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**4th IAS Conference On HIV Pathogenesis,
Treatment and Prevention:
Male Circumcision: The Cutting Edge of HIV Prevention
International AIDS Society
and Australasian Society for HIV Medicine
July 25, 2007**

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DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: We are in the Male Circumcision: The Cutting Edge of HIV Prevention. My name is David Serwadda from Makerere University in Uganda. My co-chair is Brian Morris from Sydney University. I must admit we have a late breaker in Saturday to this program, so we are going to be a little tight on time and we shall be a little bit brutal on timing and taking questions very quickly. So there's going to be a little bit of change in the program as I will illustrate.

The first presenter is Dr. Godfrey Kigozi from the Rakai Health Sciences Program. He's going to present on The Safety of Adult Male Circumcision in HIV-Infected and Uninfected Men in Rakai. Dr. Kigozi is a graduate from Makerere University and did his Masters in public health in John Hopkins University. Godfrey, please. [Applause]

GODFREY KIGOZI, M.B.CH.B., M.P.H.: Thank you very much, chairman. My presentation this morning is The Safety of Adult Male Circumcision in HIV-Infected and Uninfected Men in Rakai, Uganda. First of all I'd like to acknowledge my co-investigators from John Hopkins University, Makerere University and the [inaudible] Institute. I'd like to acknowledge the trial participants, our funders, that's the Gates Foundation as well as the U.S. National Institute of Health and the whole Rakai Programs staff.

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The objective of the analysis that we did was assess the safety of adult male circumcision by comparing rates of adverse events related to circumcision among HIV-positive and HIV-negative men.

As many of us already know, three randomized controlled trials have shown that male circumcision reduces the risk of HIV acquisition in men by between 50 and 60-percent and really know that WHO has recommended male circumcision as an additional strategy for preventing heterosexual HIV infection in men. The safety of surgery is therefore a paramount consideration in the planning future circumcision programs to minimize surgical risks and to provide guidelines for best practices in surgical procedures and postoperative care.

Some information is available on postoperative complications in children and in HIV-negative men with complication risks ranging from 2 to 10-percent if the circumcision is done by trained medical persons and under certain conditions. However, we have little information on the safety of male circumcision in HIV-infected individuals. If surgery is actually unsafe in HIV-negative men, then we would have to exclude HIV-negative men from programs, which would potentially stigmatize them or we would have to require specialized services for postoperative care which could add to program costs and complexity.

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We conducted two separate but complementary randomized controlled trials of adult male circumcision in Rakai. One trial, which was supported by the National Institute of Health was stopped in December 2006 for efficacy and the other trial, which was supported by the Gates Foundation, enrolled HIV-positive men, enrollment was stopped by the BSMD in December again because of futility.

In these two trials we circumcised 2,326 HIV-negative men and 420 HIV-positive men and this surgery was done by trained physicians using the sleeve circumcision procedure. All men who were circumcised provided written informed consent and were strongly advised to refrain from sexual intercourse until the wound was certified healed by our clinicians. Men were advised to practice safe sex, that's the ABC, and we did postoperative follow up at approximately 1 day, 7 days, and 1 month post-surgery. And during these follow up visits we assessed surgery-related adverse events, we looked at wound healing and presumption of intercourse.

Adverse events we grade as mild, moderate or severe. Moderate and severe adverse events actually required medical care or surgical intervention. All adverse events were reviewed and summarized by a medical officer at the time they were reported. We used Chi-square or Fisher's exact tests to compare adverse event rates and wound healing between HIV-positive and HIV-

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negative men. We used multiple logistic regression to assess factors associated with surgery related adverse events.

What did we find? For those of you who are interested in numbers, you can look at the upper part. Those who hate numbers can look at the bottom section. We compared characteristics of HIV-positive and HIV-negative men at enrollment and looking at marital status and education we found HIV-positive men were more likely to be married, that number that one, and less educated, comparing that.

As regards numbers of sex partners in the past year, again HIV-positive men reported more sexual partners compared to HIV-negative men.

Among the sexually active population, HIV-positive men again reported less consistent condom use, 7.5 compared to 6.5, and had higher rates of STD symptoms, including GUD, urethral discharge, and dysuria.

We looked at surgery related adverse events by severity and overall we found no significant difference in rates of moderate or severe surgery-related adverse events between HIV-positive and HIV-negative men. The rates between grade 1 and grade 3 adverse events was 3.1 compared to 3.6. Pointing to grade 2 and grade 3 adverse events because their numbers required medical or surgical observation.

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We looked at common surgery related adverse events by severity and the most common adverse events we found was infection and the rate of moderate or severe infections were 1.9 in HIV-positives versus 2.3 in HIV-negatives. The rest are insignificantly different.

Looking at bleeding and hematoma, again we found no significant difference in complications rates. Bleeding and hematoma have that rate in HIV-positives and that in HIV-negatives. The rates of wound dehiscence were a bit higher among the HIV-positives compared to HIV-negatives but again the rate was not significant, the difference.

We looked at surgery related events by timing of resumption of sexual intercourse among the two groups and what we see is that adverse event rates are generally higher in men who resume sex before wound healing compared to those who resumed sex after wound healing were certified. However, the differences are not statistically significant and this is true for both groups, HIV-positive and HIV-negative men.

We also looked at the rate of complete wound healing and what we are seeing is that the proportion of men with complete wound healing by 30 days post-surgery was lower in HIV-positive men compared to HIV-negative men. Multiple regression identified no significant sociodemographic behaviors or STI symptoms that are predictive of moderate or severe adverse events.

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In conclusion, overall the safety of circumcision was comparable in both HIV-positive and HIV-negative men. We find the rates of moderate or severe adverse events are acceptably low in both HIV-positive and HIV-negative men. And wound healing was somewhat slower among the HIV-infected men. Resumption of sex before wound healing was associated with higher complication rates, though not statistically significant.

Thank you very much. [Applause]

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: Thank you very much. I think we have about five minutes to take some questions. Alright. I take it there are no questions.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: To the microphone if you would please.

