Plenary: Male Circumcision:

Is It Time to Act?

XVI International AIDS Conference

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BERTRAND AUVERT: … a very interesting and promising intervention to prevent HIV infection. As you know, we have already, important body of evidence showing that male circumcision is protective against HIV infection.

In this session, we have five very interesting papers covering why areas like efficacy, potential impact, cost effectiveness, and with [inaudible]. So thank you very much for all being here. It's nice to see so many people that was not the case in the previous conferences and I'm glad to see you here.

So, I'm glad to introduce the first paper from Robert Bailey, a randomized controlled trial of male circumcision to reduce HIV incidences in Kisumu, Kenya, progress to date. Bob.

[APPLAUSE]

ROBERT BAILEY: Thank you, Bertrand. I'm a little out of sorts because I have never seen Bertrand with a tie on before. [LAUGHTER]

I want to talk to you today about – as this audience probably knows, there is a great number of studies, over 40 observational studies that have shown that male circumcision has a protective effect against HIV acquisition in men. There is also biological studies which have shown that human foreskin has high density of HIV target cells. Of course, the most recent and most exciting evidence comes from a randomized

control trial of male circumcision conducted by Bertrand Auvert and his colleagues in South Orange Africa showing a 60-percent protective effect of circumcision against HIV. And in a pre-protocol analysis, it's 76-percent protective effect.

The Normative Agencies, a name that someone gave to UNAIDS and The World Health Organization, in this case have declared that male circumcision should not be promoted as a HIV prevention strategy until the results of two other trials are known. One of those is taking place in Kericho, Kenya, and the other is in Kisumu. So I'm going to be reporting today, giving you an update on our trial Kisumu.

There are many people involved in this trial. The names you see on screen are just a very, very tip of an iceberg of many people, over 60 people who are involved in the trial. And the trial is supported by NIH and the Canadian Institute for Health Research.

We are testing three primary hypotheses. The first is that circumcision will reduce HIV infection by 50-percent or more in men in Kisumu between the ages of 18 and 24 years. The second primary hypothesis gets to the issue of safety. We are testing the hypothesis that circumcision will result in less than a 2-percent rate of significant adverse events. Then the third primary hypothesis gets to the issue of behavioral disinhibition or risk compensation, where we are seeing whether

there will be no difference between circumcised men and uncircumcised men in their reported sexual behaviors.

So the study population are people who identified themselves primarily as Luhya. The Luhya are a group of about two and a half million people living in western Kenya, in Yansia province and, according to multisite study, about 10-percent of Kuhya men in Kisumu are circumcised. So they are traditionally non-circumcising ethnic group. In Kisumu, there are over 39,000 young men within the age group that we are targeting and most of them live within proximity of our study clinic.

We are recruiting men who are at moderate to high risk. We do through STI clinics, DCT centers but most of our recruitment occurs through peer outreach. And the peer outreach workers, most of them, are actually participants in the trial. So those who are included or maybe included in trial must be uncircumcised. They must be HIV-negative, sexually active, defined as having had sex within the last 12 months, between the ages of 18 and 24, a resident of Kisumu with no plans to move for the next two years, and they must have a hemoglobin of greater than 9gm/100ml. They are excluded if their foreskin does not cover half or more of the glands. If they are hemophilics or have some other reason for being excluded from surgery and also if they have an absolute indication for circumcision such as phimosis.

This slides shows from an initial screening to the randomization. And 6,686 young men came to our clinic, of those 8-percent did not meet the initial inclusion criteria, so 6,159 were tested for HIV using double or parallel rapid test to determine an ungual. Of those 8-percent were HIV-negative and then referred to support group and another 1-percent were inclusive or serodiscordant. So, 5622 men were then HIV-negative. Of those, 20-percent were excluded on other exclusion criteria, primarily many had absence of sexual relationships with the last 12 months. Also others had a medical problem, usually an STI, which we treated and then they didn't return for subsequent visits. And a number were just be unreliable and some had conditions preventing sex, many of those reported erectile dysfunction.

So 4,489 then were eligible to join the study and of those, 38-percent did not end up being enrolled. Mainly because they preferred one arm or the other so they either preferred not to be in circumcision arm or not to be in control group. That is, they wanted to be circumcised. So they were naturally excluded because to be randomized they had to be willing to be allocated to either arm and have an equal chance. So 50-percent ended up randomized into the control arm and 50-percent in the circumcision arm.

There were no differences between the two arms with respect to many of the baseline characteristics. The mean age

of the cohort was 20.6 at randomization. Over 98-percent identified themselves as Luhya. And about two-thirds or 66-percent have a secondary – of some secondary education or above and only 6-percent are married or have a live-in partner. Sixty-four-percent are unemployed, another quarter or fourth of them, about 26-percent are self-employed, and only 9.4-percent actually are salaried employees.

The first three here show STIs at baseline and 27.6-percent were HSV-2 positive at baseline, 2.1-percent on urine tests for gonorrhea and 4.6-percent for chlamydia. You will notice that the circumcision arm actually has slightly more of these STIs than does than the control group, so that is something that we will probably have to control for in analyses. Age at first sex is 15.5 and the number of partners in last six months is a mean of 1.7, a median of just one. Lifetime number of partners is 6.3. Those who report consistent condom use, 21.8-percent and 10.5-percent report having been drinking during the last time they had sex.

This shows HIV prevalence at baseline. You can see that age 18 just one percent of these young men are infected but by the time they reach the age of 24, 17-percent are infected. This represents a high seroincidence. This is, of course, a cross-sectional data but it translates particularly between the ages of 18 and 23, a high incidence, around 3.5-percent of seroincidence.

This depicts the study visits from randomization through follow-up, which is for 24 months. Those men who are allocated to surgery generally go through the operation the same day that they are randomized and then they come back three days, eight days, and 30 days after the surgery. We check the wound. We ask a few questions about their sexual activity and their level of satisfaction.

Then at one month and at three months, both arms, the men in each arm are tested for HIV. And six, 12, 18 and 24 months all the men then are given another HIV test, administered a behavior questionnaire to get at risk behaviors and then we collect urine, blood, and swabs for STI diagnosis and for later immunological studies. If we detect through lab analyses that someone has a STI we recall them and then treat them for the STI.

All the men in the study get free medical care throughout the 24 months of follow-up. Those in the control group then at the end of follow-up are given the option of being circumcised, or they may wait until the results of the trial are known and then make a decision at that point.

So, we have had very good success in our follow-up. At the one-month visit, just 8-percent of visits were missed; three-month visit, about 12-percent were missed; at the six-month visit, 9-percent of visits were missed; at 12 months, 12-percent of the visits were missed; and by the 24-month visit,

15-percent of men have missed their visits. This translates to – these visits translate to 91-percent person years of visits accounted for, of all the possible visits. So, our follow-up has been very good.

The next two graphs show you some of the risk behaviors by visit. So in the blue bars, that represents baseline, gray is the six-month visit, red the 12-month visit, and so on. You can see that always condom use or consistent condom use goes up from baseline from 22-percent up to about 35-percent at the six-month visit, remains fairly stable after that initial six month visit. Similarly, condom use during last sex also rises from baseline to subsequent visits remains fairly stable throughout subsequent visits. Similarly, those men who report having paid for sex or giving gifts in exchange for sex in the last six months also declines after baseline. So it goes from 9-percent at baseline down to 11-percent and then all the way down 8- or 9-percent in the last visit. And sex in the last six month, any sex with any number of partners, also goes down slightly after baseline, although it is fairly stable throughout the follow-up.

So these data suggest that, first of all, our counseling is having some effect. It seems that condom use is increasing, sex with possible sex workers is decreasing, and so our behavioral counseling seems to be having an effect. It also suggests, even though we are blinded to outcomes by treatment

arm, it suggests that behavioral disinhibition or risk compensation is probably not a large factor. If the circumcision group were engaging in higher risk behaviors, we would probably see increases in these measures rather than decreases.

So the progress up to July 17th has been that we have recruited – we finished recruited on September 6th 2005. Skipping down here, we have completed 1,334 circumcision procedures out of the 1,391 allocated to that arm. And 69 in the treatment arm were not circumcised within six weeks, suggesting then a crossover rate of 5-percent and the crossover rate in the other direction is just less than one percent, so 13 men have crossover from the control arm to the circumcision arm.

