rate ratio of .61, p-value.017. Another way of looking at this is a 39-percent lower incidence rate in the Tenofovir gel groups. [Applause].

Now, we look at the data over time and this was a 30 month study. I want to start by highlighting that after 12 months of gel use. We had 65 endpoints, 50-percent effectiveness, a p-value of .007. In other words, we could've stopped the study at this stage and have had a statistically significant result of 50-percent protection. But as this was an endpoint of the trial, we continued to our projected 92 endpoints and I'm going to share with you now the data and effectiveness over six months of participation in the study, 12 months, 18, 24 and 30 months.

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At six months, we observed a 47-percent effectiveness, p-value of .069. After 12 months of follow-up, we had a 50-percent reduction in HIV infection, p-value.007. At 18 months, this was 47-percent, p-value .004. At 24 months, 40-percent effectiveness, p-value .013. At 30 months, 39-percent reduction, p-value .017. In other words, beyond 12 months every estimate we have here is statistically significant.

Why the diminishing effectiveness over time? Some clues may lie here in terms of how we measure adherence. We adherence in multiple ways and we also asked women to return all the used and unused applicators. Of all of the applicators dispensed, more than 95-percent were returned either used or unused providing us with a robust measure to translate use of gel in relation to coital activity.

In the blue line, we have returned gel use, return gel applicators, sorry, in HIV uninfected women. In the red line, we have returned gel applicators who became infected during the study. What's of note here is that up to 12 months of study participation what we say was more returned applicators being used in the group who eventually became positive, but then overtime what we see is a decline indicating lower use of gel beyond 12 months of study participation. In comparison to the more constant gel use in those women who were uninfected.

This is a non-ITT analysis and I said I will present this and that's why I don't have any p-values displayed in this

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particular table. I'm going to share with you the impact of adherence on effectiveness of Tenofovir gel, so we took the used applicators and used that to correlate two used applicators translates to the back24 message. If you took women who participated in the study over the study duration and we found that more than 80-percent adherence to the back24 regimen yielded a 54-percent protective effect, which was statistically significant. The intermediate adherence it was 50 to 80-percent correlation in relation to back24 adherence and coital activity demonstrated at 38-percent protection. Amongst lower adherers, this was 28-percent.

I'm going to spend the next few minutes going through the sensitivity analysis and before I do that I just want to share with you how all of the HIV infections – the total number of infections in the study was 119. Up to now, I have presented to you the data on the 98 protocol defined endpoints and that was the 96 infections during study follow-up and exit. Then we did a safety visit two months after the study exit to try and identify or verify that there wasn't any mass infections potentially in women who were in the Tenofovir gel arm.

What we established was that there were two infections in the post study exit visit that actually were infections at the study exit, so those are the two that I included there. We had one participant who did not meet the protocol definition of

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HIV infection. She had one PCR not the second. Then we had the five post study HIV infection that were truly post study infections. We had eight infections during the window period. We had two infections in that 185 women who were ineligibly enrolled, two in the window period, five during the study, a total of seven.

If we analyze the data in different ways taking these populations whether we include them or exclude them, primary outcome again 39-percent, .017. If we add the women who didn't have the second PCI, we have an effectiveness of 37-percent, p .023. If we use the purple protocol population in there is 85, we have a 41-percent effectiveness, p .017. If we included the ineligibly enrolled women that will be the 98 infections plus 5 giving us a total of 103 infections, we have 38-percent effectiveness, p-value .015. If we include all of the post trial infections 98, plus 5, 103, 41-percent effectiveness, p-value .015. All HIV infections, all 119, didn't matter whether they met the protocol definition when they happened, we have a 45-percent effectiveness, p-value .003. In short, whichever way you analyze this data, we have a range of protection between 37-percent to 45-percent and each of these analyses yields a statistically significant result. [Applause].

If you look at the impact of Tenofovir gel on initial HIV viral load in seroconverters it's an important predictor of

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disease progression post infection. What we see is no different between the Tenofovir arm and the placebo arm.

All of the data that I have presented today is available in greater detail in Science Express online. That's available at no cost if you want to read more details about this. And I know hand over to Salim to talk about Herpes Simplex V Type 2 virus. [Applause].

SALIM ABDOOL KARIM: [Applause]. Thank you very much, Quarraisha. Like all good husbands, I follow after her. [Applause]. It's my great pleasure to share with you one of the additional analyses that we undertook as part of our ancillary analyses to look at the impact of Tenofovir gel on Herpes Simplex Virus Type 2 infection.