KEVIN BACOE: I have a question. Thank you very much. Kevin Bacoe, WHO. Were you able to stratify your incidents of adverse events in the infected men by CD4 status?

GODFREY KIGOZI, M.B.CH.B., M.P.H.: We have not done that by CD4 status, but we can have a look at that.

KEVIN BACOE: Do you have any idea of the CD4 distribution of the HIV-infected men?

GODFREY KIGOZI, M.B.CH.B., M.P.H.: The men that we actually enrolled had CD4s around 350. Men who had CD4s below 350 were excluded. At the beginning of the trial we were including

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men who had [inaudible] of stage 1 and 2 in respects of the CD4 count.

KEVIN BACOE: That seems very important that if immune suppressed men were excluded, then I don't think you can really generalize that adverse events were the same across HIV-infected and uninfected men.

GODFREY KIGOZI, M.B.CH.B., M.P.H.: Actually these findings, I think in one of the slides, they are true for men who have CD4s greater than 350 as well as HIV-positive men that are at stage 1 and 2.

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: Kevin, that's a good point and I think in our analysis try to do further stratification onto that. Any other questions? I think we'd better move on.

We have to move onto the next presentation and this was a late breaker presentation in Saturday. This is Male Post-Coital Penile Cleansing and the Risk of HIV-Acquisition in Uncircumcised Men in Rakai District. This is going to be presented by Dr. Fred Makumbi. Dr. Fred Makumbi has a Ph.D in biostatistics from John Hopkins University and works with Rakai Health Science Program.

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: Thank you very much for the introduction. On behalf of my co-authors I'm presenting Male Post-Coital Penile Cleansing and the Risk of HIV-Acquisition in Uncircumcised Men in Rakai District.

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We know that HIV epidemic remains unabated especially in Southern Africa. HIV prevention interventions include male circumcision and the ABC strategy which is well known. The three RCTs have demonstrated the male circumcision efficacy and this has now been recommended by the WHO. However, there are substantial challenges to male circumcision scale up including severity, ethical social cultural and realize that many national governments, especially in Southern Africa have not yet fully endorsed this strategy. However, there are other additional prevention methods to be explored which includes penile microbicide wipe, post-coital cleansing with water and soap, though both of those which may potentially reduce HIV infectious vaginal secretions.

Use of water with or without soap following coitus is quite common in Africa. However, there are no prospective studies conducted to assess the impact of HIV acquisition in uncircumcised men practicing post-coital hygiene. Use of water and soap first in prophylaxis showed a reduction in GUDs, publications shown above. Also the study conducted in Kenya showed that bathing after sex was associated with reduced odds [misspelled?] of being HIV-positive. But this population was highly circumcised men.

We know, again from research in Kenya, vaginal cleansing using water and soap was associated with increased HIV

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acquisition among females. Therefore, we set out to assess the association between the post-coital penile cleansing and the risk of HIV acquisition among uncircumcised men. The trial in Rakai enrolled about 2,500 uncircumcised men in the control arm and 1549 HIV-negative who accepted VCT with the follow-ups at 6, 12 and 24 months. Among the data collected was the genital hygiene information. All of us know the trials was unblinded December 12 after showing efficacy of 51-percent in the interim analysis.

We especially looked at data obtained on questions on genital hygiene practices after intercourse, which included questions on whether people reported penile cleansing after sexual intercourse, and the cleansing materials used as shown. We also asked men questions on duration of time from completion of coital cleansing and this time was self-reported in minutes for each sexual partner they had sex with.

Here are some key definitions for the analysis. We have washed with all partners. If a man reported cleansing the penis following coitus with all sexual partners, he was put in that category. Washed with some, if they cleansed their penis with some but not all sexual partners. There are some who say they never washed or they reported no cleansing with any sexual partner. The research reported duration from coitus to cleansing was categorized in those three groups as shown. All this information obtained from the control arm of the trial and at

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those subsequent follow-up visits and the behaviors we assessed for the periods preceding the interview of those specific follow-up visits.

We have a total of about 4,300 intervals with the data on post-coital cleansing which we accrued from sexual active men. And we have about 83-percent of those follow-up intervals where men reported washing with all sexual partners they had sex with. We have about 2,300 intervals with the data available on the cleansing materials used. For the analysis, we estimated the HIV incident rate by a 100 person years and we have the incident rate ratios using the possible aggression models. We had co-variates fixed. Co-variates which are age and marital status which are obtained at the time of enrollment and you also had ten varying co-variates, mainly sexual risk behaviors known to be associated with HIV infection as shown on the slide.

For the co-variates in the adjusted analyses, all those variables included had to have a P value of 0.15 in an analysis, all those risk rates of 2 and above are less than 0.5, all suspected confounders and use data for the analysis. What did we find?

This table shows post-coital washing with partners, they never washed, washed, and washed with all. What we see at the end of the day, realize that men most reported in the intervals consistent washing we see was not associated with a reduction in

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HIV. The incident risk ratio was about 1.5, but that was insignificant as we see the Y context intervals. And all the analysis was adjusted for condom use, marital status, age, frequency of sex, passivity of partner HIV risk. Table number 2 shows duration from sex to penile washing, men who were asked if they washed. We did not ask them what materials used, did you use soap or not, but the question was did you wash. And the time periods were categorized as shown and what we see is that increased , HIV incidents was significantly lower if washing was delayed 10 minutes or above. We see sort of an increase in the incidents as the increase in the time duration from intercourse to washing.

Then we also looked at the methods used for cleansing and reported use clothes alone. Some used cloth and washing and those who reported washing alone. And we see an increasing degree of wetness as assessed by self-reported washing being associated with boldly significant train of increasing risk of HIV acquisition.

In summary we see that in this population, this group of uncircumcised men, the control arm of the trial, post-coital penile cleansing is common in this population. But as practiced in that group of men, it does not offer protection from HIV acquisition and these are uncircumcised men organized from sites. Washing less than 10 minutes, as shown again, after intercourse

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may increase HIV risk from this data, rarity to those who delayed cleansing. Washing alone, again, associated with a non-significant increase in HIV acquisition among uncircumcised men.