We have had 27 adverse events that are either definitely, probably, or possibly related to the procedure. All of them have been mild or moderate and we have no severe adverse events related to the procedure. Other surgical outcomes are that the level of satisfaction of the clients is very high, 99-percent report that they were very satisfied. At 30 days, one troubling result is that 10-percent of the participants report having had sex since they were circumcised, so even though we counsel men vigorously not to have sex in first 30 days or after surgery or until they are fully healed. Nevertheless, 10-percent of the participants have had sex by

the 30-day visit. And then at 90-day, 65-percent report having resumed sexual intercourse and 92-percent of the female partners who were aware of the circumcision status of their partner report that they were very satisfied and 5-percent somewhat satisfied with the procedure.

We expected – in order to have an 80-percent powered to detect a 50-percent difference, we expected to enroll 2,776 individuals. We met that goal in September of 2005. The incidence rate that we predicted for the control group was two and a half percent. The actual incidence over both arms is 1.8-percent, which suggests that if there is a 50-percent protective effect that we are just about on target in terms of incidence.

The loss to follow-up we said would have to be 15-percent or less and we have achieved that, actually and better. Crossovers 5-percent in each arm, our crossover rate in the circumcision is 5-percent. In the control, it's less than 1-percent. So, the total person years that will be accrued by the end of the trial are 4,719. As of July 17, we have achieved about 84-percent of the total person years that we expect.

So then, to summarize key events that have occurred so far is we had first interim analysis presented to the DSMV in June 2005. At that time, we were instructed to continue. We finished enrolled September 2005 and then we had a second interim analysis presented to the DSMV in June of this year and

we were again instructed to continue. The trial is scheduled to be completed September 2007. There could be another interim analysis before that time, but the date of any additional interim analysis has not been announced yet.

So at least by – hopefully by September 2007 we will be able to know whether we should be adding male circumcision to our very limited armamentarium of protection techniques that we have available to us. Thank you very much.

[APPLAUSE]

BERTRAND AUVERT: Thanks, Bob. Can I have some people who are standing at the back door? I believe there are seats in the front, if you please don't forget to use it. But may I ask you one question? My understanding that through the MSV has added the new interim analysis, which was not scheduled in the proposal, can you – do you have any – do you know the reason why they don't it?

ROBERT BAILEY: Well, as you know, I am blinded. We are all blinded to the results, so I can't tell you why. They have said that they may have us back within the next six months, but they have not set a date. So actually, you know as much as I do.

BERTRAND AUVERT: So we have time for a couple of questions.

ROBERT SANTOS [misspelled?]**:** Robert Santos from Toronto. Just curious, I wonder what impact there was on the

announcement of the South African trial results, successful trial results in July of 2005 on the participants. Were there a lot of questions? Were the crossovers from the control circumcised as a result of the South African trial? What was the impact of that announcement, if any? And how did you handle any particular questions that may have arisen out of the results?

ROBERT BAILEY: Well, as soon as those results were announced in Rio, actually, we then – we started informing all of the participants in the trial, those coming in for new visits and any coming in for medical visits. Anyone who came to the clinic, we told them about the results immediately.

They didn't seem – it seem to affect to their participation at all. All the crossovers by that time had already occurred anyway. I think the prevailing opinion among the participants and also throughout Kisumu, if not throughout Kenya, is that they really want the results of the Kenyan trial before they make any decisions about the efficacy of male circumcision for themselves.

BERTRAND AUVERT: Next questions?

JOHN COLIVER [misspelled?]: John Coliver from Sydney. You mentioned the female partners reported themselves, I think you said, very satisfied with the result. Is that meant to be a sort of neutral response or actually preferred the [inaudible] actually preferred the outcome?

ROBERT BAILEY: Well, we didn't — in our questionnaire, we were asking the men, you know, is your partner aware that you went through the procedure and if so, what is her opinion? So, the men themselves are reporting that their partners are very satisfied. [LAUGHTER] I don't know what else you would expect them to say. [LAUGHTER]

But we have done other studies that have shown that many women in this region actually would prefer their partners to be circumcised and the main reason that they give – and this is true in studies acceptability, studies in many parts of Eastern and southern Africa – is they prefer circumcised men for reasons of hygiene. So they think of circumcised men as being cleaner and carrying fewer infections.

BERTRAND AUVERT: We are running out of time so just one additional question. Thank you.

BOB PARCHELL [misspelled?]: Bob Parchell in Gender Health. I was wondering if you recruited any gay men or MSM for this study, and if so, if you account for any differences of protective effect based on sexual orientation. And also similar question related to sexual practices, can you account for any difference based on anal intercourse versus vaginal?

ROBERT BAILEY: Yeah. Thanks for that. We didn't recruit purposely gay or men who have sex with men. Only four of our men report ever having sex with men. So clearly, there is not enough power there to detect any differences. I do not remember

the figure about anal sex. I think about maybe 3- or 4-percent report having engaged in insertative anal sex. Only, I think, two of the men who had sex with men reported receptive anal sex so the numbers aren't large enough – at least in reported behaviors, the number aren't large enough to really detect differences.

BERTRAND AUVENT: Okay. Thank you, Bob. And it's my pleasure to introduce the next paper presented by Doug Shaffer about efficacy study conducted in Kenya.

DOUGLAS N. SHAFFER, M.D.: Good morning. It is my pleasure this morning to present a two-year follow-up data regarding male circumcision and HIV infection among tea plantation residents in our Kericho cohort.

As outlined I will briefly described the United States military HIV research program, Walter Reed Project, Kenya Medical Research Institute Collaboration and the primary HIV and malaria cohort study. I will describe the methods used and the formation and analysis of our male circumcision cohort. I will present most recent 24-month HIV circumcision data and actually, I will spend focusing upon baseline characteristics which may act as confounders. And I will end with three general conclusions.

The United States Military HIV Research Program mission to the prevention of HIV disease through development of a globally effective vaccine and target HIV surveillance,

prevention and treatment. Our Kericho collaboration is built upon a longstanding relationship in Kenya with the United States Department of Defense, Walter Reed Project. Collaborative HIV vaccine research began in 1988 and is conducted among the rural African highlands of the southern Rift Valley province in Kericho.

The HIV and Malaria Cohort Study is a three and one half-year prospective natural history cohort study following 2801 adult tea plantation workers and dependents twice a year since June of 2003. The primary objectives this cohort study are to establish HIV prevalence and incidence to characteristic HIV risk behaviors. Secondary objectives include to profile HIV comorbidities, to establish area population normal laboratory values, which have been done, and currently being used in our Phase I/Phase II vaccine study and Phase III therapeutic study, and to ascertain volunteers' willingness to participate in future HIV vaccine studies.

Beginning in June 2003, 2,801 adult plantation and dependent volunteers age 18 to 50 years were recruited over a six-month period. This formed our baseline cohort. This cohort has been followed every six months. Baseline and followup questionnaires have been administered. The baseline questionnaires consist of medical history, sociodemographic information, and HIV risk questions. Baseline and follow-up HIV

testing occurs following a standardized ELISA/ELISA/Western block algorithm.

From this cohort we have excluded 1,081 females, 195 men who were positive at baseline evaluation, 146 or 5.2-percent who were lost to follow-up at 24 months, and one volunteer with missing data. This resulted in our male circumcision cohort consisting of 1,378 volunteers contributing to 2,689 person years of follow-up. Analyses today will based upon routine simple statistics comparing baseline characteristics, incident rate calculations presented as first per 100 person years and hazard regression analyses.

Overall, 19.6-percent of the men were uncircumcised and 80.4-percent of the men were circumcised. While there was no significant difference between age in the two groups, approximately 31 and a half years in each group, there was significant differences with regard to travel representation and education. Of note, the vast majority of uncircumcised men were from the Luhya tribe. With regard to education, more circumcised men reporting having received a high school education or greater, approximately 51-percent.

There were also marked differences with regard to martial history and year of sexual activity. More circumcised men reported having been never married or married once, 23- and 60-percent, respectfully, while more uncircumcised men reported having been twice or greater, 23-percent. While there are

differences within the strata, more uncircumcised men reported 19 or greater years of sexual activity, approximately 33-percent. While it did not statistical significance, there was slightly more uncircumcised men here reported recent sex with a commercial sex worker.