Just by way of introduction, we are well aware that HSV-2 infection is ubiquitous and very common. It is estimated by WHO that globally about 20-percent of sexually active adults have HSV-2 infections. We know certainly from South African data that 50 to 60-percent of sexually active adults have HSV-2 infection. Certainly, within the HIV positive population, we see incredibly high rates of HSV-2 at 80 to 90-percent. We also are aware that those that have HSV-2 infection have twice the probability of acquiring HIV.

HSV-2 is the commonest cause of genital ulcer disease and it is also largely asymptomatic in women. Most women who are questions about whether they had recall symptoms related to

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genital infection in those who are HSV-2 positive have no such recollection. We also have known therapies for HSV-2, but these work by suppressing viral replication. They do not prevent or cure HSV-2.

The reason we choose to look at HSV-2 for Tenofovir was we are well aware that Tenofovir comes from a common precursor molecule known as HPMPA. This precursor molecule is the fundamental building block of three drugs that are developed by Gilead Sciences, Cidofovir, Adefovir and Tenofovir. We know that Cidofovir is licensed and used in the treatment of HSV-2 infection. Adefovir is used and is licensed for the treatment of Hepatitis B and HIV and Viread or Tenofovir is also licensed for the use against HIV, so we wanted to see whether the fact that its sister drug had this effect on HSV-2 was there any effect of HSV-2 from Tenofovir gel.

The purpose is to look at the impact of quietly related to Noprov gel [misspelled?] on HSV-2 acquisition in high risk women in South Africa. This study was done so that we looked at start samples at the end of the study, so for every woman we took their enrollment sample and their exit sample and tested it using an HSV-2 elixir that is known to have good sensitivity and specificity in the African context.

You recall that Quarraisha's presentation we had 889 eligibly enrolled women. Of those, 454 were HSV-2 positive at entry into the study and we had one missing sample at baseline,

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so that left us with 434 women who were at risk of acquiring HSV-2. Now, if you look at this trial I am presenting it is about just under half of the study population that was involved in the HIV trial. Of these 434 women, 208 were in the Tenofovir arm, 226 in the placebo arm.

At the end of the study, 202 of the 208 completed the study. We had three missing samples and we had three equivocal results. Just to explain when you do an elixir for HSV-2 there is a threshold for positivity and there's a threshold for negativity. Unfortunately, you do get occasional samples that fall in-between those thresholds and so we call those equivocal. I will represent a sensitivity analysis on how we deal with the equivocal. Of the 226 in the placebo arm, we had one missing, one equivocal result and 224 that completed the study.

Here's the study outcome, so in the 202 women who used Tenofovir gel, we saw 29 HSV-2 infections giving an incidence rate of 9.9 per 100 women used. In the placebo gel arm, of the 224 women who used placebo gel, we saw twice as many HSV-2 infections, 58 in all, giving us an incidence rate of 20.2 per 100 women used. We saw an incidence rate ratio of 0.49, p-value 0.003. In short, 51-percent protection against HSV-2 by Tenofovir gel. [Applause].

Let me briefly present a sensitivity analysis. The initial analysis I presented to you with the 87 HSV-2

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endpoints, excludes those with indeterminate or equivocal results. Remember we had four people with equivocal results. Of the 426 participants, if we analyzed these 426 and their 87 infections, we get the 51-percent protective effect with a p-value of 0.003 that I just presented. If we regard all the equivocal as being HSV-2 negative, then we still have 87 infections, but we now have 430 women and so we have a 52-percent protective effect, p-value 0.002.

If we treated the four indeterminate as if they were all HSV-2 positives that means we now have the 87 plus those 4, we now have 91 HSV-2 infections and those 91 infections occur in 430 women giving us an effectiveness of 47-percent, p-value 0.006. If we adjust for every known confounder we could look at within our data set, we get an overall effectiveness adjust of 47-percent, p-value 0.005. In short, the different approaches we've taken to analyze this data still give us overall an effectiveness that ranges from 47 to 52-percent.

I want to just end off with a short summary of the safety findings. I would be here all day if I had to present the details of the safety data. We looked at Tenofovir resistance using standard genotyping assays that are used for people that are failing therapy. In the women, both in the Tenofovir and in the placebo arm, we found no evidence of Tenofovir resistance in these women. We found no evidence of K65R, K70E or the tams. We did see some polymorphisms and

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resistance to Nevirapine but nothing related to Tenofovir. One of the big concerns that has been raised of resistance, we did not find evidence of that within this trial.