I must admit these results were sort of troubling and not expected. And like I was saying, some people may think that all should stop washing or hygiene but the results do speak for themselves that we need to understand them. What are they saying, what are they meaning. However, those are some of the possible explanations that we reported that the acidic pH of vaginal secretions may impair HIV survival. Therefore, use of water with a neutral pH may facilitate virus survival and possible infectivity, therefore, the late cleansing may reduce the viral infectivity by prolonged exposure to less vaginal secretions as we saw that duration and HIV incidents.

However, there are some limitations in this study of this analysis, this observational data in the uncircumcised control arm of the trial, the self-reported data as well. But we really have no reason to believe that they are unreliable. It is important to realize that we never collected information on the use of soap which may potentially [inaudible] mucosa. However, in this cohort of Rakai where some of these men we have selected to come into the trial, 75-percent of the men in the cohort who washed say that they used soap as one of substance, although we never picked this specific information during the trial. Realize

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also that we did not again pick any of the information on the actual practice of cleansing was done.

Recommendations? We need to do some studies and look critically to see how the virus survival in the vaginal secretions and see the significance of water or cleansing materials such as soap on HIV virus survival and this immunological response with diluted and undiluted vaginal secretions.

I'd like to acknowledge several participants, the staff and the grant which supported this research. Thank you very much.
[Applause]

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Very good. If I could just make one comment from the chair. The end value of the delayed washing group was quite low. Was it two? Did I see a value of two?

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: Yes.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: So that would make it way too low to draw any conclusion. I would think you would probably need to get quite a bigger study group for a longer period before you can really draw a conclusion about the delayed washing, which is as you say, it's an odd finding anyway.

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: The only two in those cases in a delayed was 10 or more. But when you collapse that group to within three minutes and three minutes and

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above, still there was a significant difference between those who washed within three minutes. However, like I again emphasized, these observational studies, we need to be very careful about any conclusions that we make. That's why I gave a summary other than a conclusion.

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: Okay.

Thanks. Yes?

ANDREW GERGEN: Andrew Gergen from Sydney. Thanks for the presentation. I just had a question about confounding because you presented in multivariate results to us but not the univariate results. And I'm just wondering one explanation that you could think of is that men who are washing because they believe they are at greater risk of HIV. Was there any evidence that they were at greater risk of HIV, such as were they more likely to report HIV-positive partners or more likely at risk sexual behavior?

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: A lot of the confounding that I have I just said for frequency of sex, condom use and a colleague again advised and we looked at the possible HIV status of the sexual partner and that did not have any impact from the unadjusted and the adjusted analysis. However, possible HIV infection was a risk factor for HIV acquisition.

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ANDREW GERGEN: So they didn't have any effect in the adjustment, but were they associated with any variables in washing the genitals?

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: Yes, they are associated, yes they were.

MALE SPEAKER: I have a question I didn't see entertained with regards to the [inaudible] STIs. Were there STIs in the cohort participants?

FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: Yes, again I think the publication made for the Lancet shows the GUD. Yes, the set of group had STDs and again it was one factor that was outstanding in the circumcision study. Yes, the participants had but not analyzed just for the STDs in this presentation.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Okay, one last one. Thank you.

BEN TALLEY: Thank you. Ben Talley from Melbourne. Again another question about confounding. With regard to the men who washed within three minutes versus those who washed later, was there any association with this receiving HIV-positive partner because it would be plausible that men who washed within three minutes are doing so because this is either a non-regular partner or commercial sex worker or something. I'm wondering if that explains the increased risk of transmission of men who washed within three minutes because it was a high risk partner.

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FREDERICK EDWARD MAKUMBI, B.STAT., M.H.S., PH.D.: It's interesting because again that concern, and people keep bringing it up, because even during this analysis kept on coming up until we set down and re-analyzed this data. That did not contribute. However, if a male partner perceived that their sexual partners were infected, that increased the risk of HIV infection. However, adjusting for all of that did not impact on the duration from post-coital sex to the cleansing thereafter. So we looked at that and even the frequency of sex and also constant condom use issues came up and looking at all those still did not seem to have any impact on the incidence associations.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Thank you very much, Fred. [Applause]

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: The next presentation is from Peru. How Willing are Gay Men to "Cut Off" the Epidemic? This is going to be presented by Juan Guanira. He's a graduate in public health from the University of Washington, Seattle. Walking in HIV fit for the last five years. Please. [Applause]

JUAN GUANIRA, M.D., M.P.H.: Thank you for the introduction and the title of my presentation is How Willing Are the Gay Men to "Cut Off" the Epidemic? Circumcision Among MSM in the Andean Region.

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HIV epidemic in the Andean region as well as in the U.S., Europe and some other countries is mainly concentrated in men who have sex with men. The number of cases continue to increase despite the broadly known preventative strategies already implemented. Male circumcision studies have proven to be efficacious in reducing HIV acquisition in heterosexual men by 60-percent. But differences in vaginal versus anal mucosa and types of sexual roles might compromise the effectiveness of the intervention in MSM. Formative research is of need to assess the feasibility of the implementation of such studies in the MSM population.

The objectives of this study were to assess the circumcision rates in MSM, to evaluate the willingness to participate in circumcision trials for HIV prevention among MSMS and to identify concerns, barriers and facilitators for the implementation of a circumcision trial in MSM population.

This study was a cross-sectional study. The inclusion criteria were they have had anal sex within the last 12 months, unknown HIV status or HIV negative and not having HIV test during the last 12 months and have engaged in high risk behavior. Procedures for all participants include clinical history, physical examination, behavioral assessment by computer assisted self interview and also testing with rapid test for HIV 1 and 2 and syphilis.

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This study was noted in the HIV Sentinel surveillance among MSM in five Andean cities during the first quarter of 2006. A total of 2,618 MSM at high risk of HIV infection were enrolled in this study. It's mentioned that all the 570 participants from one of the cities, Sullana, was excluded from this analysis due to issues in circumcision status assessment. The accrual for the remaining cities were Lima 676 participants, Arequipa 417 participants, Ica 414 participants and Guayaquil, Ecuador 541 participants. In the map you can see the geographical locations of these cities. Guayaquil, Lima and Ica were located in the coast and Arequipa was located in the highlands of Peru. The total sample for this analysis was 2,048 participants; 41 of them refused to be examined so circumcision status could not be assessed, 75 were completely circumcised and 1,932 were not circumcised by physical examination. A willingness to participate in a circumcision trial questionnaire was applied for those not circumcised.

