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**4<sup>th</sup> IAS Conference on HIV Pathogenesis, Treatment, and  
Prevention  
Female-Initiated HIV Prevention Technology  
International AIDS Society  
and Australasian Society of HIV Medicine  
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**KENNETH HUGH MAYER, M.D.:** Good morning, everyone. This is the session on Female-Initiated HIV Prevention Technology. My name is Ken Mayer. I'm from Brown University and Fenway Community Health in the United States. I'm much honored to co-chair this session with Dr. Roberta Black of the National Institutes of Allergy and Infectious Diseases in the United States. She has been a tireless advocate for excellent science to study the female-controlled methods of prevention, our topic today.

A very important topic - and there is going to be other very important data presented at this meeting, including late-breaking sessions - but it's very important for us to keep in mind, to do these studies ethically, responsibility requires an incredible amount of effort. There have been something of the order of more than 30,000 who consented to participate in these studies in resource constrained environments. And the investigators have invested an enormous effort in engaging the community and in trying to make optimal sense of the research. So despite some of the gratuitous comments that have been circulated in the lay media and the scientific media, I think that this field is moving forward and today we are going to hearing some very important study results.

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Our speakers will each be speaking for approximately 10 minutes and then we will hopefully be able to stay on time and have about five minutes for questions and answer. We have a very full program this morning.

Our first speaker is Dr. Sharlene Govender from South Africa and she will be speaking on "Factors Contributing to Diaphragm Size Change Among Enrolled Women at the Durban Site in a Phase III HIV Prevention Clinical Trial."

**SHARLENE MANDALYN GOVENDER:** Good afternoon to the chairs and fellow delegates. And thank you to the conference organizers for this opportunity. I would like to acknowledge my fellow authors in the preparation of this trial.

As we are all aware the statistics for HIV globally are alarmingly increasing. According to the December 2006 statistics, nearly 39.5 million people were living with HIV globally with nearly 25 million being from sub-Saharan Africa alone where nearly 60-percent of the population living with HIV are women. In South Africa, the HIV prevalence rate is 32-percent.

Although current prevention strategy such as condom use, monogamy and the treatment of STIs are being implemented these are often unavailable or not feasible due to social economic factors. Research is therefore now testing the effectiveness of our prevention technology, such as

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microbicides, vaccines, male circumcision and cervical barrier devices such as the diaphragm.

Traditionally, the diaphragm is a contraceptive female control device which covers the cervix, which research has found increases the risk of woman acquiring infections due to an increase in the concentration of receptors at the site and a fragile epithelium. The diaphragm was recently tested as a prospective HIV prevention method in a clinical trial called MIRA, where women had to initially be fitted with a diaphragm and were refitted if indicated. The result, some of the results have been discussed earlier in this conference and will be discussed later as well.

As participants had required initial fitting and subsequent refitting if indicated, the purpose of this presentation was to determine what were the factors that contributed to diaphragm size changes in order to better inform future fitting practices for cervical barrier devices. Currently, there is much debate and controversy surrounding the need for diaphragm fitting and information regarding the need is limited. A recent paper also showed that a common diaphragm size used among women across age groups was a size 17 millimeter diaphragm which I will be discussing later as well.

MIRA was a prospective randomized clinical trial which tested the effectiveness of the diaphragm and lubrication

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vaginal gel against the acquisition of HIV and STIs among heterosexual women. The trial was conducted in three sites. The one was Harare, Zimbabwe, where 2,502 women were enrolled. One site in Johannesburg, South Africa, where 1,028 women were enrolled, and two sites in Durban with Umkomaas and Botha Hill both rural areas where 1,515 women were enrolled.

Although every prospective participant was provided with a package of care, for the purpose of this presentation I will be focusing the participants enrolled in the trial. So from the 1,515 woman enrolled, 757 women were randomized into the diaphragm/Replens gel and condom arm while the remaining 758 were randomized into the condom only arm. Every participant was provided with access and ongoing access to VCT, male condom, safe sex and risk reduction counseling, the diagnosis, and treatment of STIs, and education and information regarding the diaphragm and condom use.

Demonstrations were performed by trained staff to initially just introduce the idea of the critique techniques of diaphragm association and removal using pelvic models. Following participants were allowed to also practice with the use of pelvic models. Physical exams were then done to exclude any contraindications to diaphragm use before participants were fitted by trained clinicians and nurses for the most correct diaphragm size.

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Participants had to demonstrate the ability to correctly insert and remove the diaphragm and gel before being eligible for randomization. Diaphragm sizes were checked. If the participant had a complaint regarding the product use, had experienced a vaginal delivery, or still birth in the third trimester, or it was her closing visit and she had not been refitted in the past six months. Participants were informed that they could return to the clinic at any time should they require any information or experience any problems or concerns with the diaphragm.

So, we analyzed the data using both qualitative and quantitative methods and we looked at fixed variables such as the diaphragm size at enrollment and at follow-up, what were the indications for the changes in the diaphragm size? From the data analysis, from participants in the diaphragm/Replens gel and condom arm, we found a very nice, a bow curve with distribution of diaphragms between women ages 18 to 45, with the most common diaphragm sizes ranging from 65 to 75 millimeters. The 274 women were issued with a size 70 millimeter diaphragm which could impact on future needs for fitting of diaphragm and cervical barriers devices, as this was the most common size.

Of the 757 women in the diaphragm/Replens gel and condom arm, 289 required diaphragm refits. So we wanted to

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access what were these factors that contribute to this. One of the factors as can be seen in the pie graph on the right was pregnancy related. When 96 women were refitted and had diaphragm size changes following vaginal deliveries and/or spontaneous miscarriage in the third trimester. Forty eight women were refitted following participant complaints and this could have been pain association or with the diaphragm use or just a feeling of discomfort with the diaphragm that merited a refit and resulted in a diaphragm size.

Then there were other factors which we grouped together as other factors, and these were where 145 women were fitted. And these factors were where the participant might have lost her diaphragm and needed to be refitted or had damage to the diaphragm or a clinician discretion warranted a refit in the diaphragm or as part of policy assurance where the monitor suggested a refit or with weight changes as well. So these were some of the factors that contributed to the other reasons.

So, although 38-percent of the women required diaphragm refits, we can say that diaphragm fitting was reasonably consistent, with 68-percent of the women not requiring diaphragm size changes and with them remaining on the diaphragm size initially fitted. The fact is that contributed to these changes can be briefly summarized pregnancy, participant

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complaints, and the group of other factors which I just discussed in the previous slide.

So in order to ensure adequate prevention is provided by the diaphragm as an effective contraceptive device or a possible preventive device against STIs or HIV infection, we must evaluate participant complaints and exclude any other factors that might contribute to the complaint. Another recommendation is that we monitor weight as is done with the most of the contraceptive methods. We monitor weight as gross changes normally of greater than four and a half kilograms and more could result in inadequate coverage of the cervix by the diaphragm and therefore reduce effectiveness of contraception.

We also recommend that any pregnancy outcome with a pregnancy greater than or equal to a 14-week gestation warrant a refit as changes in the uterine muscular shell could result in inadequate coverage again of the cervix. And it's very important that participants are provided with adequate and correct information and access to information regarding the diaphragm consistently and also what the indications for refit are in order to better understand this.