Also, and again not reaching statistical significance, there were trends observed in comparison of the two groups with regard to HIV risk factors and sexual frequency. Slightly more uncircumcised men reported a sexually transmitted infection and/or penile sores or ulcers within the last six months as well as a greater sexual frequency.

Finally, with regard to baseline characteristics and in consideration of HIV sources and risk factors, there was no significant difference between the two groups with regard to blood tranfusion and there was no significant difference with regard to condom use. Of note, approximately 77-percent in both groups reported never having received or use a condom in recent sexual activity.

Of those men who were circumcised, approximately one-quarter had their circumcision performed by a traditional healer – I'm sorry, approximately three-quarters had their circumcision performed by a traditional healer and approximately one-quarter had their circumcision performed by a health worker. Approximately half of the men reported having their circumcision between 10 and 14 years. Approximately one-

third had their circumcision in a age greater than or equal to 15 years, and approximately one-fifth had their circumcision less than 10 years.

After 24 months of follow-up, we observed 30 incident cases of HIV among 2,689 person years of follow-up corresponding to a 24-month incident rate of 1.12 cases per 100 person years. The 24-month incident rate for circumcised men was 0.79 cases per 100 person years. And a 24-month incident rate for uncircumcised men was 2.48 cases per 100 person years. These incident rates between circumcised versus uncircumcised men corresponded to a highly significant hazard rate ratio of 0.31 with a 95-percent confidence interval being 0.15 to 0.64.

Given our availability of baseline demographic information we created two multivariant models to explore the relationship between baseline characteristics as potential confounders to circumcision in 24-month incident HIV. In one multivariant model adjusting for demographics characteristics, age, education, and tribe, has a rate ratio increase slightly from 0.31 to 0.54. However, the 95-percent confidence interval crossed one suggesting potential note to significant difference between the two groups.

In a second multivariant model adjusting for behavioral or HIV risk factors, the hazard rate ratio remained robust with little change from the univariant 0.31 to 0.32 supporting the protective effect of circumcision.

We feel our study and analyses has several strengths. Our studies of prospective cohort with 24 months of follow-up. We have availability of sociodemographic data to begin to explore some of the confounders. Our study is based in a general world population much of the data in the current literature is derived from urban populations. Volunteers in our study benefit from extensive pre and posttest HIV counseling and availability of comprehensive HIV care and treatment.

The study limitations must be considered however in interpretation of the results presented. Our study is based upon self-reported circumcision. That is, unless the volunteer had a primary gyniatry/urinary sign or symptom, a gyniatry/urinary exam was not performed. We feel, however, there is reason to believe a high degree of accuracy with self reported circumcision. Our study is not designed or statistically powered to detect small differences within circumcised versus uncircumcised strata when considering potentially confounding variables.

Risks and harms of circumcision have not been addressed in the presentation while the obvious benefit is the topic of discussion we have given time to risks or harms of the procedure. Finally, I think it is important to recognize its hazard ratios presented, maybe bias, but HIV risks high correlated with circumcision status.

In conclusion, first our study suggests circumcision offers a degree of protection from HIV infection in adult men living in rural African highlands of the southern Rift Valley of Kenya. Second, additional controlled and randomized studies designed to describe the relationship of confounding variables but if risks and sources of HIV infection to circumcision status and incident to HIV are needed. And I think it is important to note in the opening, where we were aware there are two randomized controlled trials, one that has just been presented, and one that is ongoing in Uganda, which will have some this most important information.

Finally, careful attention must be given to risk benefit profile of circumcision as a HIV prevention measure alone as well as in relationship to other HIV prevention measures, for example, abstinence, faithfulness, condoms, vaccine and microbicides. As I mentioned we have not given time to the risks of the procedure.

The HIV cohort study in Kericho is an important epidemiological study with a wealth of unique information relevant to HIV in rural east Africa. I very much appreciate the opportunity to present our data today and I am quite appreciative to many collaborators. Dr. Debbie Burch [misspelled?] is the founder of the Kericho site and a strong advocator of HIV research and [inaudible] of care and treatment now throughout Africa in her leadership position at CDC GAP.

And, most important, I am quite fortunate to work with many Kenyan colleagues and friends for the backbone of this research as well as the program. Thank you.

[APPLAUSE]

BERTRAND AUVERT: Thanks, Doug, for this very interesting presentation. First question in the front?

KEN NELSON: Hi, Ken Nelson from Johns Hopkins. You showed different rates of circumcision in the various tribes. And I wondered, are there data on the HIV prevalence, particularly in women, in the various tribes that are available?

DOUGLAS N. SHAFFER, M.D.: Yes, that is actually currently in review at JADS but we have – the primary HIV cohort study describes the prevalence, which is different across the tribes. The highest prevalence observed is consistent with the Luhya tribe.

BERTRAND AUVENT: Richard?

RICHARD HAYES: Hello, Richard Hayes, London School of Hygiene. Thank you very much for a very interesting presentation. I just wanted to ask about your adjusted analyses. I was quite surprised that you found quite a change in the rate ratio after adjusting for demographic factors but no change when you adjusted for behavioral factors. But what I didn't see was a model adjusting for both, and it would have been quite interesting to see that.

DOUGLAS N. SHAFFER, M.D.: We have done those models. I think what was important what I wanted to show was what happens when you adjust for demographic factors. I think what I was talking about the high correlates of infection with circumcision particularly within certain tribes who have cultural risks. I think that plays a strong factor in outcome of the increased incidence. And I think that's why it's important to look to the randomized controlled trials. They can more appropriately adjust for those confounding factors. We have several other models that actually have looked combining those two factors as well as models looking at interactions between who performed the circumcision, as well as age, and I would be happy to talk about those more later. I just tried to truncate the data for the presentation.

RICHARD HAYES: Can you just tell us what the fully adjust rate ratio was?

DOUGLAS N. SHAFFER, M.D.: I would want to get the data. It actually increases when you bring in the demographic factors as well.

RICHARD HAYES: Okay. Thank you.

BERTRAND AUVENT: Okay. Next question in the front?

SCOTT KELLERMAN: Hi, very nice presentation. Scott Kellerman from the New York City Department of Health. I noticed that three-quarters of the participants had been circumcised by traditional healers. And I know that you didn't

include an exam as part of the study, but I wonder can you comment at all at what that might look like. What is a circumcision by a traditional healer? How does that compare to or differ from a circumcision by a trained health care provider?

DOUGLAS N. SHAFFER, M.D.: I think we would have to be careful. As I said, we have actually started to look at some models that look at interactions but with the healer, given the limited number of incident cases we had, I think you have to be cautious starting to look at those variables. I think what is important is that this study is based in a rural population where there is still more people that rely on the traditional healers as opposed to the more professionally trained medical officers in settings like Kisumu and Nairobi and other areas.

SCOTT KELLERMAN: I certainly understand that. I wonder though, is a circumcision by a traditional healer, is it considered to be a complete circumcision in general or I have never seen –

DOUGLAS N. SHAFFER, M.D.: Yeah. There is a lot of information – actually, a lot of published information about different types of circumcision within Kenya and there certainly are differences. I think those are important to consider. Our study really isn't designed to look into the details. It would be nice but we really don't have the cases. And I think you have to be cautious once you start going on a

fishing expedition for interest given our limited number of incident cases.

BERTRAND AUVENT: Okay. Thank you. We have time for one final short question.

Female Speaker: [Inaudible] I was wondering that you have incidence data on older SDS and, in particular, genital lacerations. Did you see any difference? And, in particular, genital herpes.

DOUGLAS N. SHAFFER, M.D.: I think the question was about incidence data with regard to other sexually transmitted infections. We do. We have a wealth of information about sexually transmitted infections, which is currently being analyzed.

BERTRAND AUVENT: Thank you, Doug. It is my pleasure to introduce the next paper. It is a modeling study presented by Kyeen Mesesan. Kyeen, 10 minutes.

KYEEN MESESAN: I will be presenting stimulations today that show how various male circumcision programs could impact the HIV epidemic in Africa. In addition to maximizing the impact of current HIV prevention campaign additional effective HIV prevention technologies are needed. Twenty-five years into the epidemic, 11,000 new HIV infections are still occurring globally everyday. Although research into preventive tools including vaccines and microbicides is promising, large-scale implementation of these technologies is years away.