We saw no increase in the overall rate of side effects. We did however see a small increase in mild diarrhea, 17-percent of women in the Tenofovir gel arm reported mild diarrhea self limiting with no therapy, 11-percent in the placebo gel arm giving us a p-value of 0.015. We saw no renal toxicity though it must be noted we excluded women with preexisting renal conditions. We had 54 pregnancies in 53 women. We saw no signals or any safety concerns in that group. The 31 babies born during the study had no congenital abnormalities. We saw no liver side effects or no increase in hepatic flares in the 34 women who had Hepatitis B infections within this trial.

Lastly, when we looked at trends for condom use over the period of the study, we saw no deterioration in condom use. We also asked women at the end of the study if they knew which gel they were on and about 19.5-percent said that they thought they were on Tenofovir gel. When we looked at the actual allocation exactly 50-percent of them were actually on placebo, so we know the blinding worked. In that group of women who thought they were getting Tenofovir gel, we looked at whether they showed any evidence of deteriorating use of existing

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proven technologies for prevention like condom use, partner change rates, we saw no evidence of that.

In summary, the CAPRISA 004 findings, we show no substantial safety concerns, no Tenofovir resistance. We found safety in the Hepatitis B infected women and we saw no evidence of risk compensation of behavioral disinhibition. We've shown a 51-percent reduction in HSV-2. We've shown a 39-percent protection against HIV overall and a 50-percent protection in HIV after one year of Tenofovir gel use. In women with high adherence, we show 54-percent effectiveness.

I want to conclude with just four points. First, we all recognize and understand the importance of women and particularly young women bearing the brunt of the HIV epidemic in Africa. Tenofovir gel potential adds a new approach to HIV prevention as the first that can be used and controlled by women. It can help empower women to take control of their own risk of HIV prevention. We take the view that CAPRISA 004 Study is the first step.

Additional studies are urgently needed to confirm and indeed to extend the findings of this trial both for safety and effectiveness. Once confirmed and implemented, Tenofovir gel has the potential to alter the course of the HIV epidemic. Mathematical models show and provide estimates that if we could implement Tenofovir gel in a way similar to the way in which we did it in the trial. We could prevent 1.3 million new HIV

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infections and over 800,000 deaths over the next 20 years in South Africa alone.

I'd like to end off with an acknowledgement to our funders U.S.AID and the South African Department of Science and Technology for their very generous support, to the Minister of Health I want to say a big thank you and particularly I want to thank our premier of our province Zweli Mkhize who really was the inspiration together with his wife for much of our work and indeed he served on the CAPRISA Scientific Advisory Board when we made the decision to proceed with the study. My thanks to Conrad and to Guillard Sciences for providing the gel and for all their wonderful support and to FHI for their incredible support and continued technical assistance.

There are many, many people involved in a study of this magnitude and you can imagine the infrastructure that it takes and all the contributors to that, but really the heroes of this study are not the two of us. We are merely the messengers. It is the big research team that undertook the study, but most importantly this study is really there because of the dedication and commitment to the study participants who made this possible. Thank you. [Applause].

GITA RAMJEE: Thank you very much. I know you'd like to keep on standing, but in the interest of time we have to continue. I'd like to thank Salim and Quarraisha for their wonderful and very comprehensive prevention of the results. We

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have time for three questions on just clarification and later we'll have time for discussion, so we'll take three questions all at once and then Salim or Quarraisha will address them and please introduce yourself.

GU.S. CAIRNS: Mic isn't working, oh, yes it is. Gus Cairns, AIDS Map. Was there an overlap between the women who seroconverted to HSV-2 and the ones who seroconverted to HIV? Is there a reinforcement thing going on here?

GITA RAMJEE: Okay. Second question.

MALITA AUDINSOR: Malita Audinsor [misspelled?], South Africa with [inaudible]. Just one around condoms, were women encouraged to use condoms or not during this trial and is there a split between rural and urban in terms of placebo, with Tenofovir? And then, of course, the results in terms of HIV positivity as well in the same split versus rural and urban? Just to ask around biases do you know what split of women were married versus multiple and single partners? Then also the age ranges would be interesting [laughter] to know.

GITA RAMJEE: That's a lot of questions.

MALITA AUDINSOR: But it is - sorry [inaudible].

GITA RAMJEE: Thank you. We'll take the last question.

ARDIS MOE: Ardis Moe from UCLA. Was there any information on the partners of the women and whether or not they understood whether or not the women who were on placebo versus real drug?

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GITA RAMJEE: Okay. Salim or Quarraisha.