I would like to acknowledge and thank the participants of the study, the research team at the HIV Prevention Research Unit, the Bill and Melinda Gates Foundation, MIRA, obviously Dr. Powell at the University of California at San Francisco and

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Gamore [misspelled?] for their assistance in this presentation.

Thank you.

[Applause]

**KENNETH HUGH MAYER, M.D.:** Thank you. You may want to stay up there. This presentation is now open for discussion. Please come to the mike and introduce yourselves those who have questions.

Is there any reason to wonder whether having to have changes in diaphragm in the course of the trial had any impact on adherence to usage?

**SHARLENE MANDALYN GOVENDER:** It might have, it might have. Unfortunately for this presentation I did not analyze that data, so it could have been a possible reason as well for it.

**FEMALE SPEAKER:** Yeah, I was just curious, were any of the participant complaints actually their male partner complaints or was it just always the participant complaining about discomfort?

**SHARLENE MANDALYN GOVENDER:** Well, there was some incidences where the participant's partner had maybe complained that they had felt the diaphragm institute but the majority of the complaints were the participant was just uncomfortable with the diaphragm.

**KENNETH HUGH MAYER, M.D.:** Dr. McDermott?

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**JEAN MCDERMOTT, M.D.:** Yeah. Jean McDermott from the Foglerty International Center. Yeah. Can you tell us a little bit more about this refitting and what, were the people who their sizes went up, their sizes went down? If you redid that curve, what would it look like for after people were refitted? So, in other words, do you have really drastic changes or are they just going in and down one size and probably that wouldn't change so much the efficacy of the diaphragm?

**SHARLENE MANDALYN GOVENDER:** Well, in the presentation, I did, unfortunately that information was available before this presentation, but in practice very often the sizes change just by one size or two sizes.

**JEAN MCDERMOTT, M.D.:** Do they go up or down, mostly?

**SHARLENE MANDALYN GOVENDER:** Most of the time it was down.

**JEAN MCDERMOTT, M.D.:** Down?

**SHARLENE MANDALYN GOVENDER:** Mm-mmm.

**KIM COLLINS:** Kim Collins from the study. I was just wondering what the cost for diaphragm is and if that's a barrier for what you are doing.

**SHARLENE MANDALYN GOVENDER:** Well, in South Africa it is not available in the government clinics. And it is offered in the private sector. And they range from anything from, I think,

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around 50 to 100 drens [misspelled] for the device, so that's in South Africa alone but it's not commonly used at all.

**KIM COLLINS:** Yeah, so it's about \$70 to \$80 in your place, in great amounts and that's often a barrier for some people to use it [interposing]

**SHARLENE MANDALYN GOVENDER:** The cost itself, yeah.

**KENNETH HUGH MAYER, M.D.:** Thank you, Dr. Govender, and we will hear more about the diaphragm and diaphragm gel adherence in the safety trial in Harare, Zimbabwe, from Dr. Ariane van der Straten, representing a team from the United States and University of Zimbabwe in Harare.

**ARIANE VAN DER STRATEN, M.P.H., Ph.D.:** I just wanted to make a quick remark about the cost of the diaphragm. So the initial, maybe a slightly higher than other contraceptives, but it's a reusable device that can be used for many years so the cost per use is being unfair cheap.

So, today I'm going to be talking about another study, which is not the MIRA. My other colleagues are later, Liz Montgomery and Connie will talk again about MIRA but in this presentation is about a study called Diaphragm and Microbicide Safety Trial which was conducted in Zimbabwe and funded by Conrad. The title of my presentation is "Diaphragm and Gel Use in a Safety Trial in Zimbabwe."

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So DMS study design was a Phase I randomized controlled trial to assess the safety and acceptability of six months of use of diaphragm with active gel. Diaphragm was placebo gel and active gel alone. The participants and staff investigators were blinded to the gel in the two diaphragm arms but were not blinded to the gel in the gel only arm. The study was conducted in Harare.

The main eligibility criteria for the trial was for women to be 18 to 49 years old, sexually active, non-pregnant, using an effective contraceptive, having no record of urinary tract infection or STI, and a healthy cervix, and being able to correctly insert and remove the diaphragm prior to randomization.

I already presented findings on the safety of the trial and today my objective of this presentation is to talk about products used and examine level of product used during the trial compare assigned product adherence between diaphragm and gel groups versus gel only group and to examine predictors of endurance.

This is a slide depicting the study flow for the trial. We screened 476 women and randomized 119 into the three groups, diaphragm and placebo gel, diaphragm and active gel, and active gel only. There was no difference in early withdrawal or termination between the three arms. For the purpose of this

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analysis, we did combine the two diaphragm and gel arms into one group of 77 women. Among those, we had to exclude one woman who had no follow-up data and one woman who report no sex during the six month of follow-up. So our total analytical sample is 117. We had a median follow-up visit of five ranging from one to six visits.

Our study products were the Ortho latex diaphragm like in the MIRA trial you previously heard about. And this was fitted by a trained clinician. In terms of gel, our active gel was 6-percent sodium cellulose sulphate, which is a contraceptive agent and has a good anti-microbial activity, and our placebo was KY Jelly. We also promoted and distribute activity condom use, condom at every visit.

In terms of product use, we used, it was currently dependent use of the products and the instructions we gave to the women was to prior to each act of sex in the diaphragm and gel groups to empty one gel applicator in the dome of the diaphragm and then insert the diaphragm in the vagina. Then to empty another gel applicator in the vagina one hour or less prior to sex and to use a male condom for every sex act. In the gel-only group, women were told to empty a gel applicator in the vagina one hour or less prior to sex, and to use male condoms for every sex act.

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We did monthly interview and looked at product use at last six by ACASI. We also looked, by the clinician form at the last stage products were used and we assessed monthly problems with study products. At exit, we looked at frequency of using the diaphragm for three months which was our main measure of adherence and we asked women whether they always, sometimes, or never used their assigned study products. We also assessed acceptability and product rating.

In terms of analysis, we conducted a GEE for time dependent analysis to look at repeated measure of product used at last sex and we used multivariant logistic regression to compare women reporting always using versus less than always using their assigned study products.

On this slide, it's shown the baseline characteristic. Overall, characteristics were well balanced between arms. And overall the median age of women was 29. The median weekly sexual frequency was 5.4. It was predominantly a married monogamous sample with 96.6-percent of women being married and 76-percent of women having only one lifetime partner. Women had experience with male condoms at baseline, 85-percent had ever used a male condom and 27-percent reported always using one in the past month. In contrast, only 38-percent had ever heard of the diaphragm and only three women, that is 2.6-percent, had ever used a diaphragm prior to the trial. Similarly, only 22-

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percent had ever heard of a vaginal gel and only five women had ever used a vaginal gel. The primary contraceptive method that women used was the pill, 72-percent, other methods used were injectable, implant, IUD and TLN. And again by design we asked all women to be on hormonal contraceptive or long-term contraceptive to be enrolled in the trial. The HIV prevalence in this sample was 26-percent.

This slide shows products used overall and by group. First, we assessed through monthly assessment and we present cumulative average of product use. As measured by the clinician form, we first looked at the combination of diaphragm and gel use among women in the diaphragm and gel group and 89-percent of the visits women report that the last time they use a diaphragm they also used gel which shows that there was a high level combined method used in the diaphragm and gel groups.