This table shows the selected demographic and behavioral characteristics for all participants. The mean age of the participants was 26-years-old across all the cities. Most of the participants had at least high school education, also. The sexual role in the five years was assessed using a five point litress [misspelled?] scale that ranged from exclusive insertive to exclusive receptive. For further analysis because the

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effectiveness of circumcision will only protect those insertive, the two first categories will be considered as insertive and the other two as receptive.

This graphic shows the rates of syphilis and HIV and also the estimated incidence of HIV via the [inaudible] across the cities. Lima and Guayaquil have the higher rates of HIV and syphilis compared to Arequipa and Ica. Being Guayaquil the greatest affected with HIV rates of more than 18-percent.

Circumcision rates are consistently low across cities with a mean of 3.7-percent, being higher in Lima and Guayaquil compared to Arequipa and Ica.

The univariate analysis of the willingness to participate in a circumcision trial among those not circumcised show a [inaudible] to the city where the participant lives. People living in Arequipa and Ica, cities with less than 1 million inhabitants, were less likely to be willing compared to Lima, the most populated city. And people living in Guayaquil, second most populated city in this study, were more likely to be willing. In the multivariate analysis having higher education was independent associated with the willingness to participate. Also, just to mention, that those insertive were more willing than those receptive, but the difference was not significant.

Concerns about participation in a circumcision trial were assessed and the main concerns were to have a surgical procedure,

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side effects of the surgery like pain, swelling, or secretions, and that your partner would insist having sex without condoms. No minor concerns related to the follow-up period of the HIV testing were reported.

MSM at high risk in the Andean region have high rates of HIV and STIs. Circumcision rates in MSM are low across all the cities. No association between circumcision and HIV infection were seen when all the sample was analyzed, but a trend to a significant protective effect was seen when only those insertive were analyzed. Higher education and living in the large cities are independently associated to be willing to participate in a circumcision trial for HIV prevention in MSM. And minor concerns of undergoing circumcision are related to surgical procedure and misperception of protection.

Because of the design, convenience based samples, self-selection bias and recall bias are the main limitations. But moreover, low rates of circumcision in the samples decreased the power to find the associations between circumcision and HIV infection and finally the results cannot be generalized to other populations.

Then we may conclude that because the low rate of circumcision, the high incidence of HIV and the high rates of willingness, a circumcision study to assess the efficacy in the

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prevention of HIV is feasible in the MSM population of Lima and Guayaquil.

I would like to acknowledge all my colleagues that participated in this study, especially to those participants in all the cities. Thank you.

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: Thank you very much, Juan. [Applause] Alright, thanks very much. Any questions? Yes, please.

HANS YAGER: Hans Yager from Munich. You showed us nicely that you had to exclude 570 people from analysis because of issues in assessing circumcision. Could you share with us what those issues were?

JUAN GUANIRA, M.D., M.P.H.: Well, that was an entire city that was not included in the study because the physician didn't assess correctly circumcision status in that city. So, we realize that circumcision status was not well assessed and when we asked the staff of that city, we realized they were not assessing the circumcision as was supposed to be done.

HANS YAGER: Could you share what those difficulties were because we all have to learn from this [inaudible]?

JUAN GUANIRA, M.D., M.P.H.: For example, they confused the phimosis status with circumcision, so they considered people with phimosis as circumcised, so it was a problem with training in that city.

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FEMALE SPEAKER: I am [inaudible] from USI, India and would like you to know you are doing a wonderful study. I think this one of the first studies that I've seen here that's trying to do a segmentation of what we call the behaviors and the non-behaviors and I think this ability that you cannot have sufficient numbers where segmentation, that you cannot have the kind of correlation that you are trying to hold with. So, I'm just trying to understand, was this kind of a ballot study? Are you trying to follow it up with another study where you can ensure having enough numbers for the groups?

JUAN GUANIRA, M.D., M.P.H.: Yes, in fact we can do a second part in Lima to enroll 900 more participants. This data is now being evaluated, but the relationship between circumcision and HIV infection still was not significant but was really close to the significance was the old ratio where about 0.33 and the value was 0.07.

FEMALE SPEAKER: And just one other comment. The population characteristics that you were using like the age or the other characteristics that you have just shown expect for the sexual behavior, I think those are the population characteristics. A program can work on it in a targeting approach. But those cannot be the determinants of the behavior, which if you want to change the circumcision and promote and motivate the men to circumcision, there cannot be determinant. So

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I don't think, circumcision whether a man would go for it or not, those should be further explored and investigated.

JUAN GUANIRA, M.D., M.P.H.: Thank you for the comments.

We do the analysis for the circumcision association for HIV and also having account the type of sex the participant have with the last partner, because it depends not only if the participant says it was insertive this person, but also the kind of sex they have with their partners. They can say they are mainly insertive, but in the last partner had receptive sex with condom, without condom, insertive sex with condom, without condom. We try to control all those characteristics to do this analysis.

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: Thank you very much. I'll hand over the chair to Brian to continue the chair in this.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Thank you. The next talk will be by David Templeton on behalf of his colleagues at the National Centre in HIV Epidemiology and Clinical Research and the National Centre in Social Research at the University of New South Wales here in Sydney. And the title of the talk is Circumcision Status and Risk of HIV Seroconversion in the HIM Cohort of Homosexual Men in Sydney.

DAVID JAMES TEMPLETON, M.B. CH.B., DIP. VEN, GRAD. CERT. FORENS. MED., M.A.C.L.M., F.A.CH.S.H.M.: Thank you, Brian. I was discussing the results of this talk to some of the participants

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of our study to some of the representatives of the gay community and organizations in Sydney last week unawares of what I was actually saying without providing them a snippet of the information I was providing today. And then even worse, as you can imagine to an audience of predominantly gay men change that to a taste of the information I was providing today. So I'm simply going to say today I will present our research on circumcision status and risk of HIV seroconversion in the Health in Men cohort and thank you to the organizers for allowing the opportunity to present on behalf of my colleagues.