Adult male circumcision is available now and is a relatively affordable, safe and acceptable. It is also highly effective. As we have heard, last year the first randomized controlled trial for male circumcision conducted in South Africa was stopped after interim analysis showed that circumcision decreased female-to-male transmission of HIV by an astounding 61-percent.

We are not awaiting the results for the other two large male circumcision trials underway in Uganda and Kenya. If these trials also show significant reduction in HIV transmission we will need to consider whether large scale implementation of adult male circumcision programs should be added to our current arsenal of HIV prevention tools.

We have three study questions. First, how do current rates of circumcision affect predicated trends in the HIV epidemic? We explore this effect over a 20-year horizon. Second, what impact would an expanded adult male circumcision program have on a developing country epidemic? We consider a five-year program with varying coverage goals and look at the population benefits in terms of infections prevented and changes in HIV prevalence. Third, how might potential changes in risk behavior post-circumcision influence these outcomes? Specifically we examined changes in condom use behaviors.

We use the township of Soweto as an example to show the potential impact of expanded male circumcision programs in

Africa. Soweto is located southwest of Johannesburg and close to the community of Orange Farm where the first trial of male circumcision was recently conducted. We developed a mathematical model to examine what might happen if expanded adult male circumcision programs were implemented in Soweto.

For those of you familiar with these methods, this is a dynamic transmission model linking male and female populations with differential equations governing movement between various states in the model. The basic idea is to use the model to stimulate the course of a HIV epidemic using data and assumptions regarding population characteristics, HIV transmission and disease progression, circumcision and sexual risk behavior.

We assessed the impact of various programs on heterosexual transmission of HIV in particular varying circumcision ethnicity and program coverage levels as well as the potential for changes in sexual risk behavior following program implementation. Selected model inputs include: an initial population of 823,000 sexually active adults, and HIV prevalence of 12-percent for males and 20-percent for females, disease progression times and infectivity values calculated from data out of rural Uganda, for circumcised males a 61-percent decrease in the likelihood that HIV is transmitted when an uninfected male has sex with an infected female partner, a current circumcision rate of 35-percent for the male population

with expanded programs covering an additional percentage of uncircumcised adult males each year, a 50-percent baseline probability of condom use in all partnerships which is male negotiated, and numbers of sexual partners per year varying from zero to three depending on disease stage.

This first graph will show the results of a 20-year stimulation of predicted trends in Soweto adult HIV prevalence without considering a reduction in transmission due to current rates of male circumcision. The model predicts that female population HIV prevalence will increase from 20- to 21-percent and 127,000 new infections will occur over the next twenty years. Similarly the male population HIV prevalence will increase from 12- to 25-percent and 191,000 new infections will occur over the same period.

When we consider the reduction in HIV transmission due to current rates of male circumcision, the predicted trends in Soweto adult HIV prevalence change. The female population HIV prevalence now decreases to 17-percent and 102,000 new infections will occur over the next twenty years. Similarly, the male population HIV prevalence will only increase to 17-percent and 142,000 new infections will occur.

So, as we show here, the reduction in transmission due purely to current rates of male circumcision is significant even without an active effort to expand circumcision programs.

Next, we consider the impact of a five year expanded male circumcision program targeting an additional ten percent of the uncircumcised males each year, which is our base case scenario. We are now looking at figures for the entire adult population. On the horizontal axis is the 20-year time horizon and on the vertical axis to the left is the total number of infections prevented in yellow. The stimulation shows that over 20 years this program could prevent 32,000 of the infections predicted for Soweto.

On the vertical axis to the right is the prevalence of HIV in the population in blue. This first line shows the expected overall population prevalence if no program were implemented. This next line shows the prevalence with implementation of the program, which would reduce the 20-year prevalence of HIV from 17- to 14-percent. Therefore, even a modest expanded male circumcision program targeting an additional ten percent of uncircumcised males would provide significant benefits.

If instead we consider targeting an additional 20-percent of uncircumcised adults males each year in an expanded circumcision program over twenty years, the program could prevent 53,000 infections in Soweto and the prevalence of HIV in the population would be decreased even further to 13-percent. Thus, the benefits would be even greater for a program with a higher coverage goal.

This is a table showing the number of infections prevented over 20 years for various five year expanded male circumcision programs. On the side are the two coverage level, ten and 20-percent, and along the top are various possibilities for circumcision protective effects. Given our best guess at present for the reduction and transmission due to male circumcision of approximately 60-percent, stimulations predict 32 to 52,000 infections prevented as shown previously. However, regardless of the protective effect from circumcision pending from the other two trials for male circumcision in Kenya and Uganda, and here we show our range from 20- to 80-percent, modest circumcision programs will still provide significant benefits.

We next considered the impact of a change in risk behavior following circumcision program implementation, if for example, we implemented a program with a 20-percent coverage goal but in this scenario circumcised men decreased their condom use by 30-percent. Over 20 years with this increase in risk behavior the program could only prevent 18,000 infections in Soweto and the prevalence of HIV in the population would be decreased only to 15-percent. Thus, if risk behavior increased the benefits of the program would be diminished.

Because we are not yet sure whether the reduction in HIV transmission is truly 61-percent nor do we know how much risk behavior might change, this graph allows us to look at all

of the equivalent combinations of male circumcision protective effects on the horizontal axis and changes in condom use on the vertical axis that would prevent zero infections. This stimulation again assumes a five-year program with 20-percent coverage levels and looks at 20-year outcomes.

In this instance, we are interested in seeing whether the program would have any effect in preventing infections. So this curve separates circumcision programs into those that would be harmful or helpful. All combinations of circumcision effect and risk behavior change below the curve would increase the number of infections while all combinations above the curve would prevent infections. Any program resulting in increased condom use would be beneficial and that represented by the area above the horizontal axis. If the protective effect of circumcision is between 0- and 63-percent, or to the left of this arrow, and the program causes any decrease in post-circumcision condom use, then whether a program has a net benefit or harm depends on whether it's parameters lie above or below the curve.

But if the protective effect from circumcision is at least 63-percent or to the right of this arrow off the graph, then any five-year circumcision program with 20-percent coverage levels will provide a net benefit over 20 years in terms of infections prevented, even if post-circumcision condom use decreases all the way to zero.

Assuming that the protective effect of circumcision is actually 61-percent then the program would be beneficial as long as post-circumcision condom use did not decrease by more than 94-percent from baseline levels or to less than three percent.

In conclusion, the protective effects of male circumcision on HIV transmission significantly affect predicted outcomes and should be routinely included in HIV epidemic models. Circumcision is already having a tangible impact on the HIV epidemic and represents an important prevention technology available now. Even modest expanded male circumcision programs can confer substantial health benefits to males and females in South Africa and other population with similar epidemic profiles and these programs should be implemented immediately.

Although these findings are sensitive to the impact of circumcision on subsequent risk behavior, all programs resulting in decrease risk behavior and even most programs resulting in increase risk behavior would still be beneficial. Programs to reduce risk behavior will remain an important component of successful prevention campaigns including circumcision programs. Thanks.

[APPLAUSE]

MALE SPEAKER: Thanks, Kyeen. Modeling paper has been published presenting across medicine. How will you compare the two studies and are the outcomes of the two studies consistent?

KYEEN MESESAN: Yes, the paper that was published recently, the methodologies are somewhat different. We both used dynamic models but the paper that was just published was looking at outcomes for sub-Saharan Africa, Africa as a whole. And this study actually looks just a small community so whereas this model is quite detailed and looks at a lot of subtle things that the big study doesn't look at, it can only make generalizations for a small community whereas the PLOS paper can make very large generalizations about what this would do across Africa.

So this study is really only sort of an example of what might happen in one town as opposed to you know across Africa. In general, the fact that circumcision will have substantial health benefits in terms of infections prevented and changes in HIV prevalence is still the same.

MALE SPEAKER: Thank you.

BERTRAND AUVENT: First question in the front.