The next rows shows the products used at last sex as measured by ACASI, again cumulative average. Overall, 70.5-percent of sex acts were covered by a study product during this study but this differed by groups. In the diaphragm and gel group, 66-percent of last sex acts were protected by the assigned study product versus 80-percent in the gel only. When we looked at the mean endurance outcome which was a product used in the past three months at exit, overall 58-percent of women said they always used their assigned study product and

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this did not differ by group, 59-percent in the diaphragm and gel group versus 56-percent in the gel only group.

This is a slide showing product use at last sex by visit. The red line depicts the women in the gel group and the blue depicts women in the diaphragm and gel group. The odds ratio for using study product at the last sex was 0.48 with a P-values of 0.017. So there was significant difference between the two groups as measured at last sex.

However, when we looked always using the past three months, there was no effect, there was no treatment effect and the odds ratio for always using study product comparing diaphragm and gel versus women in the gel-only group was 1.15 with a non-significant P-value.

We also looked at other predictors of always use, age was significantly associated with a greater likelihood of always product. In unit variant analysis, every ten years in relationship were but they didn't remain significant in the multivariant adjusted model. Sexual frequency, partners having multiple partners, contraceptive use, and HIV status were not associated with always use. And neither was problems with the study products which by the way was extremely low, only nine women report any problems with the products over the course of the trial.

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However, use of condom at every sex act was strongly associated with always using study product and this association remains significant in the multivariant analysis with odds ratio of 3.85. Using study product for pregnancy and other disease prevention was univariantly associated with always use but not in the multivariant model. And similarly, strongly liking one's study product was not – was significantly associated in the univariant but not in the multivariant model.

Women who reported that their partner thinks that using a product is a good idea, were more likely to always use their product as well.

In summary, when we looked at our measure of always use or adherence as always use or in compare it to our measure of product use at last sex we didn't get the same picture. Our summary measure showed no difference by group in always use whereas when we looked at product use at last sex women in the gel group report higher product use than women in the diaphragm and gel group.

The independent predictors of always using the assigned product included consistently using condoms, age, and partners' approval for product. The overall acceptability of assigned study product was high but it was not independently associated with product adherence. And few problems were reported with

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products - however, adherence or always using product was lower than expected, especially in the context of a trial.

In conclusion, product adherence was measure, was similar between groups even though diaphragm and gel combination may seem more complex to use than a gel alone. Adherence to both condoms and products was strongly associated. This may bias effectiveness results in future trial of female controlled methods, as it will be difficult to extricate the effect of the female control method from that of condoms. And given the slightly different picture we got from our different measure of product use better more objective biomarker measure of products and of condom use are needed so that we can decrease our reliance on self reported use of products.

I would like to acknowledge my colleagues at UCSF, University of Zimbabwe, and Conrad. Thank you.

[Applause]

**KENNETH HUGH MAYER, M.D.:** Thank you, Dr. van der Straten. We can take a couple of questions if people would like to come to the microphone.

Given the finding of the increased usage of product and diaphragm with partner acceptability, any thoughts about how you might be designing a future study to enhance adherence by engaging partners as well for these trials?

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**ARIANE VAN DER STRATEN, M.P.H., Ph.D.:** Yeah, I do think that it seems sometimes a bit as a dilemma that we are looking for methods that women can control and use discreetly yet in this trial and in the MIRA as well, virtually all women informed their partner about product use and it seems like partner approval is important. I think that it made a very bad context in Zimbabwe. It's a context where men are still seen as the decision maker for family planning and for HIV prevention and therefore their approval is required. And probably engaging male partners and my colleague Liz Montgomery will talk more about that later but engaging the male partner in disease prevention methods or use of contraceptive will probably increase adherence.

**KENNETH HUGH MAYER, M.D.:** Thank you. Dr. Alstata [misspelled?]

**WAFFA ALSTATA, M.D. [misspelled?]:** Yes, Waffa Alstata in New York. I'm sort of thinking about the whole issue of adherence in the prevention context and in some ways we accepted it in the treatment arena that use of antiretrovirals are what we call unforgiving, that you need to have 95-percent or 100-percent adherence with combination antiretroviral treatment in order to prevent resistance. It's seems like that there are perils somehow that will become evident in prevention and maybe if we take what we have learned from the treatment

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world where the intensive adherence support that is provided between visits as well as during visits and sort of aiming for you know this whole idea that it's going to sort of unforgiving adherence in a way that's going to probably lead us to success. So, I think there, it dawned on me that there are parallels from the treatment arena to the prevention arena and if we keep in mind this whole idea of the unforgiving or the very, very, very high rates of adherence that we have learned to need to achieve in the treatment world.

**ARIANE VAN DER STRATEN, M.P.H., Ph.D.:** I absolutely agree and I think that one of the way to deal with this issue is to, the methods or protocols that decrease Kito-related use and user dependency and that's one of the possibility with the diaphragm in this case. This was promoted as a Kito dependent method but it could be for example diaphragm could be used continuously and could be segregated from sex and that has been shown in another study we published a couple of years ago to be associated with consistent diaphragm use.

So I think there are ways, even with the methods we have now, to increase adherence by changing the way we promote and the methods to the women.

**KENNETH HUGH MAYER, M.D.:** Thank you, Dr. van der Straten.

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Our next speaker is Dr. Atiene Sagay, represents a multinational team from Nigeria, Australia, and the United States, will be discussing Genital Tract abnormalities among female sex workers who douche with lemon, lime juice in northern Nigeria.

**ATIENE SAGAY, M.B.B.S., F.W.A.C.S., M.R.C.O.G.:** Well, this morning, we are going to be looking at genital tract abnormalities among female sex workers who douche with lemon or lime juice in Nigeria.

But they are not douching for sex. It's a widespread practice among various cultures worldwide and common septics [inaudible] in water and dirty water at a commonly used agents of douching with lime is one that started well over 300 years ago and it is still being practiced in many communities across the world. But particularly, that is a common practice in Nigeria.

Some researchers have looked at lemon, either as soft drinks as they [inaudible] the Crest one, or lemon itself as having anti-microbial properties and can immobilize the matters once were and people suggested that it could be a candidate microbicide. While we know better than that now, that it takes more than just the credentials of a more [inaudible] for matters of killing HIV to be a microbicide so several workers have looked at the part of lemon on cervical explant tissues.

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They say that the cytotoxicity of lemon is as bad as that of nonoxin [misspelled?] 09 and this was done by Lockmore and Schmidt. This study sidebar unpublished.

There is other work done by Conrad, Conrad King. This looked at sexuality active women who volunteered to use lemon or lime douche in different concentrations. They did show that there was a dose-dependent epithelia damage on the cervix and vagina. Although in private, this sort of evidence was not found in terms of destruction because in primary sites they have looked at introducing lemon, the douche with lemon, every day for a period of one month and find out there was really no evidence that there was destruction of the vagina epithelium. So where does that leave us?

The act of douching itself has its problems. And it's evidence that over 30 years ago, in the United States there is a drug, a douching agent, Lysol and other taboo douching agents that would remove from the market by manufacturers because they were consider as bad as cancer.