First, I'll briefly present some background on this topic and then outline the methods of the Health in Men study. I'll then present some related analysis that we have performed in the Health in Men study including demographic predictors of circumcision status and a sub study that we carried out validating self-reported circumcision status by clinical examination. Finally, I'll present the main parts of our analysis on circumcision and risk of HIV seroconversion in our cohort.

We had an excellent presentation yesterday morning from Professor Bailey in which outlined the benefits of circumcision in African and we've heard that several times this morning, that among heterosexual African men there's no particular inclusive evidence that it reduces HIV incidence and by around 60-percent. However, in contrast there's relatively few un-conflicting

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studies among homosexual men. The first study was carried out in the early 90s in a clinic based population and reported more than twice the risk of HIV and positivity among uncircumcised men. However, a more recent clinic based study that was presented last year in Florida and reported no association of circumcision status with prevalent HIV infection among STD clinic attendees in San Francisco. Also, a smaller study among homosexual men who had recently seroconverted to HIV and who reported insertive unprotected anal sex as their probable high risk exposure leading to the infection, there was no association of circumcision status in that study either. The only other prospective cohort study which has looked at this issue was published a couple of years ago in JAIDS and found an adjusted odds ratio of 2 so increased HIV risk in uncircumcised men after controlling for sexual behavior, drug use and demographic factors.

The Health in Men study recruited Sydney gay community attached men between 2001 and 2004. At recruitment, participants underwent a HIV test and HIV-negative men were enrolled into the study. Detailed sexual and other behavioral data was collected every six months at alternating face-to-face and telephone interviews. All participants were offered testing for sexually transmitted infections at each face-to-face interview and approximately 90-percent agreed to this testing each year. In addition, participants self-reported sexually transmitted

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infections diagnosed outside the study in the previous 12 months at that face-to-face interview. Circumcision status was self-reported at baseline and validated by clinical examination in a subgroup of participants. All participants underwent an annual HIV testing and an annual match with a National HIV Register was performed to identify participants who are lost for follow-up to the study and whose HIV infections were diagnosed elsewhere in Australia. For our statistical analysis we used Cox regression.

A diverse recruitment strategy was used for the Health in Men study. As you can see, most participants were recruited at gay community events with only a small number recruited at the clinics. Therefore, we consider our study population to be broadly representative of Sydney gay community attached men.

Over 1400 men were enrolled with an 80-percent retention rate at two years. The median age of participants was 35 years and median follow-up time was 3 years. Participants lost to follow-up did not differ significantly in terms of their circumcision status compared with the entire cohort baseline. 95-percent of participants self-identified as gay or homosexual.

Critics of some past research on this topic have cited inadequate control for demographic factors which could confound any association with circumcision status and HIV seroconversion. So we previously sought to elucidate some of these factors. We found that two-thirds of participants reported being circumcised

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at baseline with the vast majority circumcised as an infant. On multivariate analysis older age was strongly associated with being circumcised as were ethnicity and country of birth. When we excluded the 17 Jewish and Muslim participants, all of whom were circumcised, there was no association between religious affiliation and circumcision status. Also, there was no association between circumcision status and level of education or income.

Correlation with clinical examination findings and self-reported circumcision status has been reported previously by some authors to be poor, and we were unable to find any published research on validation of self-reported circumcision status among homosexual men. So we sought to validate participants self-reported circumcision status. From February to June this year, 87-percent of HIM participants approached at their annual face-to-face interview agreed to be examined by the study nurse and the study nurse was unaware of the reported circumcision status at the baseline interview. I suppose unsurprisingly all gay men managed to say if they were circumcised or not correctly. So there was 100-percent concordance between baseline self-report and clinical examination findings in that subgroup.

Overall to the end of 2006 there were 49 HIV seroconversions in the Health in Men study, an incidence of 0.80 per 100 person years. For our analysis of circumcision status and

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HIV risk we excluded six participants whose HIV infections were only identified by matching with the National Database and for whom the behavioral data we had was over 12 months old. In addition, we also excluded another participant who notably also seroconverted and was the only one who reported a surgically reconstructed foreskin at baseline. And, therefore, the analysis of circumcision status and HIV risk was based on 42 seroconversions. Univariate analysis revealed no association between circumcision status and HIV seroconversion. And actually when we included the six seroconverted identified by matching with the National Register that had little effect on the hazard ratio presented here.

Because of its strong association with being circumcised we forced age into the multivariate model despite a lack of univariate association with HIV incidents. Of the other demographic factors associated with circumcision in HIM neither ethnicity nor country of birth were associated with HIV seroconversion and weren't included in the multivariate model. We also controlled for unprotected receptive anal intercourse according to the reported sero status of participants sexual partners as this was the single sexual behavioral variable most strongly associated with HIV seroconversion on univariate analysis. Finally, we controlled for self-reported anal warts and study confirmed anal gonorrhoea as these were the only STIs

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significantly associated with HIV seroconversion. After controlling for age, unprotected anal sex by partner, sero status and these anal STIs, there remained no association between HIV incidents and being circumcised with an adjusted hazard ratio of 0.88 in circumcised men.

As most gay men are infected with HIV via receptive unprotected anal intercourse and thus there is no potential for their own circumcision status to protect them against HIV, we performed a stratified analysis on participants who are more likely to have contracted HIV by insertive anal sex. Now obviously a word of caution here. This analysis is based on very, very small numbers and so the confidence intervals are very wide. However, when we did this analysis of the nine who reported no unprotected receptive anal sex, there remained no association even when we controlled for age.