SALIM ABDOOL KARIM: I'll take the first one, so let me answer Gus's question, so we looked at that issue in great detail. You must remember that the effect of Tenofovir gel on HIV is independent of its effect on HSV-2. In other words, in those women who are HSV-2 positive, we see the protective effect of Tenofovir gel. In those women who are HSV-2 negative, similarly we see the protective effect of Tenofovir gel. If we adjust for HSV-2 status, the effectiveness of Tenofovir gel remains 38-percent statistically significant.

If we look at the real question I think Gus is asking is in those 87 women who became HSV-2 infection, what effect did we see of HIV incidence in that group? The challenges of those numbers are too small. We have a very small number of infections and so you can't really analyze that group, so all we can do is adjust for it and show that it does not account, HSV-2 does not account, for the Tenofovir effect on HIV.

We looked at the reverse, so does HIV influence the effect of Tenofovir on HSV-2? That analysis shows us at this point because we have eliminated number of HIV positive individuals, remember that we don't enroll HIV positive individuals, and if we look at the HIV negative individuals and those who became infected, we see no interaction term. In other words, when you look at Tenofovir, it has two independent mechanisms. One as an anti-retroviral drug impacting direction

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on HIV. Secondly, as a drug that's impacting on HSV-2, thereby in the long term will lower the overall prevalence of HSV02 and therefore lead to a lower risk of HIV in the long-term. Our study was not designed to assess that.

QUARRAISHA ABDOOL KARIM: In the interest of time, I didn't provide detailed information on study procedures that we followed in the study. Each woman enrolled in the study had a monthly visit. During that monthly visit, she had pregnancy testing, HIV testing and because this is a safety study of an experimental drug we also had clinical assessments. Because it was an experimental drug and we didn't know whether it worked, every month women received very intensive and independent counseling on HIV risk reduction. They were provided with condoms, both male and female, and they were advised each month we don't know whether this works please use a condom. This could partially also explain some of the diminishing effect that we saw with time in the study.

This study was not powered for analysis by site, but we do have balance in both sides in terms of randomization and overall we had balance and comparability between the sites in terms of the arms women we randomized too. There was a question on acceptability and partner acceptability, we administered a very detailed questionnaire at study exit to try and get some objective feedback on acceptability and influences

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of gel use both in arms of the woman, the dosage strategy, partner, community and peer norms.

Just in terms of partners about 68-percent of the women reported the partner being aware that she used a condom, sorry, that she used the gel. We didn't have partners objecting to the use of gel and there's a lot of data around that that we can share, perhaps, in the symposium later.

SALIM ABDOOL KARIM: And, perhaps, just make the point that if you look at the science paper there's an email address. If you have questions on the paper or any of the data we've presented, please feel free to email us and we'd be happy to respond.

TIM FARLEY: Thank you very much Salim and Quarraisha. I'm sorry that we have to cut the discussion short, but we have another very important presentation from Angela Kashuba. Angela is Associate Professor at the University of North Carolina at Chapel Hill and the Director of the UNC Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core. Her research focus is in anti-retroviral pharmacology as it applies to prevention of HIV transmission and she will be telling us about this aspects of the results of the CAPRISA 004 trial. Angela, over to you.

ANGELA KU.S.HBA: Thank you very much. It is my honor and privilege to be presenting the results of this study for the CAPRISA 004 study team. The objectives of this

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pharmacology study were to quantify Tenofovir concentrations in cervical-vaginal fluid and in vaginal and cervical tissue to first of all determine if Tenofovir exposure can predict HIV seroconversion and to determine what the variability was in drug exposure with coitally dependent dosing.

Also, because it's the intracellular Tenofovir diphosphate that is the active form for the drug, we wanted to quantify this in vaginal and cervical tissue to determine the extent of exposure and also to determine whether there was a predictable relationship between Tenofovir and it's diphosphate in these tissue. Finally, because of the results of the HSV-2 analysis, we wanted to if Tenofovir cervical-vaginal fluid concentrations can predict HSV-2 seroconversion.

Here are the number of subjects and samples analyzed for the HIV infection analysis. Out of the 98 women who were infected, we obtained samples from 37 women who were on the Tenofovir gel and from 13 women on placebo. In the women who were uninfected, we received samples from 24 who were on the Tenofovir gel and 16 who were on placebo. For the HSV-2 analysis, in the women who were infected with HIV and those who were using Tenofovir gel, we received samples from five who became HSV-2 positive and six who remained HSV-2 negative. In those women who were not infected by HIV, but using the gel, we received samples from 12 women who became HSV-2 positive and 74 who remained HSV-2 negative.