MALE SPEAKER: The question, we do not really know what behavioral disinhibition or risk compensation is, we do not know. A trial that has been completed was ended early so we know nothing from that. And we don't know anything about the two trials except when you cross, when you look across both

conditions, it doesn't seem like it might be even going out in the short term but we don't know what the long term is.

So here is my question, when you look at the, when you included the sort of sensitivity test and the parameters you included for behavioral disinhibition, did you include parameters for increased STDs? Because as condoms go down we would expect other STDs to go which are first driving many of the HIV infections in this part of the world. Are there parameters included for increase STDs in the model?

KYEEN MESESAN: That is a really good question. We actually in this model have not included parameters for STDs. We model risk behavior as an increase or a decrease in condom use. We also have the ability to model it as an increase or a decrease in the number of partners and I think that is excellent point for further research.

BERTRAND AUVENT: Next question in the back. Please keep your questions short, please.

KELLY CRIMM [misspelled?]: Kelly Crimm from JAGPICO and I was curious why you didn't include in your model an estimated reduction of male to female transmission and my understanding is that the Rakia [misspelled?] study team has estimated from data on discordant couples that there is an approximately 30-percent reduction in transmission from men to women.

KYEEN MESESAN: Yeah. That is an excellent point. I didn't have time to address that. What we have done for the

present is only model a reduction in female-to-male transmission. Only because that is the only study for which there has now been a randomized trial that has given results. I think Quinn [misspelled?] and colleagues presented data at CORA [misspelled?] this year showing that they are in the process of collecting that data so that we actually will have a real number to use in the future. But in the interim, I actually choose not to use any of the non-clinical trial data in this model. But that's definitely going to be an avenue for future research.

BERTRAND AUVENT: Can we have the question that was just been asked in the back – the man who wanted to ask question, yeah. The blue shorts. Can you – Yeah. Please. Yeah, go on. Okay. Sorry. Next.

DAVID STAMPS: David Stamps, USAID, just a point of clarification in your model. Condom use first off did your model predict consistent condom use. Secondly, were you modeling actually reported levels of condom use today in Soweto or was it a theoretic or hypothetical level as baseline?

KYEEN MESESAN: Okay. To answer your first question, we definitely do not model consistent condom use. We incorporate into the model a 14-percent effective condom failure rate over each partnership so that's the first issue. We also incorporate when we do risk behavior change. We incorporate changes in

condom use post-circumcision. And your second question was – sorry, just remind me.

DAVID STAMPS: Just – was your baseline the actual reported level of condom use in Soweto, or was it a theoretical level?

KYEEN MESESAN: It's a theoretical level backed up by several studies. I have the references on the talk and I can give them to you backwards. There are a number of national surveys coming out of south Africa, not from Soweto in particular but do show, I think there is at least two major national surveys but do show that condom use is approximating 50-percent in this population. But it is also an assumption. It's sort of a rough assumption.

BERTRAND AUVENT: Okay. Next question? Next question in the back.

MALE SPEAKER: So I would like to know what you think about the argument that male circumcision is a sexual mutilation. And also if in your program of mass circumcision if you think about having program of support that will help men or boys that might be traumatized by those mutilations or circumcision?

KYEEN MESESAN: Yeah. In this instance, I'm just trying to show what would happen if we rolled out a mass program. I think there is actually a lot of research that is going to have

to go into making it acceptable, making it safe, making it wanted by the public, and not forcing it on anyone. I agree.

BERTRAND AUVENT: May I add that we talking about adult male circumcision and most of the older few trials are consenting people age more than 18 year old so they –

MALE SPEAKER: It's not because you are an adult and might not be traumatized by the lost of your foreskin.

[LAUGHTER]

ALICIA SANDER: Hi Alicia Sander, from South Africa. Just two quick questions for you. I wonder whether you took into account the fact that the men who have, especially the black men who have high HIV prevalence are the older ones, older than 25 years of age whether you took that into account because they are the ones less likely to enter into circumcision if they are not circumcised right now. And then secondly, just to – when I look at your graphs on incidence, the incidence of HIV among women in that particular age group over 15 to 24, hopefully the ones who are suppose to be sleeping with those men is actually high about 4.5-percent goes up the 3.7-percent by age 24. And then from men of that same age, its actually much, much lower going I think as high as about 1.7 –

KYEEN MESESAN: Yeah.

ALICIA SANDER: — so when I see an incidence drop I begin to worry that they are actually showing the opposite of what was seen in terms of incidence in the country.

KYEEN MESESAN: To answer your first question, in terms of an age structured model, we have not separated this out by age groups. And that would be further research in making a more refined model. There is some work showing that you can sort of make a very good approximations without adding an age structure into the model. So, we haven't done that yet. And you are right that there are lots of reports in terms of older men having sex with younger women in South Africa. And actually we have some research, I work in south Africa with the PHRU there and there is some research to show that that is occurring but in Soweto, in our population, it actually doesn't seem to be as high as one would think. In terms of the graphs, those actually aren't incidence graphs, those are prevalence graphs so it's the prevalence of the entire population and it's the population of adults age 17 and older so it is actually the entire adult population. But we do model the numbers you are talking about for the prevalence of young, we model that as the incoming population and we do use those numbers in terms of who's coming into the population.

BERTRAND AUVENT: Okay. Thank you. Jim, a very short question. Final question, very short.

JIM UNKNOWN: That is very kind. Jim [interposing]

BERTRAND AUVENT: Very short.

JIM UNKNOWN: – from the WHO. It is not so much a question but a plea for the modeling. I think its extremely useful material but I think there is one statistic, which would be very valuable to come here. It's how we would see a reduction in prevalence translated into prevalence of HIV in pregnant women because this is a statistic which is routinely used over many countries to monitor the HIV epidemic and I think that would be very helpful to come out of all of these models. I think that certainly help the programming and the expectations that one could expect from increasing male circumcision programs perhaps. Thank you.

BERTRAND AUVENT: Thank you, Jim, and thank you, Kyeen.

[APPLAUSE]

JAMES KAHN, M.D.: Good morning, I'm Jim Kahn, and I will be speaking on the – oh, sorry. She is going to tell you who I am. [LAUGHTER]

RENEE RIDZON, M.D.: Our next speaker is Jim Kahn from UCSF. [LAUGHTER] And he is going to present a cost effective analysis that derived from the Orange Farm data that has been published. And I just also want to add thank you very much to audience for your rich amount of questions. I wish we had time to cover them all perhaps we can ask the speakers to stay extra time and you can individually ask them questions as well. So, go ahead, Jim. Thank you.

JAMES KAHN, M.D.: Thank you. I will be talking about the cost effectiveness of male circumcision in reducing the spread of HIV in the general population in sub-Saharan Africa.

By way of background, as we know, an important RCT conducted in Orange Farm showed a protective effect for adult male circumcision of 60-percent in reducing transmission from women to men consistent with observational studies. And in the context there is still limited resources for HIV prevention we feel it is important to look at the economics of a biological intervention of this type. Thus our goals were to assess the cost effectiveness of male circumcision for Gauteng Province South Africa where the trial occurred and then also to use the analysis to estimate the cost effectiveness in sub-Saharan Africa settings with different epidemiology or costs.

We looked at two major types of outcomes. We estimated HIV infection averted and then we estimated the cost per HIV infection averted and we did that two ways. First, we did it unadjusted for averted lifetime cost of HIV. In other words, we looked at the program costs divided by the estimated infections averted. Then we would key to that adjusting for the averted lifetime cost of HIV. That is if you were averting infections, those people don't need medical treatment. Then we estimated a new ratio or, as you will see, savings from the program.

These are our inputs. To estimate the cost of the program, we looked at the cost of each male circumcision,

including an allowance for promotion. We also looked at the frequency and cost of side effects. To estimate the effectiveness, we examined the HIV prevalence and estimated the HIV incidents in the men being circumcised. We, of course, included the protective effect of male circumcision on female to male transmission and the reduction of that protective effect due to risk compensation. In other words, when people feel they are better protected they may increase their risky behaviors.

We also looked at the multiplier effects due to epidemic dynamics for example, the indirect protection to women. Then finally, in order to get a full economic picture, we looked at the savings from the medical cost of HIV infections averted.

We estimated the cost of male circumcision is $50US based on data from the Orange Farm trial relying on general practitioners in the community plus we allowed $5 for community promotion for each male circumcision.