So, in conclusion, we find no association of circumcision status with incident HIV infection with cohort of community attached Sydney gay men. This lack of association is not really surprising given that multivariate analysis of anal sexual behavior as risk factors for HIV in HIM found in association with receptive and not insertive anal sexual practices. The strengths of our study design included validation of circumcision status and the analysis of and control for potential confounding factors. However, the low HIV incidents especially in those

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reporting no unprotected receptive anal sex limits any firm conclusions that can be drawn. I just noticed in the previous speech by Dr. Guanira that he reported 30 to 60-percent of the population in the Andean region reported exclusively insertive anal sex. So perhaps an investigating further in this issue in populations where there is greater diversion to exclusively receptive and insertive practices may provide more information on this topic. However, and despite the convincing evidence of circumcision in HIV incidence in African heterosexual men, we feel the few and conflicting data that exists in homosexual men suggests that it would be premature to consider promoting circumcision as a HIV prevention intervention in this group.

So I'd just like to finally thank my collaborators and colleagues at both National Centres in Sydney. I'd especially like to thank Professor Andrew Grulich and Dr. Jeff Jin, my boss at Sydney Southwest, Dr. Cathy O'Connor, for allowing me extended leave to undertake this research, our funders, of course the participants and the excellent HIM study team. And I'd just like to refer you to Jeff Jin and poster which has got more detail and analysis of anal sexual behaviors as risk factors for HIV seroconversion. Thank you for your attention. [Applause]

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Thank you very much. Are there any questions? Perhaps as people are coming to the microphone I just might ask one of my own. You mentioned the

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possible lack of power in this study, I think you had about 1,000 subjects. Of course, the study by bookbinding that you referred to, in fact had 3,257 homosexual men in six different U.S. cities, so it was a much more powerful study and that as you said showed a doubling of the risk in the uncircumcised men. Of course, the other cases of heterosexual men and there have been a number of studies as well where the rights between three and fourfold of the men are uncircumcised, and that's again in the U.S.A. You pointed out these discrepancies. Why? Why these major differences between the American results and these results here in Sydney and some of the other studies that are actually in America as well?

DAVID JAMES TEMPLETON, M.B. CH.B., DIP. VEN, GRAD. CERT. FORENS. MED., M.A.C.L.M., F.A.CH.S.H.M.: That's certainly something that we've considered. I mean obviously I think in America, certainly I think the circumcision rates are much higher. I believe in the binder studies circumcision rates approach 90-percent compared with ours which are about 66-percent at baseline and certainly the ethnic mix in the U.S. is quite different. You have much higher proportions of ethnic minorities, the African Americans, the Hispanics and proportionately account for a much larger number of the population. And they have in their populations much different in their circumcision rates to those in the Caucasian population. So I guess there are quite a

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lot of potential differences and potential confounding factors. And certainly we wouldn't feel that our results from Australia could be extrapolated to other developed countries, certainly the U.S., because of some of those differences.

JOSHUA HERMODENA: My name is Joshua Hermodena. I'm from the Philippines. I'd like to tell you that I'd be very glad that Filipinos are 90-percent are circumcised so we don't [laughter]. My question is reflect on all your percentages today. My question is regards your work on the National Database. Do you have any clue or any developed guidelines in other countries that would break with your work? The absence of guidelines in each country that poses a challenge in each of us in our interventions.

DAVID JAMES TEMPLETON, M.B. CH.B., DIP. VEN, GRAD. CERT. FORENS. MED., M.A.C.L.M., F.A.CH.S.H.M.: Are you asking about guidelines of circumcision?

JOSHUA HERMODENA: I'm not saying the question 100-percent. Today does your work reflect with the National guidelines or is there any guidelines that have been created?

DAVID JAMES TEMPLETON, M.B. CH.B., DIP. VEN, GRAD. CERT. FORENS. MED., M.A.C.L.M., F.A.CH.S.H.M.: Certainly in Australia based on certainly many pro and anti circumcision groups as there are in many other parts of the world. I guess that certainly those groups would quote many published studies which have shown benefits and risks associated with the practice. But from an HIV

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prevention point-of-view aside from mentioning the African studies which, of course, are impossible to generalize to an Australian population and there are certainly no guidelines on the basis of circumcision preventing HIV in the Australian population.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Perhaps I could just add something. Things are in progress with the Royal Australian College of Physicians. Their previous study has been heavily criticized and the publication, The Australian/New Zealand Journal of Public Health by myself and colleagues early last year and as an response to that I realized that an evidence based review using public health people and not just pediatricians was required and that's under way and that is supposed to be reported at the end of this year. And I think the evidence, not just HIV aids, but many other conditions which you can find in the brochures which I've left around the room and outside which you're welcome to take as many as you wish, clearly indicate a plethora of benefits across a whole range of conditions and diseases both in men an in their sexual partners, male and female.

DAVID SERWADDA, M.B.CH.B., M.SC., M.MED., M.P.H.: Let me add to that for the presenter. The first two presentations we heard from Uganda. And as you know, some of the trials that are associated with reduction of HIV with a physician with

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circumcision are done in Uganda. Ugandan government is actually in the process of formulating guidelines for up scaling circumcision and this guideline will be out fairly very soon. So yes, there is an effort to have guidelines, country guidelines, specific guidelines and modifications of the guidelines as generated by WHO and UNAIDS in March.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Okay, I thank you very much. [Applause] The next talk is by Greg Londish at the School of Mathematics, the University of New South Wales here in Sydney. The title of the talk is Mathematical Modelling of Male Circumcision in Sub-Saharan Africa Predicts Significant Reduction in Adult HIV Prevalence Even When it is Limited to Certain Age Groups.

GREGORY LONDISH: Thank you very much to the organizers for allowing us to present our research.

With the recent growth for evidence of male circumcision in reducing the risk of HIV infection in heterosexual African men, we investigated the impact of a circumcision based intervention in sub-Saharan Africa. Specifically we had three objectives. The first was to determine by how much HIV prevalence could be reduced if only part of the population was circumcised. Second, was to determine which group should be targeted if total coverage isn't possible. And third, how sensitive an intervention would be to increases in risky behavior.