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All samples were analyzed by sensitive LCMSMS methods. These methods quantified simultaneously, Tenofovir and Tenofovir diphosphate using deuterated internal standards. The lower limit of quantization for Tenofovir in plasma was .25 nanograms per mil. In cervical-vaginal fluid, it was two nanograms per mil and in tissue it was one nanogram per biopsy. The lower limit of quantization for Tenofovir diphosphate was five femtamils [misspelled?] per biopsy.

These methods were very accurate and very precise. For the pharmacokinetic analysis, samples that were below our limit of quantization but were still detected, they were set to 50-percent the lower limit of quantization of the assay and then samples that were below the limit of detection where we saw no drug at all, they were set to zero nanograms per mil. All of the data are reported as median in range.

Here are the results for blood plasma. For women on Tenofovir gel, the concentrations can be seen on the left-hand portion of the slide in these two columns and for placebo in this column. Tenofovir concentrations on the y-axis range here from zero to one nanogram per mil. For those women who were on the gel and became positive, the median concentration was zero, with a range of zero to 0.1. For those who remained HIV negative, the median concentration was 0.1 with a range of zero to 0.8. There were no women on placebo who had detectable Tenofovir in their plasma. These low concentrations are in

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keeping with the observations for adverse events, for HIV RNA and for resistance.

Evaluated another way, the proportion of women who had detectable concentrations in their plasma and became HIV positive was 12-percent and those who remained HIV negative was 50-percent. Now, these samples were obtained a median of four to six days after the last dose of gel, so these concentrations might seem a bit high for measure them between four and six days after gel, but they're in keeping with the dwell time of Tenofovir and cervical-vaginal fluid.

This is the analysis that we performed on an additional 250 samples from 172 highly adherent women in 004 who remained HIV negative. The composite profiles are here and whether you look at mean value in pink or median value in green you see a half-life of about two days. Over the first few days after dosing, most of the concentrations are above 1,000 nanograms per mil.

Here's the CBF analysis for Tenofovir concentrations. In the women on Tenofovir gel who became HIV positive, their median concentration was a nanogram per mil and it ranged from zero to 300,000. In HIV negative women, the median concentration was 520 and it ranged from zero to 1.3 million. This is about the concentration of the gel itself. In placebo, most of the women did not have detectable cervical-vaginal fluid concentrations except for two which were approximately four

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nanograms per mil. In one of these women, we do have data on when she instilled the gel and it was two days before, so based on the slide that I previously showed you it is highly unlikely that this woman was actually using Tenofovir gel. It could be more likely that this woman had a partner who was on Tenofovir because we have previously seen that Tenofovir concentrates in seminal fluid, but this is strictly speculation and are investigating these women more carefully to understand if this was a consistent exposure.

Evaluated different the proportion of women with detectable concentration sin cervical-vaginal fluid for those who became HIV positive was 45-percent versus 96 percent for those who remained HIV negative. These samples were obtained a median of four to five days after gel use and these concentrations are in keeping with the previous slide that I showed you.

Now, we did an analysis just on these concentrations here of women who are on Tenofovir gel who became HIV positive and who remained HIV negative. This is the relationship that we see. On the y-axis is percent infected and on the x-axis is concentration of Tenofovir in cervical-vaginal fluid. We have grouped these women according to their log concentrations. Total number of women can be seen in the shaded bar and the number of infected women in each of these groups can be seen below. Although, the numbers get small the higher the

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concentration in cervical-vaginal fluid, you can see a fairly compelling relationship between cervical vaginal fluid concentrations and percent infected.

In the women who became infected, we also obtained Tenofovir diphosphate and Tenofovir concentrations in cervical and vaginal tissue biopsies. On the left-hand side of the slide, you can see Tenofovir concentration on the x-axis and Tenofovir diphosphate on the y-axis. Whether you look at vaginal tissues in pink or cervical tissue in green, you can see a fairly linear relationship between the two. We think this is important because it's the first time that anyone has evaluated what the extracellular concentrations look like relative to the intracellular concentrations. Now, that we have this relationship, we can more easily calculate dosing once we know what the target concentration is for efficacy, for protection.

If you compare vaginal tissue concentrations in this graph on the x-axis to cervical tissue concentrations on the y, whether you look at Tenofovir in the light blue or Tenofovir diphosphate in the darker blue, we also see a linear relationship between the two. This becomes important because this suggests that wherever you sample in the female genital tract you can get an understanding of what the entire genital tract is seeing and this will be helpful from ucosial pk studies moving forward in the future.