Today we are not sure whether lemon douching used for sex has that sort of effect. It has any effect in impact on the vagina epithelium or it increases HIV acquisition. No one is really sure. It is true that some non-clinical research has been done but this we think is the first attempt to actually

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look at what the impact of lemon is in women who have been using it.

So the question there is, does lemon in vagina douching help for sex have any impact on the lower genital tract epithelium? Now this is a cross section of our study of consecutive volunteers and these are existing users. We commenced our work by focusing on mobilization and consent for therapies sex workers were recruited in just Nigeria. And this study got [inaudible] the review board of the Jos University Teaching Hospital.

The study questions asked were administered by trained nurses who got that information by general practices and the gynecologists who was blinded to the women's responses obtaining PAP smears and performed colposcopy on these women. And those who were found with abnormalities received treatment free of charge. The clinical procedure that is the colposcopy procedure involved looking the vulva under magnification and that was followed by a spectrum examination and visualization of the cervix, fornices, the vagina, and then lavaging we [inaudible] and then performed colposcopy examination on these areas. We sampled a sample bridge.

For [inaudible] analysis we enter the doctor entry was done on Epi-Information version 3.3.2. And we tested [inaudible] the pie squared and the orchestration with 95-

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percent condense interval. We used a multivariant logistic regression to assess the independent effect of lemon and lime use on the cervical dysplasia.

In all we recruited 398 female sex workers. They completed the questionnaires but because of a number of reasons, 24 of these did not come back for colposcopy. The main reason of course was that a number of them were having their period at the time and they were asked to come about they are all clear but about 24 out of 70 who were having their period during the period did not come back. So we had 374 comprising lemon users and 293 non-lemon users.

The age ranges between the lemon users and non-users was not different, 28.0 there. The range and the mean, no difference. And then we have religion, again most of the people that we, most of the sex workers were Christians but the lemon users were in the same proportion among the Christians and Moslems. Looking at marital status, the majority of people there were actually either single or divorced or widow. Duration of sex work it just showed that also that those who have been in the sex work for more than five years, this group a higher proportion tended to be among lemon users.

Now in the colposcopy, findings were divided into those were not our findings, those that have cervix [inaudible], those that had warts, and those that also speculate as lesions

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[inaudible] inter epithelium lesions. And using the colposcopy findings we did not really, the differences did not really reach significant difference at any of the levels. Although you see 20-percent of lemon users there, [inaudible] lesions and 15-percent of the non-lemon users. It did not reach significance.

[Inaudible] cytology, we did find that those have squamous cell [inaudible] lesions, 20-percent there and then this 11.2-percent, that difference was significant. And when we added low grade and the high grade squamous cell [inaudible] lesions we found that the difference there was significant.

Now it was still significant even after our, we confounded for HIV status. And the HIV status you will see that among the lemon users was 48.8, non-lemon users 48.2. Really there was no difference in HIV prevalence between lemon users and non users. This statistic you will find on another presentation that was done by the team and it's out on the post session.

So, in summary we have looked, we see here that though the significantly higher prevalence of squamous interact cells lesions among lemon users in comparison to non users after confounding for HIV status. And there was no difference in prevalence in societies [misspelled?] or genital warts. And we found no evidence of operations or bruises.

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This study had several limitations. First we relied on self reporting by subjects and had no means of verifying claims. We could not control for other factors like degree of dilution of lemon juice, timing of douching, and frequency of condom use. And because of the cross section on initial of this work we could not be confident that lemon use preceded the development of dysplasia. And also confounding by association may be arisen if the use of lemon juice associated with other practices that increased the risk of dysplasia.

So in conclusion, we are saying that the practice of douching with citrus juice may be a risk factor of cervical dysplasia. And further studies to explore the association between douching and lime, douching with lime juice and cervical dysplasia are warranted causing communities where this practice is common. I have made this presentation on behalf of all the authors and we are grateful to others who supported this work. And the funding for the work came from public donation, the Berlin Project on [www.aids.net.au](http://www.aids.net.au). Thank you very much.

[Applause]

**KENNETH HUGH MAYER, M.D.:** Thank you, Dr. Sagay. There may be time for one question. I see somebody coming to the microphone.

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**ELLEN LAJEFFERIES [misspelled?]:** My name is Ellen Lajefferies from Scarlet Alliance, the Australian Sex Workers Association. There is a lot of, there are so many issues that I think sex work communities around the world want to raise in regard to the way that the use of lemon has, lemons as douching has been looked at and analyzed by researchers. But I do have a specific question and wanted to follow up with a comment.

My specific question is were sex worker communities engaged in a way that meant that they had an involvement in this research project contribution to the way the project was designed, contribution to the kind of outcomes that were being sought? I know that there was no acknowledgement of sex worker communities in this list. And I want to know was that considered at any time.

**ATIENE SAGAY, M.B.B.S., F.W.A.C.S., M.R.C.O.G.:** You know, because of time I just critique that we had [inaudible] mobilization. Actually the whole process of mobilization was a period that we used to work with the sex workers. This took a fairly long period of time before we could actually start the research work. So we took time to work with them and they missed several inputs we were going to carry out this study in main government hospital. They said, no, they will not go there. They would prefer private place. You know, there were lots of changes we had to go, we had to do in order that we

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would meet with what you know they would be happy with. And they were part and particle of the work I was in.

And if you look at the acknowledgements there, I say that we are grateful to all those who participated in this study. And they are the main participants. I didn't mention them by name but they were part and particle of this work and they participated in the designing and the implementation.

**ELLEN LAJEFFERIES:** Okay, well, I guess I would like to say that if they were such meaningful involvement of sex workers in your study, then it would have been a benefit to the audience to have mentioned that. But for the benefit of international sex worker networks and communities those groups are not resourced enough to actually be in contact with other groups in their own region or in, among African groups or with other groups around the world. So I would question how they are being resourced and supported to be involved. If that simply includes resourcing sex workers enough to make the practical outcomes of what you are seeking to do, a reality when these, this kind of research has to be for the benefit of the communities that are involved as well. It has to be for the actual benefit of the sex worker communities involved.

And I think those specific statistics that showed that, that you showed that have a degree of cultural meaning already and that is that sex workers have been involved in the industry

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longer out of the sample that you took, when not practicing lemon or lime douching. And that the cultural imperatives of the way that information and knowledge is passed among sex worker communities perhaps has, is an actual variable that should be considered in this. Because sex worker communities aren't, these practices aren't operating in a vacuum. They are operating because they have cultural meaning and they have a perceived positive outcome for the sex worker communities that are involved. And if people that had been involved longer are choosing not to do those practices then what is it about lemon and lime douching that means that the longer you are in the sex industry, in that particular sample, the less likely you are to actually do that. That speaks to me more powerfully than a lot of the other things.

And you know, this isn't necessarily targeted at you but the general approach of research is towards lemon and lime douching in a number of different African sex worker communities has raised ethical concerns for sex workers all over the world about the way that our cultural practices are invisibilized when it's turned into a simple set of statistics and actually valuable information about sex worker cultural like how we share our information, the way we share our information becomes lost which means that this kind of research whether it's about microbicides or anything else is actually

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stymied by not including the voices of sex workers communities that do have a high and critical understanding of these issues.