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Our model was to create a mathematical model to simulate the cost of an HIV epidemic in a sub-Saharan African population under different intervention scenarios. In our model we divide the population up into groups based on gender, age, sexual activity, circumcised and uncircumcised in HIV infection. Given the setting of Africa, we limited transmission modes to heterosexual contact and mother-to-child infection. With sexual contacts we assumed that mixing was dependent on age alone, with men mixing preferentially with younger women and female sex workers. Our model starts the epidemic in 1980 with initial conditions taken from historical data and simulates the epidemic until 2020. Given that time span, we also simulate demographics of the population including fertility and death rates.

This slide shows a simplified diagram of the model and you can see that at first the population was split up into uninfected and infected male and female. The population is then split up further into a core group and a non-core group. The core group is a high risk minority comprising between zero and 20-percent of the population and each member has about three to five times the number of sexual contacts per year compared to a non-core member of the same gender. The reason for this is that a core group is often responsible for maintaining an epidemic in a population where it would otherwise die out. We then split up men into circumcised and uncircumcised and though it's not

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illustrated on the diagram, each group is split up into 80 age groups spanning one year each and the infected class is split up into five different stages of HIV infection. The red arrows indicate a major transmission mode of heterosexual contact from men to women and vice versa.

For each intervention scenario considered, we generated a paired set of simulations, a control set and a set with an intervention starting in 2007. Each pairing in the set in the simulations have the same parameter values and this allowed us to calculate the reduction in HIV prevalence due to the intervention alone. To account for the uncertainty in our parameters, for example the relative risk of circumcised men, is approximately 60-percent. That can range between 30 and 70-percent. So to account for this, we used a Monte Carlo method to generate the main reduction in adult HIV prevalence as well as a 95-percent control set intervals. In this we repeated our simulations 500 times for each scenario, and used Latin Hypercube Sampling to select the parameter values. The parameters and their values were taken from published data of observational studies, clinical trials and other models.

To confirm the validity of our model, we compared data of male circumcision and HIV prevalence in different African countries in 2003 with the same data produced by our model. This graph shows the two data sets. The circles represent the

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observational studies, and the lines and squares representing our model. And you can see that on the whole, the model and the observations agree. There are some countries that lie outside the 95-percent comparison incidents of the model, but more recent estimates of HIV prevalence in these countries have been lower lying well within the bounds of the model. The data also suggests that there are additional specific region factors that we have not modeled.

The first of the scenario results that I would like to discuss is the reduction in HIV prevalence when only part of the population is circumcised. In this scenario we started with different levels of male circumcision, and from 2007 began circumcising additional percentage of the population. This graph shows the decrease in HIV prevalence depending on the additional percentage circumcised and you can see that the reduction is roughly proportional to the additional percentage circumcised. To put this in the context of an actual African country, take Zimbabwe for example. In 2003 Zimbabwe had an adult HIV prevalence of approximately 25-percent and only 10-percent of men were circumcised. If, starting this year, Zimbabwe were to circumcise the remaining 90-percent of its male population, our model conservatively predicts HIV prevalence drops to 13-percent by 2020. If only 50-percent of the population is circumcised under this intervention, HIV prevalence could drop to 18-percent.

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We also considered targeting men if total coverage wasn't possible. And we first considered targeting men depending on their age. This table shows the reduction of adult HIV prevalence depending age group is circumcised. And you can see that the greatest reduction occurs when men between the ages of 20 and 25 or 25 and 30 years old are circumcised. This suggests that the optimal age group to reduce HIV prevalence in 2020 is centered around the age of 25.

We also considered circumcising men depending on their sexual activity. As I said before, the core group is a high risk minority of the population and this table shows the reduction of adult HIV prevalence depending on if the core group is targeted or excluded. You can see that if the core group alone is circumcised, the reduction in prevalence is 37-percent of what could have been achieved if all men were circumcised even though the core group only makes up 10-percent of the population on average. Conversely omitting the core group leads to reduction of HIV prevalence of only 73-percent of what could have been achieved had they been included. These results suggest that when total coverage is not possible, priority should be given to men between the ages of 20 and 30 years old and, if identifiable, men who have an above average number of sexual contacts per year.

The last scenario results I'd like to discuss is the sensitivity to an intervention to an increase in the number of

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sexual partnerships. It is difficult just how a desired increase in sexual activity will translate into the actual number and distribution of sexual partnerships in the population. And to resolve this we created two extreme scenarios. The first scenario involves circumcising all uncircumcised men starting in 2007 and the percentage of these men in the low risk group would enter the high risk core group. This doesn't increase the total number of partnerships in the population, as women do not change their behavior in response under these assumptions. Instead it increases the competition for high risk relationships and contact with female sex workers. This graph shows a reduction in adult HIV prevalence depending on the percentage of men who enter the core group. And you can see that on average the intervention's effectiveness is reduced but it still provides some reduction in adult HIV prevalence.

The second scenario was similar to the first in the sense that the same percentage of men move from the non-core group to the core group after they were circumcised. But this time the same percentage of women entered the high risk core group as well. So in this case the total number of partnerships did increase. You can see that on average the intervention is negated when approximately 40-percent of these men and women increase their number of sexual contacts per year.

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Now these two scenarios provide two extremes of what could happen under an intervention. And so our model would suggest that it takes significantly more than 40-percent of these men and women to increase their sexual contacts per year before the intervention is undone. Still we would suggest that some kind of counseling is required to maintain the effectiveness of intervention.

So, in conclusion, our mathematical models show that circumcision can lead to significant reductions in adult HIV prevalence without requiring every man to be circumcised. It also shows that this reduction in HIV prevalence is proportional to the additional percentage of the population that is circumcised. The model also demonstrates that when total coverage is not possible, priorities should be given to 20 to 30 year old men and if identifiable, men who have a high number of sexual contacts per year. Lastly, the model shows that an intervention is relatively robust to increases in risky behavior, but some kind of education about the exact benefits is needed to maximize its impact. Thank you very much.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Questions? Yes.

BERRY HALL: Yes, I'm Berry Hall from the International Community of Women Living with HIV and AIDS. And this is directed to all the presenters and I wanted to know was there any discussion or concern or reporting by any of the subjects before

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or after they were circumcised as to whether or not there would be a change in sexual pleasure or sensation because of circumcision?