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Finally, here is the correlation between Tenofovir cervical-vaginal fluid concentrations and HSV-2 infection. Again, percent infected with HSV-2 is on the y-axis and Tenofovir concentration is on the x-axis, total number of women is in the shaded bar and number infected is below. You can also see a relationship between lower percent infected with HSV-2 and increasing concentrations of Tenofovir.

In early development, Tenofovir was thought not to be potent against HSV-2 because of its in vitro EC50 of 240 micromolar or 10,000 nanograms per mil. This concentration is difficult to achieve taking a drug orally but is very easy to achieve taking a drug topically. If we compare those women who had concentrations less than 10,000 nanograms per mil to those that had concentrations greater than 10,000 nanograms per mil, you can see 24-percent infection in this group and 6-percent infection in this group and this was statistically significant.

In summary, in women using Tenofovir gel, they had very low systemic exposure and that was also associated with the limited AEs that we're seeing, no attenuation of HIV replication and no plasma HIV resistance. More HIV negative women had detectable blood plasma concentrations at 50-percent versus 12-percent and this is likely a surrogate for adherence.

Tenofovir concentrations in cervical-vaginal fluid ranged from zero to 1.3 million. More HIV negative women had detectable CBF concentrations at 96-percent compared to 45-

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percent and higher cervical-vaginal fluid concentrations of Tenofovir were associated with lower HIV seroconversions and lower HSV-2 seroconversion, so taken together I think these data suggest that CBF concentrations are a promising marker for adherence and also a potential means to determine target concentrations of protection.

Finally, in cervical and vaginal tissues, there was a linear relationship within and between Tenofovir and Tenofovir diphosphate which will definitely help inform sampling strategies for future trials. I'd like in particular to thank the sincere generosity of the women in 004 who donated their samples, the extraordinary efforts the 004 study team went to collecting these samples and also two individuals in the UNC Center of AIDS Research Clinical Pharmacology and Analytics Chemistry Core, Eric Kraft and Nicole White, who had the monumental tasks of developing these very complex analytics methods and perfecting them over the past two years. Thank you. [Applause].

TIM FARLEY: Thank you. Thank you very much, Angela, for those very interesting data. I must say I'm absolutely fascinated by the precision and the quality of the analytic chemistry. We have time for just a few questions of a technical nature for Angela, questions for clarification. If you'd like to come to the microphones and identify yourself please, microphone number four.

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MARK MILANO: Hi, Mark Milano from New York. It seems that the real barrier to adherence in the trial was a requirement to use the gel 12 hours before sex, pretty difficult to determine if you're going to have sex 12 hours from now or not. Did you look at whether you can achieve an acceptable concentration with a lower time? Are there studies planned to see if you can apply the gel an hour or a half hour before sex and still achieve a concentration that's going to be effective? That seems to be a pretty critical need if the gel is going to be used in the future.

TIM FARLEY: Very good. Okay. I think we have another question. Do we have another question? That's good. Angela, please, would you like to address that question?

ANGELA KU.S.HBA: Sure. So, first of all, the study instructed women to take the gel within 12 hours, so it didn't have to be 12 hours before, it could've potentially been right before, but your point is well taken. How long does it take the cells within the mucosal tissue to phosphorylate Tenofovir to an extent that's protective and we actually don't have those data yet.

TIM FARLEY: Thank you very much. In order to introduce some more general discussion and put this in context I'd like to invite Sheena McCormack who is a Clinical Epidemiologist coordinating HIV prevention trials at the Medical Research Counsel Clinical Trials Unit working

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apparently on vaccine trials and microbicide trials. She was the co-pi of the MDT program, MDP 301 Trial, that looked at the safety and effectiveness of pro2000. Sheena will introduce some of the context of the trial and then I hope we can have just a few minutes for a more general discussion. Sheena, over to you.

GITA RAMJEE: And, Tim, four minutes, we're saying

TIM FARLEY: Four minutes, alright, four minutes.

SHEENA MCCORMAK: So thank you very much to the organizing committee for the opportunity to speak on this very auspicious occasion. I'm going to go straight to a table that's adapted from a paper that Nancy Paty [misspelled?] and Julie Wassonite [misspelled?] and co-authors published on AIDS earlier this year and I strongly recommend that you read that paper because it gives you a more thorough review than I can give you today, but you'll see in the column down the side here the categories of the different interventions that have gone into randomized control trials to see if we could prevent transmission, horizontal transmission. This doesn't include the mother to child transmission.