I know I have taken most of my time [interposing]

**KENNETH HUGH MAYER, M.D.:** THAT'S a very important point and we want to thank you for it. And I think you have made it very articulately. This is not the forum that would carry forth this discussion because we need to move on but Thank you very much for your comments and thank you, Dr. Sagay.

[Applause]

**ROBERTA BLACK, Ph.D.:** All right, we are halfway through our speakers and so it's time for a really quick commercial break. for those of you who are interested in the microbicides 2008 conference, there is a pamphlet on the table outside the door down here if you would like to pick it up to get a little bit of information. So on that note, we will move quickly to our next speaker who is Dr. Constancia Watadzaushe who will be speaking on achieving a 95-percent cohort retention rate in a Phase III trial of the diaphragm and gel in Southern Africa.

**CONSTANCI WATADZAUSHE:** Well, thank you. Just a quick correction. I'm just Constanci Watadzaushe. I'm not a doctor.

Good morning. I'm going to present on a high cohort retention in a clinical trial of diaphragm and lubricant gel that was conducted in Southern Africa. The method of improving

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the corrective health in Africa was a Phase III randomized controlled trial to examine the effectiveness of the diaphragm and lubricant gel in preventing HIV acquisition among women.

A total of 5,045 women participated in the study across three sites with five study clinics. The clinic sites were based in our area Zimbabwe, Durban, Sudan and South Africa. The sites we looked at were rural, peri-urban, and urban with formal and informal settlements.

The study participants were on average 28 years of age, ranging between 18 and 50 years, 45-percent had high school education, 23 were employed, 59-percent of these women were married and 68 were living with a partner. The average age of sex debut was 18 years and it ranged between 10 and 31 years, 22-percent is circumcised in partners, and 20 did not know.

The trial design is assuming 4.7-percent and allowed to fill up over a period of three years over an estimated HIV incidence rate of four percent across all sites. Loss to follow-up was defined as no closing visit with no HIV input data. It is essential to limit lost to follow-up first to ensure validity of results. And it was important to ensure lost to follow-up was not different by study group.

Lost to follow-up qualify over a period of 12 to 24 months, depending on their date of enrollment and closing

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visits were done between 12 to 24 months also depending on their date of enrollment.

Before the trial was implemented there was concerns about immigration, long follow-up periods, which was a maximum of 24 months. There was also concern about those in the control group may receive no benefit of staying in the study that long. In view of this the following strategies were therefore implemented prior to implementation of the study.

Staff was trained on the importance of retaining participants through out the trial and how this could be done. Adequate resources for follow-up were allocated and sites were encouraged to recruit as many [inaudible] so that outcome participant ratio was manageable.

Other resources were allocated especially in the clinics. This enabled them to have one to one contact with participants while in the clinic and also establish a rapport with the participants. Community lunches were done to sensitize the community. And most importantly, the staff was trained to obtain very difficult information from each participant.

The information that was collected from each participant was done for efficient tracking, for tracking purposes. Information obtained included the participants' home address, phone number, and directions maps were drawn on the locator form where addresses where nonexistent.

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We also obtained the participant school, grandchild's name, the name of the school and the address. This was done to show in the event of the participant move from their current known address, the child was unlikely to change school therefore remain a reliable contact. A second [inaudible] was also obtained after the prior relative. For each of the statistics the participant was asked indicating initial relatives of care to either phone or to contact the participant by phone or post and whether it was okay to mention their study name.

The following strategies were used during the implementation of the trial. Reminder letters were sent to participants' home before the next scheduled visit was due. If participant missed a scheduled visit she was either contacted by phone or making home visit within 24 hours. In MRC, there have been, peer educators were used for outreach.

As the trial progressed, we improved our customer service to try and make the participants [inaudible] as far as their participation in the trial was concerned. We offered after hours clinics for those participants who were finding it difficult to get home, to get time off from work. We created a suggestion box for participates. We provided transport for those who were living in areas where transport was difficult to access. Clan members and officers are appointed at each site to

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interface with participants regarding their waiting periods. We also played movies, family movies, and set refreshments in waiting room areas. And for those participants who put their children to the clinic, child care was provided while they are having their visits.

To encourage our participants to keep coming for their visits we give them tokens gifts at [inaudible] visits, eight months, a year, and we were halfway through their visits. We also held a participant lottery, the drill was done quickly from previous visits that already been attended. And incremental reimbursement was also done as the visits accrued. This one gives a competition drive to we approve area of risk. These were also done at different sites and not across all sites.

We also focused on participants like genders how to reach these participants who had to reach for one or the other. They either relocated or kept promising to come for visits. For those in my particular rural areas or other towns, rural [inaudible] trips were done to give those participants bus fare to come to the clinics. For those who said they do not have time to come to the clinic, a peer team member visited them at home and their closing visit was done in their home. And for those participants, who were repeatedly, were difficult to bring back to the clinic, a coordinator or PI visited them at

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home just to talk to them and sometimes this helped us bring issues that were happening at the clinical in the field that prevented them from coming for their visits. And a final pitch for participants who had not closed out at the last scheduled visit was done for two months to try bring them all back to the clinic for the closing visit.

This slide is just showing the visit at [inaudible], the visit the study group. As you can see the study at [inaudible] we visit range between 83-percent and 95-percent and there was not much difference between the two study groups.

Our last follow-up scheduled visit was done on October 4, 2006 and 89-percent of the enrolled participants had closing visit. Intent to follow-up and tracking of participants were not closed by this date was done for two months and the closing visits rose to 92.5-percent. Overall, 4.3 of these participants were classified as lost to follow-up, meaning they never returned for their closing visit and had a final HIV endpoint.

But for those with, there are some who didn't come for their closing visit but some of these participants, some follow-up data and contributed some more months to the analysis and that was never the intent for the enrollment.

In conclusion, preemptive planning continues monitoring of application rates combined with additional track and time ensure how general participants achieving eradication is most

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intensive and requests for the allocation of financial and strategy from human resources. Many of our success was strategies was trough driven therefore it is important to involve all members of staff in retention discussion and to share ideas across all sites. Thank you.

[Applause]

**ROBERTA BLACK, Ph.D.:** Do we have any questions for this speaker? Nancy?

**NANCY:** First of all, you did a fantastic job but I just thought it narrowance and say oh, we are already doing this but I just thought of something that and you know in so far as you do pro-protocol analyses given all the problems that we have with adherence and measuring adherence, I wonder if we could think about using people who are difficult to follow-up as maybe a surrogate measure of adherence and to sort of look at people who are difficult to follow-up per protocol or subgroup analysis based on that. And I think it might be interesting to see because the hypothesis would be that those who were easier to follow were more likely to adhere. Just a thought.

**FEMALE SPEAKER:** I have I guess a comment as sort of a question. I think what amazes me is retention is so important in these microbicide trials and the MIRA trial and requires such creativity and really a lot of thought and understanding

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your participants. I think that it's really phenomenal that your, that the staff of the study was really so aware the needs of their participants and really concerned that so carefully in trying to come up with solutions to make sure that their participants returned. So I just think that's it's, that's really terrific that you were able to do that.