Mild side effects occurred in the short and long term for a total of 5-percent in the Orange Farm trial requiring one out patient visit which from other data we estimate at $13. Serious side effects occurred 0.4-percent of the time requiring two hospital days or approximately $330 in medical costs.

The HIV prevalence among men in Gauteng Province according to prudential surveillance data is about 26-percent.

If the epidemic is stable, that leads to an estimated incidence of 3.8 per 100 susceptibles per year. The protective effect 60-percent from the Orange Farm trial, risk compensation in the Orange Farm trial was about 18-percent, we increased that a little bit for our base case analysis to 25-percent risk compensation. We then developed, adapted an existing simple dynamic model that allowed us to estimate the epidemic multiplier that is the number of infections averted in the entire population as compared with the number of averted in the men who get the circumcision and that is 1.5. We did not include any effect of male-to-female riskiness.

The lifetime cost of HIV treatment from studies in South Africa we estimated at $8000 U.S., which is midpoint between the cost without and with ART. We did a 20-year analysis.

Here is what we found. As previously noted, the cost of male circumcision is approximately $55 per male circumcision. The cost of adverse events taking into account their frequency and then the medical care cost associated with those events is approximately one dollar yielding a total cost per male circumcision of about $56 U.S.

The HIV infections averted per male circumcision again based on the protective effect, risk compensation, and an estimate of the epidemic multiplier is approximately 0.43 infections averted per male circumcision. Many of those

infections occur in the future and when we bring all those estimates to the present using discounting at three percent per year, we estimate 0.31 discounted HIV infections per male circumcision. Then dividing the cost per male circumcision by the discounted infections averted we estimate $181 per HIV infection averted without adjusting per averted medical costs. When we adjust for those averted medical costs we estimate a net savings of approximately $2,400 per male circumcision.

We did a variety of sensitivity analyses. This slide shows the sensitivity of a cost per HIV infection averted to the unit cost and protective effect. The underlying value of 181 is our base case value. As you can see on the upper right, if the protective effect is 40-percent and the cost is $100 or twice what we assumed, the cost per HIV infection prevented is $688. In a case of a lower cost of $30 and a higher protective effect the best – the lowest cost per infection prevented in $93. All the numbers in this table yield net savings when you adjust for averted medical costs.

We also looked at alternate epidemic scenarios to be able to project the findings to other locations. In a lower steady state situation, that is with HIV prevalence of 8.4-percent instead of 26-percent and incidence at 1/100 susceptibles/year the cost for HIV infection averted is estimated at $550, still yielding a net savings of $753 per male circumcision. If the epidemic is declining for example,

the prevalence is 26-percent but risk behaviors have decreased for other reasons the cost per HIV infection averted is $1200. Again, still with net savings of $264 per male circumcision. If there is a focus on young men with a lower prevalence but high incidence and growing prevalence, the cost per HIV infection is actually slightly lower than the base case.

We looked at some program scenarios as well. We estimated at baseline $5 per male circumcision for recruitment and community promotion. If in fact, you incur that kind of costs for eligibles but only one in ten get the male circumcision that leads to a cost of $100 per male circumcision and net savings still of $253 per male circumcision. To reach a net cost of zero dollars, that is no cost and no savings, break even, the cost per male circumcision would to have to raise 45 fold to nearly $2500 or the protective effect would have to drop two thirds from the best estimate to 21-percent while the risk compensation remain the same.

Scale has almost no effect on the cost per HIV infection prevented.

[APPLAUSE]

If we place these results in the context of what is known about the cost effectiveness of HIV prevention we see that adult male circumcision at a $181 per infection prevented is in the middle of the cost effectiveness estimates. It is less expensive than voluntary counseling and testing for

example, and more expensive per infection prevented than peer education for sex workers.

In conclusion, we find that adult male circumcision in sub-Saharan Africa appears to save money for a wide range of epidemic and economic conditions. We also want to emphasize that these data are from — We used the best available current data, which are largely from the Orange Farm clinical trial and other existing sources. As male circumcision programs come into being and scale up, we believe there would be an important opportunity to study the economics as well as the effectiveness in the context of real operating programs. With that maybe in an opportunity to look at how to optimize efficiency of the implementation of this important intervention.

Thank you.

[APPLAUSE]

RENEE RIDZON, M.D.: Okay. We have time for questions. Please keep them short, keep the answer short so we can try to accommodate as many questions as possible. Please go ahead.

MALE SPEAKER: We have heard three or four presentations that start with an assumption of 60-percent effectiveness for male circumcision derived from the Bertrand Auvent study in South Africa. I wonder whether that is appropriate because actually this is an intention to treat analysis, but if you assume circumcision really happened, you should take the as

treated analysis of effectiveness which is slightly higher. I wonder whether Bertrand Auvent would want to comment on that.

BERTRAND AUVENT: I think it's a very good question and comment. I don't really have things to say except that I'm surprised that all these papers based on the value of 60-percent are giving very positive outcomes so I'm glad it is assumed higher efficacy. Of course, you [inaudible] it would be even better so for me 60 is a value that we have to into account. Maybe it will change with the two other trials but for the moment, I think I had rather stay to this value.

RENEE RIDZON, M.D.: Okay. Next question. In the front.

NINA CAMAROON [misspelled?]**:** Hi Nina Camaroon from [Inaudible] University. I'm wondering if any of the modeling and especially sort of public health planning assuming that the two trials come back with similar results, what kind of modeling is being done on the saving in terms of lives, not cost, for childhood circumcision and what kind of public health planning we might already be doing in terms of having that part of postnatal care.

JAMES KAHN, M.D.: That is an excellent question and, obviously, doing childhood circumcision is a public health opportunity. We did not examine that specifically in this analysis so we talked about considering that as well. Next?

FEMALE SPEAKER: Hi, I just wanted to know, does the analysis take into training costs and initial scale-up,

especially in the beginning, I think safety is going to be a big concern if this is implemented.

JAMES KAHN, M.D.: The training cost in the Orange Farm trial were very, very low and it involved a short one time training session and we are not large enough to affect the cost of delivery the male circumcision.

FEMALE SPEAKER: However though if this is scaled up and actually implemented as a policy, there will have to – there will be a lot of training costs to really scale this up effectively and safely.

JAMES KAHN, M.D.: Yeah. I think one of the tradeoffs as we scale up programs will be if you rely on clinicians who have less prior training but are less expensive and you do need to do more training around the male circumcision. How will that tradeoff will be about their lower baseline earning rate versus the need for extra training. That will be an important thing to look at. Thank you.

EVAN SHANKER [misspelled?]: Evan Shanker from the Hebrew University of Jerusalem. We are documenting now the massive male adult circumcision voluntary, mostly of eastern European immigrants to Israel that are in the thousands and I wondered if you could alluded to the point of taking into account that traditional healer, a modhal [misspelled?], would perform male circumcision in about seven minutes, including the blessings and the prayers, to a child eight days old. What

would be the most important valuable you would put into a cost-effective estimation taking into account actually that procedure not being on adults but actually at birth?

JAMES KAHN, M.D.: Thank you. If you allow me to bring together part of my personal life with my kids and my professional work. [LAUGHTER] I think it makes sense to look at who are the appropriate providers of male circumcision in different settings. Obviously, the potential for that strategy in Israel is different from the potential for that strategy in South Africa. And I think you have to look at what, who is providing acceptable and safe male circumcisions in the context in which you are working.

DENVER VON VANDERBILT: It's Denver Von Vanderbilt. Jim, your comment that scale-up did not actually affect your cost model much came as a little bit of a surprise. I was wondering why one would not achieve some level of herd immunity, some level of increasing benefit with larger coverage. Very analogous to a vaccine, and why didn't you see that in your model?

JAMES KAHN, M.D.: Thank you, good question. And I should have expanded on that more. I want to first clarify that what I'm talking about, scale-up effects, it has to do with the epidemiologic effects as your question address, not the economic efficiencies of scale up. Regarding the epidemiologic effects, we found that they were countervailing forces that

were in fact somewhat more herd effects but also then the in a sense the earlier circumcisions are acting on a community at higher risk, the later circumcisions are acting on a community at a lower risk because of the earlier circumcisions and it tends to balance out. I would happy to get into the technical nitty gritty if you want. It was the interesting part of it.