You'll see here a very small number of trials for which we have a statistically significant benefit. The authors go into the details of why we have no effect here. It's not always no evidence of benefit, but overall the picture is a

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disappointing one. So, yes, it is exciting and you all felt that in the room today.

It is proof of concept for ARV prophylactics as well as proof of concept for microbicides. It actually is slim alluded to proof of concept for prevention of HSV-2 as well. But is it sufficient evidence to roll each out globally? Well, let's have a look at the estimates and the confidence intervals for those positive results.

Along the bottom here of the chart not to 100, just to explain that 100-percent means that there was no infection, no seroconversions in the intervention group and that there were approximately the expected number of seroconversions in your placebo group that you expected when you panned your study sample. The not percent means that the numbers in both groups were approximately the same.

I'll go straight to the three circumcisions trials which is sitting here in the middle and you'll see there that all of them are reporting over a 50-percent protection, so that means if they are 50 infections in the intervention group, you've got 25 in the placebo group, approximately, a 50-percent reduction. Importantly, the lower bound, the 95-percent confidence interval, which is down here at the end of the line that line is telling you approximately where your study thinks the true benefit is and the lower bound of that line is well clear of no benefit. It's really suggesting a very important

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benefit, so it's no surprise that circumcision efforts are being made to rule out circumcision.

Here we have the vaccine trial which I have to say did produce a warm glow in the vaccine research arena, but I think with CAPRISA we're talking a little bit more about a hot flush [laughter] because we're just a little bit further clear of chance being the possible explanation and it makes a lot of sense. You've got the greater protection that you see in the more adherent users. You've got that protection against HSV-2. The constituency that you saw across the analysis over time and over whether or not you included all the women who had seroconversion in the currently enrollment group, etcetera. It's also very consistent with the fact that ARVs do very effectively prevent mother to child transmission.

The data that Angela has shown you and also from other studies that comrade Joe Schwartz has produced showing this very high level of drug in the genital tissues that correlation with the clinical data that Angela showed you, it's very compelling. Then the intermittent McCart [misspelled?] studies that CDC have run Malit [misspelled?] and the group there are also very supportive, particularly because they have PK2 which correlates with the protection in the McCart model.

The limitations are that lower bound around the 95-percent confidence interval, the p-value. It is not the strength of evidence of two trials which is what the regulators

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want to license, a new modality, and remember that vaginal microbicides using ARV for vaginal use it is a new licensing indication. It's not like the oral drugs, which are already at least licensed and available. It is, of course, a single trial population, so you need to know what's in the pipeline and you can see here if you scan down we've got five effectiveness trials that are going to report IPAX [misspelled?] quite soon, oral. Where's that arrow going? Oral, oral, oral, oral.

They're all Tenofovir of their based regimes either alone or in combination with FTC trivata [misspelled?] daily, daily, daily, daily, daily, daily, but they are in very diverse populations, couples, MSM, IDU, women and they are global, Thailand. We've got Kenya, Uganda, sub-Saharan in Africa as well as five countries and several countries in sub-Saharan in Africa including South Africa, but vaginal microbicides we have MT03, the voice trial only that's looking at Tenofovir, same concentration as CAPRISA and daily.

I would say what is missing and it relates to the question that we've just heard address to Angela effectiveness or otherwise intermittent vaginal dosing particularly giving it perhaps before sex and if you don't manage to give it before giving it after. Also, importantly, how long case those intervals be between testing? It's not practical to roll out something where you're testing someone every four weeks for pregnancy and HIV. How long can those intervals be safely

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without an unacceptable level of resistance? Of course, re-trial and re-trial effectiveness.

What else is missing, I'm going to skip over those, but Angela already alluded to the PK. Excited, definitely yes. Ready to roll out. I think you've already heard this from the CAPRISA team, not quite there yet. It is proof of concept on three counts. The ARV is prophylaxis. Microbicides is a rooted delivery. We know from all the trials that have been before how much women and their partners actually like these products and proof of concept of protection against HSV-2.

The window for placebo control trials is definitely open at the moment, but it could be closing and prioritizing those questions is really urgent. That's a research perspective because I guess that's what I am, but you can't ignore because I am also a doctor the challenge of delivery effective treatment to those that need it in resource limited settings. We've heard a lot of that today over this conference and I'm sure we're going to hear more. It is a challenge that we have to face.