**CONSTANCI WATADZAUSHE:** Thank you.

**ANN FERRIER:** Hi, my name is Ann Ferrier. I'm also a researcher and from the Netherlands. And although my focus is on adherence and I have seen a lot of issues with follow-up in children and the moms and I really commend you on providing some many services, the transport, child care, extra hours. I think these are all really fantastic things. I'm wondering if this wouldn't also be an interesting predictor of adherence in the future. We are seeing, you know in terms of return to clinic visits, even for people who required additional services. I don't know what your, in your trial what your plans are for you know continuation and follow-up but that would be my question is how much more in this phase or the next phase will they be expected to return and how much more retention issues do you expect with, and therefore the adherence issues.

**ROBERTA BLACK, Ph.D.:** Do you want to maybe summarize  
[interposing]

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**ANN FERRIER:** Yeah. One thing if the question, my question is really do you anticipate when you are having problems with retention already in some and you know having to put so much effort into clinical trial of this type, how much can expect adherence without all of this attention and financial burden, especially in resource-poor settings?

**CONSTANCI WATADZAUSHE:** I'm sorry. I hope I understood what you were asking. The trial is completed so right now [interposing]

**ANN FERRIER:** This is Phase III, right?

**CONSTANCI WATADZAUSHE:** It was a Phase III trial. It's completed and the final result will be presented tomorrow in the late breaker session. So the retention rate you saw today is what we got. But we are going to, we are planning to do analysis and see and we actually did ask participant which were the best they preferred way of contacting them. What made them, what they perceive as the most useful way to keep in touch and make them come back to the clinic? And we will certainly analyze and publish that. That may answer some of the questions.

**ANN FERRIER:** Yeah, that is basically what I'm looking at is what happens post this phase of the trial in terms of the continuing follow-up adherence post phase of clinical trials

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Phase III because we don't have a lot of data coming through at this time on what happens there after.

**CONSTANCI WATADZAUSHE:** We also followed a subset of participants post trial and this hasn't been analyzed yet but we will have data on that.

**ANN FERRIER:** Thank you very much.

**ROBERTA BLACK, PHD:** All right, Thank you. I think since the last question was so lengthy I think we are going to have to move on so that we don't lose our timing here, but perhaps if you wanted to contact the speaker after, you could ask your question. I'd like to move on now to the next speaker, Dr. Elizabeth Montgomery, who will be speaking about "Female-Controlled HIV Prevention Methods in Zimbabwe: How Involved Are the Primary Male Partners?"

**ELIZABETH MONTGOMERY, M.P.H.:** Thank you to the organizing committee for inviting me to present today. Perhaps I should also make a small correction that I am not a doctor. The title of my talk today is "Female-Controlled HIV Prevention Methods in Zimbabwe: How Involved Are the Male Partners?"

Before I begin, I would like to recognize my co-authors and collaborators at the [inaudible] UCF Program in Harare, Zimbabwe, the University of California, San Francisco, and my Ph.D. supervisor at the London School of Hygiene and Tropical Medicine.

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In this presentation, I'm going to be describing the Male Involvement Study, which is a sub-study appended to the MIRA trial. I will first give a bit of background on male involvement and then briefly describe the parents study, MIRA, and then go into the Male Involvement Study and present some preliminary data.

Despite being somewhat ill-defined, the male involvement is widely promoted and presumed to be beneficial. Several UN conferences have issued official statements like this one from the Program of Action from the Beijing Conference on Women, which states that the shared responsibility between men and women in matters related to reproductive and sexual behavior is essential to improving women's health. Promoting male involvement emerged in family planning realms, the idea being that if men were encouraged to come to family planning clinics or take part in programs, it would garner their support and improve health outcomes for women.

The same logic has since been applied to the HIV/STI arena. The hypothesized benefit of involving men has been corroborated by several qualitative and exploratory studies on hypothetical future microbicides and other female-controlled methods.

In this research, which has been done throughout Eastern and Southern Africa, as well as in several other

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studies, there has been almost universal support for the idea that men must be involved in the process of testing and eventually using these new methods. Often, respondents in these studies have cited potentially adverse consequences if men are not involved and later find out that their female partners have been using these methods. It is unclear when women report that they want to involve male partners where this motive is coming from, whether it's out of a genuine desire to share, fear, or a combination of thereof.

But despite the theoretical endorsement and exploratory research supporting male involvement, it is important to note that some studies have shown that promoting male involvement has, in fact, been shown to endorse men's authority. As in the Male Motivation Project in Zimbabwe, this was a social marketing campaign that aimed to involve men more in family planning and found that after the campaign more men reported that they were the decision makers about family planning. So highly involved might also mean highly controlling and this has been seen in a study in South Africa looking at gender and HIV risk.

Finally, male involvement may have a neutral effect, and this is important information as well, as we run around trying to involve them.

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I'm quickly going to describe the parent study. You're already heard a little bit about it. MIRA was a phase III trial of the effectiveness of the diaphragm and Replens gel to prevent HIV in Southern Africa. We randomized 5,000 HIV-negative, non-pregnant women to one of two study arms, shown here. It was a multi-site, open-label trial and all women received a comprehensive HIV prevention package. Women were followed quarterly for 12 to 24 months, depending on when they enrolled. The MIRA trial consent forms explain that male partners are invited to come to the clinic for free HIV counseling and testing and staff was told that they should tell women to invite their male partners to the clinic for any other reason. However, there was no formal intervention to get male partners to come in.

The Male Involvement Study was conducted, as I said, as a sub-study as the Harare site of the MIRA trial. Half the trial population, which was just over 2,500, was enrolled at this site. Participants were recruited from the community and municipal clinics in the area. This was not a high-risk population.

The primary aims of the Male Involvement Study were to measure quantitatively and explore qualitatively the effect of male involvement on women's adherence and acceptability to our study products. While these are the aims of this study, I'll

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only present some preliminary indicator of male involvement. I haven't yet correlated these indicators with the outcomes here.

There were six data collection sources for this Male Involvement Study, the backbone of which is the Male Partner Involvement Form, which is a 58-item, interviewer-administered questionnaire that we conducted at two time points. The form was constructed from previous research and anecdotal discussions during pilot testing and it exploring domains of partner communication, participation, control and attitudes about study products.

Now, I'll go onto the results. This is just a brief summary of our study population for the first 2,325 of the 2,500 women enrolled at the Harare site. Please, note that 97-percent are married and the mean number of lifetime sexual partners is only 1.3, so in the following slides when I present data on partners, in the majority of cases the women are reporting on their husbands and their husband is their only current partner, if not their only lifetime partner. The data thus far showed that the vast majority of women discussed joining the study with their partner, 98-percent. In fact, they not only discussed joining, they asked permission to join.

As indication of the importance of this communication, two-thirds of women said that they would face problems at home if they joined the study without first asking for permission.

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Communication about day-in/day-out study participation is also quite high, as 90-percent of women told their partners they were coming to the clinic the day of the interview and over three-quarters said that their partner asks about their visit every time they go to MIRA. Around two-thirds of men remind her to go to her visit.

So these measures of communication imply involvement, at least in terms of talking about the study. Men are not only highly aware of study participation. They are also reportedly highly supportive of women's participation and are interested in the study. In terms of men actually coming to the MIRA clinic, there is perhaps a slightly conflicting picture. Whereas 75-percent of women knew or remember from the consent forms that he was invited to come for VCT and 93-percent said they did invite him to come, only 4-percent of male partners came for counseling and testing. However, almost three-quarters of women said he would come for VCT if she asked him to.