MARGE BAER: Marge Baer, Reproductive Health Matters. And a couple of questions, are you taking into account –

RENEE RIDZON, M.D.: One question, please. You have four people behind you. Sorry.

JAMES KAHN, M.D.: I'm happy to answer all their answers afterwards, but please.

MARGE BAER: – well then the one question is given that this is only session on male circumcision in entire conference is there going to be somewhere where we can have a proper debate and discussion of these issues apart from a few questions?

[APPLAUSE]

JAMES KAHN, M.D.: I tend that to the moderator.

RENEE RIDZON, M.D.: Yes.

DANIEL HARPER: Daniel Harper in UNSAID. I'm glad there is at least one session, there wasn't one session at the last AIDS conference. Most of what I wanted to say briefly was already mentioned. I think the modeling is very interesting and I think that is great that it's fairly conservative modeling

but as Bertrand pointed out even with that conservative assumptions you are finding these findings. The PrEP analysis in the Orange Farm trial and this is in the published papers was 76-percent and we are doing work in Swaziland where we estimate the cost per male circumcision to come down to about $25. Also the Kericho trial funded by Gates Foundation may find some reduction male-to-female, direct reduction. So it is possible at least hypothetically that if you add in the male to female reduction to lower cost and the higher possible female to male reduction you could even find more dramatic cost aligning and so on, couldn't you?

JAMES KAHN, M.D.: Absolutely right. [LAUGHTER]

RENEE RIDZON, M.D.: Dr. Hankins [misspelled?], a quick question please.

KATE HANKINS, M.D.: Dr. Hankins, UNAIDS. Just a question. The Orange Farm trial showed no significant differences in condom use between the two arms or in the numbers of the partners. There was increase in frequency of sex. Have did you get first of all the 18-percent that you used to bump up the 25-percent for risk compensation. Where does that come from?

JAMES KAHN, M.D.: That was a, I believe that was the frequency of contacts. It may not have been significant but we then – nonetheless took it as a point estimate.

KATE HANKINS, M.D.: So you complied a –

BERTRAND AUVENT: Kate? That was the increase of frequency of sexual contact that we observed during the first nine months. We had [inaudible] person so we have to condense this value.

KATE HANKINS, M.D.: Okay. Good. Thanks.

BERTRAND AUVENT: And – Okay.

FEMALE SPEAKER: Well, I had a number of questions but we are asked to ask only one and I don't know which one to ask precisely. [LAUGHTER] But maybe of the more importance for me is to know is this debate true for circumcision for adult male or it is also true for people who have circumcised with STD.

JAMES KAHN, M.D.: Well, from the points of view of our analysis we looked at circumcision in adult males. Looking at it in children might affect the cost of doing the procedure and it would also affect this discounting that I mentioned and the benefits would be further in the future. I suspect the results would look pretty similar but we have not done it.

RENEE RIDZON, M.D.: Okay. One more question. I am sorry, and then we are going to have cut it off. I apologize.

JUDY WAISSRIGHT [misspelled?]: Judy Waissright, University of Washington. Very nice Jim, thank you. My question has to do with whether in the next generation of your modeling you would consider folding epidemic phase in terms of multiplier factor because one might expect that in earlier

phase or more concentrated epidemics where you have higher rates of gerbil STDs there would be a greater impact through that pathway then in generalized epidemics.

JAMES KAHN, M.D.: That is an interesting point. The epidemic multiplier had to do with two things, one was change over time, which is what you are alluding to in the epidemic course, and the other has to do with passive protection to women but I like the suggestion. Maybe we can chat about it.

FEMALE SPEAKER: My question or rather suggestion is to alter panelists and I would like to find if –

RENEE RIDZON, M.D.: No.

FEMALE SPEAKER: – in the, I mean male circumcision in Africa, if you are going to consider to actually engage the traditional healers because in most of the African traditions these healers have been – I mean you had traditional healers that have been conducting circumcision for centuries, for a very long time and instead of having maybe a whole new group of people to train and you know – if you would consider engaging people that are have been doing this for a long time.

JAMES KAHN, M.D.: I would ask if Bob or Bertrand wants to comment.

RENEE RIDZON, M.D.: Quickly.

ROBERT BAILEY: Just very quickly, yeah, I think it's an excellent idea and many people have discussed it. Though the problem is, the little data that we have from traditional

circumcisers shows that actually their rates of adverse events are extremely high. And so they would require at least, probably as at least as much training as any clinical officers or medical officers. So there could be real advantages since they are close to the community but there may not be advantages in terms of cost of training and roll out.

RENEE RIDZON, M.D.: Okay. I'm sorry. We cannot take any more questions. I'm sorry. You will have to do it afterwards because we need to give our next speaker an opportunity to talk within the time frame.

The next speaker I have the pleasure of introducing is Dr. Kawango Agot from the Union Project. It is her site in Kisumu that is performing the circumcisions in yet one of the other randomized clinical trials that is ongoing. And she is going to be giving us prospective from what they are seeing at that site presently.

KAWANAGO AGOT, M.D.: Thank you. The presentation is on male circumcision, a prospective study that will assess the behavior disinhibition among the Luhya of western Kenya. Its not related to the study but Dr. Bailey mentioned or talked about.

The study is supported by [inaudible] National Center and which is – and the USAID through the population council and AIDS [inaudible].

So in terms of background I won't go into any of this because you have that just mentioned that circumcision has shown some help, also some protective effect on women. And as we know that if it is not helpful to women, it's not helpful at all.

[LAUGHTER, APPLAUSE]

So if the two randomized controlled trials that are ongoing confirm this results of south Africa then the male circumcision may increase and — [inaudible] less susceptibility have been conducted in nine African countries with 45- to 80- percent of circumcised men reporting that they would accept circumcision were it to be provided as long as the issues around cost and feel pain and all the other adverse events were addressed.

But many reasons that they cited for wanting to — for accepting circumcision included improvement in genital hygiene and [inaudible] sexual pleasure both to self and to partner, and reduction of [inaudible] STIs or HIV in a [inaudible].

So if male circumcision were to become [inaudible] the men may get circumcised in the false belief that they are protected and therefore may subsequentially adopt more risky sexual behaviors. We conducted a study to assess this in — among men who elected to be circumcised. It wasn't a randomized controlled trial. The study was based in two public health care settings where the circumcision routinely occurs. And our

argument was that clinical trial settings are usually highly controlled with really, really screening out all unhealthy, or those who don't meet eligibility requirements and really high level training and high level monitoring and so on. Therefore, we wanted to look at the other side of a typical healthcare setting where the circumcision would routinely occur and to find out whether, what kind of response we shall get in terms of behavioral disinhibition.

So, as I said this was a prospective cohort study with 12-month followup at months one, three, six, 12 – at six, nine, and 12. We enrolled 648 circumcised men and half of them [inaudible] circumcision. Not all – yeah – [inaudible] to be circumcised and half of them remained uncircumcised. The men were matched with regards to age but then age within two years [inaudible] age, [inaudible] and residence. Participants choose the group to which they belonged. As I mentioned, it wasn't through a randomization process. [Inaudible] at followup visit medical – at enrollment and every followup visit medical exam was performed, medical history was taken, and behavioral questionnaire administered. And we had additional visits by the [inaudible]. It was kind of modeled pretty close to Kisumu trial, which I call it.

The outcome measures were reported sexual behaviors known to place men at risk of acquiring HIV. One was married men reporting sex with partners other than their spouses and

then married men reporting sex with partners other than those that they defined as regular girlfriend. We looked at this. We divided this into two. Both we just reported risky sex per week – whatever, not in a week, per week – as more than zero and below 0.5 per week and over 0.5 per week and those were reported risky and unprotected. So one is just having sex with somebody that is not as [inaudible] and not have a regular girlfriend. And another is having sex, unprotected sex with [inaudible] and then regular partner. We also looked at condom use, ever consistent and also number of risky sexual partners for men.