Managing the risk of resistance whether it comes from non-adherence to treatment regimens of mono therapy because people are seroconverting without realizing it whilst being exposed to a single drug is going to determine the shape of the epidemic over the next two decades and consultation is going to be absolutely key to managing that risk, but we can and must

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manage that risk. The consultation has to go on with communities. Ethics committees and governments will be critical to the success of this.

It's a step in the right direction, undoubtedly, particularly for women where the need is so great. A step in the right direction, but it is a step in a path. I want to thank the CAPRISA team for giving us that step, but I hope in the discussion we're going to hear from the communities what their priorities are, so thank you very much. [Applause].

TIM FARLEY: Sheen, thank you very much for putting this result in a broader context and possibly bringing some of the enthusiasm that we saw today, quite rightly, down to the realities of where we go next. Before opening for the general discussion, I would like to invite the honorable Minister of Health, the honorable Aaron Motsoaledi to say just a few words about the trial and what he sees as the implications from his perspective. The honorable minister. [Applause].

AARON MOTSOALEDI: Program director, indeed, a step in the right direction. On behalf of the Department of Health of the Republic of South Africa and the government of the republic, I used to state that we are very, very encouraged because it is definitely promising. For the first time, we are now dealing with the missing link in the fight against HIV/AIDS especially the prevention part.

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As we know young women in their reproductive years, bear the brunt of the disease more than any other group in the population and up to so far in our [inaudible] we've been having weapons which are useful to [inaudible]. We have a male condom used only when the men is willing. Many women don't have any say in that. We have the female condom used again only when the man is prepared to accept it. Many young women don't have a say in that. We have got massive medical [inaudible], which for instance has been brought out in South Africa against again, ATCR [misspelled?] men who are going to be protected.

For the first time, we are now dealing with the missing link, a weapon for young women. This might be the beginning of the answer to the questions we've been asking for ages. For using this gel 12 hours before and 12 hours after within this period of 12 hours means that regardless of the wills of the men, young women will now take their lives into their own hands.

At the Department of Health in the Republic of South Africa, we shall do everything in our power to take this metaphor and to do whatever is possible to make sure that our country, our continent and the rest of the world benefits from the results of this very, very exciting and promising study.
[Applause].

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Anything in the preventional arsenal prevention against HIV/AIDS is to is to [inaudible] welcome by all of us, so for this reason I want to take this opportunity to thank CAPRISA. Professor Salim Abdool Karim was actually my classmate at University, so I'm also taking personal victory. [Applause].

I also take this opportunity take the Premier of KwaZulu-Natal province, the biggest province in South Africa in terms of population where the HIV prevalence is the highest, where the study is taking place, Howie has been supporting the team, him and the King of KwaZulu-Natal also launched the massive medical [inaudible].

By the way, Dr. Zweli Mkhize was also our schoolmate, so there is some form of relationship here ranging over 50 years. It was only that he was at least ahead of the two of us. I also will take this opportunity to thank our sister department in South Africa, the department of science and technology for being correspondence of this study.

I also wish to thank the U.S. government. The sponsorship through U.S. aid has been very important to us and I wish to thank all the young women who participated in the studies. They are our heroes. What is left is for those of us in positions of authority to make sure that everything is taken forward and to make everything possible. I thank you.
[Applause].

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TIM FARLEY: Minister, thank you very much for those remarks and for putting this trial in a more personal context and in the context of all your old school friends. [Laughter]. Unfortunately, we do have to close this session and we have run out of time, so we're not going to be able to have a discussion now. I apologize, but do not feel disappointed.

There is another session this evening which will take place at 6:30 which is a session organized by the global campaign for microbicides. When those of you who have questions, and I do hope that this evening we will be able to have a more general discussion not just on the technical issues, do come to that session. It is at 6:30 P.M. and it will be in mini room 10, just the other side of the building. Please also note that there was a session planned for later this evening at 8:30 P.M. in the Hilton Hotel, but that session has been cancelled and will be rolled in with the global campaign satellite again at 6:30 P.M. tonight in the mini room 10.

Now, just a few summary remarks I think we have heard absolutely fantastic and landmark results. My colleague Gita just reminded me that she and I started out together a long time ago. About ten years ago to the day at the Durban AIDS Conference, we heard the results of the Nonoxynol-9, Trial which was the first potential microbicide that went into a

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Safety and Effectiveness of 1% Tenofovir Vaginal Microbicide Gel 40
in South African Women: Results of the CAPRISA 004 Trial
7/20/10

phase three trial. It did not work. We've had a whole series of products that did not work and -

[END RECORDING]

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