Here it appears there is a difference between communicating that he is invited to come, versus the woman formally asking or insisting that he come. We measure not only men coming for VCT, but for any other reasons and 10-percent of partners did come for one of her visits. This includes those who came for testing or those who just came and said in the

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waiting lounge. We also looked at whether partners dropped her off or picked her up at the clinic and 16-percent and 11-percent respectively reported at least one instance of this during the course of the study.

In the MIRA study, we tested for HIV and STIs quarterly. Almost all women reported that they disclosed their HIV and STI results to their male partner at least once during the trial. Only 36-percent of women reported that their male partner had been tested for HIV, as far as she knew. Perhaps not surprisingly, the women reporting this were told his results. Of course, many more of these partners may have actually been tested and not disclosed results.

In terms of our study products, 87-percent of women reported that male partners strongly supported or supported the idea of using the diaphragm during sex. Similarly, almost all women report their male partners strongly liked or liked the diaphragm, and many women report that it was not at all difficult to convince him to use it. We explored some other indicators of male involvement with regard to the diaphragm. While only a small proportion said that their male partner helped to insert or remove the diaphragm at any time, almost two-thirds said their partner asked about the comfort of the diaphragm, whether it was fitting correctly and how she was storing it or cleaning it.

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Finally, I have some preliminary data here on disclosure of use of the diaphragm and gel. Almost three-quarters of women reported that they overtly reminded their partner or told him that they were using the products each and every time they had sex. However, secret use was important for women, at least some of the time, because 15-percent of women reported that they purposely hid diaphragm use at some point and 12-percent reported they purposely hid gel use.

I want to acknowledge that there are at least two potential sources of bias with this study. The first is that women in the MIRA trial may be different than other women in the community and, in particular, may have very different partnerships than most women or they would not be permitted to join the study in the first place. Secondly, as with many data collected via self report, the study may have social desirability bias. For example, women may have felt that study staff wanted to hear that their partners were supportive when they really weren't.

In summary, very few male partners came to the clinic, despite open invitations. However, most women reported that their partner was aware of their involvement and the majority reported that he was supportive. According to women, there is a fairly high degree of support and approval. During most sexual episodes, women communicated use of the diaphragm and

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gel to their partners and secret use was quite rare. You may recognize somebody in this picture.

The next steps and further analysis are to correlate indicators of male involvement from the – and the Male Partner Form with women's adherence and acceptability outcomes and to correlate indicators of male involvement with biological outcomes, then to look at characteristics of women with different levels of male involvement.

Finally, I'd like to acknowledge the Bill & Melinda Gates Foundation, which supported the MIRA study and this study, as well as the MIRA study participants.

[Applause]

**ROBERTA BLACK, PH.D.:** Do we have any questions for this speaker?

**FEMALE SPEAKER:** Thank you for the presentation. I'm Dr. [inaudible] from Bangladesh, working in Concern Worldwide [misspelled?]. I am very happy for this presentation, which I think is very relevant. At the time of HIV/AIDS, we are going toward feminization of the disease and involvement of males is very limited, I personally and professionally think. I have a few questions to ask, if I may.

First question is that you said that only 4-percent of the males came to the clinic, but their support was 95-percent to the women. Could you give me some reasons why this is so?

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Could you give me a little bit of in-depth understanding of why this has happened?

**ELIZABETH MONTGOMERY, M.P.H.:** Do you mean on the disparity between why they were supposedly so supportive, yet didn't come? Well, we are doing some qualitative work with men and with couples to explore this more deeply. It could have been purely logistics that the men were working and weren't able to come to the clinic. Anecdotally, we've heard that they didn't want to come because it is perceived as a women's place or they didn't see the benefit in coming, not because they weren't supportive, but that they purely didn't think it was necessary to come.

**FEMALE SPEAKER:** If I may ask a second question, you said that no specific interventions were taken for the male participants. I would just like to know if there has been any study done where specific measures were taken for male intervention for them to be more involved.

**ELIZABETH MONTGOMERY, M.P.H.:** Well, I do happen to know there have been several different types of approaches to encourage male involvement, lots of sort of couples-based studies comparing couples' approaches to women-only approaches, and those have shown that involving men is efficacious in terms of whatever outcome they are looking at.

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**FEMALE SPEAKER:** Thank you. So my only suggestion is that maybe we should have more in-depth studies done, taking more intervention measures to involve the male in these types of trials. Thank you.

**ROBERTA BLACK, PH.D.:** Up in the balcony?

**HARVEY MACADON [misspelled?]:** Yes, my name is Harvey Macadon from Boston. I think these studies have been very interesting. Aside from the point of each one, they raise a sort of a collective issue of sort of best practices of enhancing adherence to prevention methods, but they're very different methods. One is use of the husband's involvement and one is an intensive use of community workers who are involved in the study or were kind of study investigators. You could also look at a third model, which would be the sort of Partners in Health model of using kind of active members of the community as people who help with this. I'm just asking because I'm not a researcher, but a clinician and someone who tries to teach what the best practices are. Is anyone looking at what the best practices are to try and enhance women's participation in prevention activities? It seems like Nancy Padian [misspelled?] may be the person to answer this question since she's involved in all the studies, so I don't want to put you on the spot. I was just kind of asking everybody in general whether that is being looked at.

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**ELIZABETH MONTGOMERY, M.P.H.:** Comparing the different approaches?

**HARVEY MACADON:** Yes.

**ELIZABETH MONTGOMERY, M.P.H.:** Nancy, do you want to address that?

**HARVEY MACADON:** I think this is the main issue. This session will raise these questions and these things will be repeated many times, in terms of what the best ways are. I can remember going to India at the end of the week and hearing sort of comments about this session and about husband's participation and whether it works or doesn't work. I just think that it would be good to come to some sort of best practice.

**ELIZABETH MONTGOMERY, M.P.H.:** I agree with you. It would be useful.

**ROBERTA BLACK, PH.D.:** I think – just my own personal opinion – that there is a lot of sharing among the clinical trials. Many of the sites are doing multiple trials. I think there is a lot of sharing of these creative ways of improving the operations and the conduct of the studies. I think that's being done not only in presentations like this, but also in private discussions. I think that there is a lot and we are learning a lot from all these trials that are being conducted, a tremendous amount. I think it is terrific that this kind of

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information is being shared in this kind of venue. Nancy, did you have something?

**NANCY:** Well, I probably shouldn't have gotten up because I'm not 100-percent sure I understand the question. At least for study –

**HARVEY MACADON:** The question is not the results, but the enhancement and who is comparing the different modes of enhancements.

**NANCY:** Well, I think that Bobbi is right. People are comparing it. That said, though, I think the fundamental issue – again, in our study anyway – was not what we needed to do to get women to participate. It is the adherence, which is the trickier bit. Absolutely, these methods are being shared, but getting people to participate in these trials and remain in them isn't as big an issue as you might think it is, if I understood your question.

**ROBERTA BLACK, PH.D.:** I'm sorry, but I think we're going to have to move on to the last speaker. We're running a little bit late here.