GREGORY LONDISH: Well, ours was a mathematical model so no people were involved. I'm going to pass it over to other people.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: If I can comment on that issue of sensitivity, sexual pleasure, sensation, all of the very good research that's been conducted shows no difference. I think case closed, especially the most recent studies published this year on sensation during arousal using thermal imaging.

GREGORY LONDISH: We didn't get any complaints.

GODFREY KIGOZI, M.B.CH.B., M.P.H.: In Rakai we have looked at sexual satisfaction in both men and women and we're actually seeing very high levels of satisfaction after surgery, levels as high as 99-percent.

GARY ROGERS: I'm Gary Rogers [inaudible]. I've got a question for Greg. You chose HIV prevalence as your outcome in the model, so therefore you must have made some assumptions about death rates, and I'd be interested to know how treatment and falling death rates would affect your outcomes, but also ask why you didn't choose incidents without the prevalence?

GREG LONDISH: Well, to answer that in the opposite order. We did use incidents, just brevity of time and space means I

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couldn't present it today. Hopefully we'll have a paper out soon that does include incidents. As for treatment, we didn't specifically model treatment of HIV infected people. We just wanted to concentrate on the impact of circumcision alone. Obviously that's something to look at between the similarities between circumcision and other interventions and treatments.

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Okay, thank you very much. [Applause] The next talk will be given by Bertran Auvert on behalf of his colleagues. Bertran Auvert is from the INSERM unit 687 in France and the title of the talk is Cost of the Roll-Out of Male Circumcision in Sub-Saharan Africa. Thank you.

BERTRAN AUVERT, M.D., PH.D.: Good morning. We've done this study with a team of 10 researchers indicated on this slide.

The objective of this study was to calculate the health economic estimates of the roll-out of medical adult male circumcision in sub-Saharan Africa. So this study is limited to medical adult male circumcision. We are not going to consider traditional circumcision or infant circumcision. And the idea was to calculate five estimates; the number of circumcisers needed, the cost of the roll-out, the net cost when we take into account adjustment for averted HIV medical cost, the cost per HIV infection averted which is cost-effectiveness, and the number of circumcisions to avoid one HIV infection.

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This study was limited to a given number of countries. In order to select these countries, we applied the rule of countries having relatively high HIV prevalence. In this case it was more than five percent and countries with low HIV male circumcision prevalence and in this case it was 80-percent.

So using these two criterion we have selected 14 countries and to this list we have added the Yungbuck [misspelled?] province of Kenya and Uganda. So as a result we have list of 16 countries covering the Southern part of Africa and the Eastern part of Africa and some of the other countries for a total of 96 million people among these 16 countries with a total of 30.5 million of uncircumcised males and South Africa in this represents 26 persons of these 30.5 million showing the important role that South Africa can play in this roll-out.

The method was using a mathematical model developed for this study. This model has three sub models, a demographics model, a cost model, a HIV model. It's a very classical susceptible infected model with people in groups indicated on that slide with circumcised men, uncircumcised men, women, children, adult HIV-positive, HIV-negative and the set of differential equations controlling the movement of people from one group to another.

The model was run for each of these 16 countries independently and then the results were put together and you have

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the full results. So for each city we have a list of 32 input parameters. Of course, it's a very crude presentation of reality and using this model we have calculated the numerical value for five estimates plus using the Monte Carlo simulation some idea of the confidence interval of each estimate.

So let me describe very quickly some input. We have the affect of male circumcision, we have the percentage of males who will not accept intervention, we have the duration, here it's five years duration of time. When we apply the intervention that means that in this case we will take five years to circumcise most of the males accepting the intervention.

We have two delivery models. We have the private model and the public model. And in the private model we have the cost of male circumcision which includes also the cost of counseling, BCT and treatment of adverse events. In the public delivery model it's a bit more. We have more parameters, for example the salary of each circumcisers. Now we have the HIV model, we have for example the cost of ART.

What are the results of the first estimate of number of circumcisers needed? We find that we need about 2,300 circumcisers to roll-out male circumcision in these 16 countries during the first five years. And then after the first five years, we just have to circumcise those becoming adults, so it's a much lower number. In this case, we found that after the first five

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years for the years six, seven and so on we need only 600 circumcisers, which is about 0.07 circumciser per 10,000 adults.

The cost of the roll-out. If we consider the cost for the first 10 years, it's very similar in the private and the public model and it's between 0.9 billion of U.S. dollars for the first 10 years to 1.6 billion of U.S. dollars. If you calculate it per adult per year, then an average is between 0.9 and 1.7 U.S. dollars per adult per year. The value is much higher during the first five years, about 2 and then after the year five, year six, seven and so on, it's only 0.5 U.S. dollars per adult per year.

The net cost when you take into account the averted HIV medical cost, then during the first 10 years it costs something, it cost about 600 million of U.S. dollars and then if we calculate it over a 20 year period of time, then it's saving money, and we are saving about 3 to 4 billion of U.S. dollars.

The cost per HIV infection averted varies from about 100 to 3 to 400 per HIV infection averted adult in the first 10 to 20 years.

The number of circumcisions to avoid one HIV infection varies from four to nine in this simulation exercise.

In conclusion, I want to say that it's a crude analysis because as you can see the model is a crude implementation of reality. We have only 32 parameters. We didn't take into account traditional circumcision, we didn't take into account

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circumcision of newborns or babies. But as a result it's expensive but I think it's reasonable, it's not too expensive. It cannot help us to choose what kind of implementation model we have to use as a public or private. As a result we're very similar using the two delivery models. I think the choice will be done using other information like local context and so on. And clearly cost is not the main issue, maybe it more other issues like availability of providers are probably more important than the cost. Thank you very much. [Applause]

BRIAN MORRIS, PH.D., D.SC., F.A.H.A.: Are there any questions? Just come to the microphone. No questions? How about questions from the speakers in the front here, any questions? Sounds like you've convinced us all or everyone's keen to get to lunch, so with that I'll just ask everyone to join with me in thanking once again all of the speakers. [Applause]

[END RECORDING]