[Applause]

Our last speaker is Dr. Jeremy Paull and I'm fairly certain he has a Ph.D. [Laughter], speaking on "SPL7013 Gel (VivaGel), a topical microbicide in development for prevention of HIV and genital herpes, shown to be well-tolerated and

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comparable with placebo after seven days administration is healthy males." Jeremy?

**JEREMY PAULL, B.SC. (HONS), PH.D.:** Thanks, Bobbi.

Hello, everyone. As Bobbi suggested, I'm going to present on a clinical study that actually directly involved males by testing the product in them.

VivaGel is in development as a topical vaginal microbicide for prevention of sexually transmitted HIV and genital herpes. I think the rationale for female-initiated microbicides is borne out in the extent of the HIV epidemic, the HSV epidemic in the developed and developing world, and the link between HSV infection and increased risk of HIV. The active ingredient of VivaGel is a dendrimer molecule called SPL7013 that has shown activity in the prevention of HIV and HSV *in vitro* and in animal models. In addition, we've seen significant contraceptive effect in rabbits and recent significant inhibition of sperm function *in vitro*, so there's a potential as a contraceptive agent as well.

Two clinical trials have been completed on the product to date, one in female volunteers and the one that I'll talk to you about today in male volunteers. The product is also currently under clinical investigation in two other ongoing trials through the STI-CTG group and the MTN group in sexually

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abstinent and sexually active females and further expanded safety trials are planned.

The rationale for conducting a study in males for a product that's intended for females – first of all, we have a promising clinical and non-clinical safety profile to-date. All topical microbicides require a favorable risk/benefit profile, must be tolerable and must be acceptable – as we've heard – to both male and females end users. When a product is used in women, it may result in incidental exposure in men and eventually a product may be developed for use by men. Therefore, we must assess the safety, tolerability and acceptability of this product in men, hence this trial. When assessing the safety and tolerability in men, we have to take into account the different anatomies of the circumcised and uncircumcised penis and therefore we stratify for circumcision status.

The primary objective of the study was to assess the safety of the product compared with placebo when applied topically to the penile epithelium and urethral mucosa. The secondary objectives included the assessment of the systemic safety of the product, systemic absorption of the active ingredient of the product SPL7013, and then an assessment of the acceptability of the study products.

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The primary endpoints for assessment of those objectives were participant reports of genital signs and symptoms and observation of other genital findings, which are listed there. Secondary endpoints included all other adverse events and abnormalities, plasma concentrations of SPL7013 and expectations and experiences of the study product. Data from the last point is to be presented separately in the future, so I won't talk too much about that today.

To be eligible for the study, participants had to have signed informed consent, had to be healthy males at least 18 years of age, negative for HIV and a range of other STIs, must have had no STI within three months of screening, had to at least demonstrate that they were able to comply with the procedures and restrictions of the study, even though some couldn't, and they had to have no history of allergy, significant drug reactions or other complicating dermatological conditions and no existing genital signs and symptoms or piercings.

Participants received 2 grams of the product applied topically, once daily for seven days. The study was double blinded and placebo controlled. The placebo was the base of the SPL7013 gel, without the SPL7013. Participants were randomized in a 2:1 ratio of active to placebo. As I mentioned previously, they were stratified according to circumcision

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status. The study was conducted at the Melvin Sexual Health Centre in Melvin. The PI was Marcus Chen.

A total of 36 healthy male volunteers were enrolled into the study. Of the 36, 24 received SPL7013 gel once daily for seven days and 12 received placebo gel once daily for seven days. Within those groups, half were circumcised and half were un-circumcised. There was a seven-day follow-up and a series of five visits throughout the study. I've listed the range of assessments that were conducted and included a genital exam at each visit, as well as other review of adverse events, PK sampling and sexual history and so forth. Participants in each of the treatment groups were all matched with respect to demographics and other baseline characteristics. The mean age of the participants in each group was similar across the groups. There was a similar ethnic distribution as well. All subjects were considered to be adherent to the dosing regimen, which meant that they had at least six doses. The mean daily duration of exposure to the product was also similar between the groups at approximately a mean of about nine hours.

In terms of the assessment of the primary endpoint and looking at genital events, there were 12 participants who reported as least 1 genital AE, 17 in total. All of those AEs were assessed as grade I, or mild. There was similar proportion of participants in each treatment group who had

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these genital AEs, and 15 of the AEs were assessed to have a potential causal relationship to the study product, being possibly or probably related. And 25-percent of participants had experienced those in the active group and 33-percent in the placebo group. There was no statistical difference between the proportions of participants in each group who had those AEs. The majority of the AEs commenced during the seven days of treatment, during the assessment period and the majority had duration of less than 24 hours and often as little as 30 seconds. The most commonly occurring events were penile or genital itching, 12-percent of participants in the active group and 8-percent in the placebo group. Penile redness was also seen at 4-percent in the SPL7013 gel group and 25-percent in the placebo group. Again, there was no statistically significant difference there. There was no apparent difference with respect to circumcision status.

We also assessed, as I mentioned, non-genital or other AEs, and there were 32 of these in 19 participants. These were, again, all grade I. All grade II non-genital AEs that were considered potentially related to treatment were in the placebo group. There was one abnormality which, again, occurred in the placebo group. In terms of the absorption of SPL7013, there was none detected in the samples analyzed and

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that is consistent with other studies we've done, both clinically and non-clinically.

In summary, I guess the expectations and experience section – the SPL7013 or the study products were acceptable to men and would be considered acceptable if they are eventually proven effective at preventing STIs.

In summary, I guess the results of this safety study showed that the product was safe, well tolerated and comparable with placebo and did not result in systemic absorption of the active ingredient when following the use of this product once daily for seven days. I guess this data combined with other clinical and non-clinical data suggests that VivaGel warrants further development and investigation as a microbicide.

I'd just like to acknowledge some people. There are quite a number of people there, but the study was funded under an NIH contract through NIAID's through Division of AIDS and was conducted in collaboration with a range of collaborators at Melvin Sexual Health Centre, [inaudible], the Burnet Institute and other groups there. I guess we're always interested in technical, scientific and commercial collaborations and partnerships, so I've put some contact details there. These slides will appear on the IAS Web site. Thank you.

[Applause]

**ROBERTA BLACK, PH.D.:** Do we have any questions for the speaker? I actually have a question. That is, I believe that VivaGel may be unique, in terms of your development for two different indications, both genital herpes and HIV. I wondered if you could just comment sort of generally about your development strategy.

**JEREMY PAULL, B.SC. (HONS), PH.D.:** Sure. We understand that VivaGel is the only microbicide to have an investigational new drug application with the FDA for both genital herpes and HIV prevention. I guess the prevention of genital herpes is a key target for this product. I guess the sort of likelihood that that product is applicable in a developed and developing world setting – I guess it has benefits in both regions. I guess the rationale for pursuing the genital herpes indication is that everyone's trying to find new ways to do clinical trials and develop these products, and I guess we feel that the prevention of herpes indication, given the level of the epidemic in the developed world, perhaps gives us a different angle to pursue the development of that product. I hope that answers your question.

**ROBERTA BLACK, PH.D.:** Thank you. Are there any other questions? All right, I'd like to thank the speaker [applause] and I'd like to thank all the speakers. We had wonderful presentations this afternoon. Thank you very much.

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[Applause]

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