So, in terms of results. The baseline characteristics show that there was no difference between those who elected to be circumcised and those who remained uncircumcised with regards to age, mental status, the income, and efficient condom use, STIs and other behavioral risky sexual partners [inaudible]. it was interesting that the study, the eligibility was 18 to 49 years old and what you see is that those who [inaudible] the study are only between 20 – well about between 18 and 27, 28. So a lot of young men came. All the guys did come. But we found difference in those who reported [inaudible] erection, difficulty achieving erection, risky sex acts in the previous three months, and unprotected sex as in the previous three months. And also those who reported difficulty in session

or during intercourse. And we adjusted for these in our analysis.

So in comparison for those who reported risky sexual behavior, this is not unprotected, this is unprotected – sorry. Overall risky sexual behavior at one month there was a difference for those who reported, who had over 0.5 sex acts per week, were higher, significantly higher among those that were circumcised which of course is obvious. The circumcised guys are still healing plus we got post-op instructions both verbal and written. Therefore, we believe that they took those seriously.

Then we see that for the rest of the month there is actually no significant difference between circumcised and uncircumcised group. Also overall, the 12-month overall.

Now we see more or less the same trend with unprotected sexual behavior in those reported not using condoms versus condom use. But this – those who reported more than 0.5 sex acts per week, there was no difference across from month one all the way to the end. But what we didn't realize is that those who reported more than zero but below 0.5 sex acts per week there was a significant difference.

In terms of those who reported condom use and number of recent sexual partners, we also seen in terms of risky sexual partners those who reported more than one risky sexual partner per month had a – was significantly higher in uncircumcised men

of course, obviously, given that the other guys were healing but we didn't see any difference from month one all the way to month 12 in terms of those who reported recent sexual act. But the thing that is a little worrying is the fact that [inaudible] percent of the men were – had sex among those who were – among those who were circumcised had sex before one month despite counseling.

So in terms of some of the results at month 12 followup, a 6-percent of participating men did followup, 89-percent in circumcised men and 83-percent uncircumcised men. And men more likely to be lost at follow-up was single, had lower income and had completed high school. Obviously, these are men who are jobless and therefore migrated out to look job opportunities. And of circumcised men, 47-percent cited protection from STIs as their reason choosing to be circumcised. And others who are improvement in genital hygiene and to avoid injuries dealing with sex.

One month following circumcision, men was 61-percent less likely to report all [inaudible] after a week and 63-percent less likely to report over one but equal to less than 0.5 sex acts per week. The same trend is observed in terms of protected risky sex except that at month one for those who reported more than 0.5 sex acts per week there was no significant difference between the two. [Inaudible] 11 months we didn't observe any difference.

So [inaudible] I will say fast in terms of discussion we have a number of limitations, one is that the clans were not randomized as a condition of control and that we do not test for HIV/AIDS when I'm able to assess the effect of HIV status or behavior but we are arguing that if the completion was to be rolled out then they won't be need for this vigorous clinical trial requirement.

The duration of followup was also rather short. That was 12 months, initially it was only six months, and only with the support of USNAID did we extend to another six months. But we are doing basically – or following up plans in the Union trial up to 66, 67 months and we are hoping that we will get additional information in this area.

The frequent visits and [inaudible] put out [inaudible] effect on risk behavior. And maybe the two groups will be closer and of course we had a little concern about self report. Except for the erectile dysfunction problems and STIs in the last three months, the rest of the background behavior was no different. Sexual behavior [inaudible] increase [inaudible] position did not differ between the two group and even though 47-percent choose circumcision, protect themselves against STI or HIV, their behavior after circumcision did not differ than those who choose circumcision for other reasons.

Our results suggests that within the context of [inaudible] counseling on risk reduction, any benefits of

circumcision is not likely to give [inaudible] – adversely affected in this population and we call for similar studies in other settings. Just [inaudible] for the funding from the [inaudible] National Center, NIH, and the University of Washington's AITP and Population Counseling USAIDS and the study team and the brave participants who agreed to be circumcised.

[APPLAUSE]

RENEE RIDZON, M.D.: Okay. I have questions and it appears the back mircophone may not be working, so I don't know if you want to come to the front but go ahead. Identify yourself, one question each, quickly please.

GARY DALCETTE: My name is Gary Dalcette from the Tribe University in Australia. I wanted to register growing concern among the social scientists at this meeting about discussing circumcision being decontexturalize [misspelled?] from cultural and political consequences. This panel has not included anybody who was analyzed [APPLAUSE] circumcision as a cultural act. Anthropologists can tell you a lot more about circumcision that it is not prevention technology. This is a deeply meaningful social and cultural act as our Jewish and Moslem friends can tell us and that the anthropologists can tell us. To decontexturalize this act from its context is one of the lessons we learned that we should not do in this epidemic from the start.

And even if some kind of effectiveness is demonstrated, there are many public health tools we don't use in this epidemic because of their moral and ethical consequences such as quarantine. We know that quarantine can work in infectious diseases but we don't use it and we opposed it because of the moral, ethical and political consequences for people with HIV. So why these kinds of questions are not being addressed on a joint panel of social scientists, community people, and the kind of science you people do to think you fetishize this act and makes it impossible to have a really considered debate about its public health consequences.

[APPLAUSE]

RENEE RIDZON, M.D.: I think we can move to back microphone because I believe it works.

ROBERT GLITZMAN [misspelled?]: Thank you, yes, it does work. I'm Robert Glitzman from Columbia University in New York. For the last speaker here I was very struck that there was a significant difference between those who elected for circumcision and those who didn't based on deviation of I guess, penile deviation and also difficulty achieving erection. In other words, if men who had those problems were opting for circumcision, and I'm wondering if that suggest sort of a misunderstanding of why they would undergo circumcision or why circumcision, what the benefits of that might be.

KAWANAGO AGOT: Okay. I would say in the first one that as one of us had called for more intensive debate I leave that to the moderators, that you know people need to debate this issue more openly and with more time.

In terms of erectile dysfunction, we recognize that there is a lot of news on the press, a lot of talks going on around and also a little hope I would think because from the little bit I hear that erectile dysfunction is one of the greatest fears of men. And they would look for any solution, anything that may help and I think they must of come with a feeling that perhaps circumcision may offer some kind of way out of what their problems are. And it does show us that from my belief [inaudible] circumcision were to be wrong now this could be the group that may rush for circumcision but maybe for the wrong reasons. That is my guess.

ROBERT GLITZMAN: But I'm wondering then what that suggests about implementing this more broadly if people are going to be going into it with a misunderstanding of what benefits may be, whether down the road there might be consequences of that misunderstanding.

KAWANAGO AGOT: I think it does come from really proper consistent education on what is the extent. We don't want to popularize it as the [inaudible] or the issues but we have to really build to our education, information about what the condition can do after what label and what it can't do so that

people don't go into it thinking that he going to solve all your problems and that is not – you are going be protected from HIV in the first place.

ROBERT GLITZMAN: Thank you.

JAKE PETERS: I'm Jake Peters from a Canadian AIDS treatment information exchange. At the beginning of the opening – during the opening ceremonies Melinda Gates made a statement that circumcision reduces incidences of HIV and AIDS. And Dr. Agot you alluded to the question I'm going to ask which is that many people may feel that circumcision may be the solution to the problem. But I think – while making these kinds of statements –

RENEE RIDZON, M.D.: You need to stand a little closer to the microphone.

JAKE PETERS: – making these statements generally I think can contribute to a problem where people really do – they will wonder what is the point of using – it confuses the issue. But use of condom compared circumcision and the kind of language and messages that come out that are contributing to rise of new infection rates are similar to the language that is used and the medications being described as for example, cocktails when you have naïve youth coming out feeling that HIV is not problem because all they need is the cocktail. It's very simple solution to a very serious problem. It's a misrepresentation of the truth and if you are looking at people

who are in sub-Saharan Africa who are not available – done have access to education or what we take for granted in this society. They are going to be confused by hearing statements saying that circumcision – they are just going to wonder what is – what is the – there is a conflict here. You say that out of the one hand that HIV prevented by circumcision to some extent and yet they will feel then what's the use, what's the need to – why would they need to use condoms. Do you understand what I'm saying. There is confusion –

KAWANAGO AGOT: I'm trying to.

JAKE PETERS: – these young people.

KAWANAGO AGOT: Yeah. But what I can say is that as we mentioned by the previous speakers that when we are talking circumcision we are not talking about it as a stand-alone prevention strategy. We are saying that if the studies conclude that its beneficial, it would have to incorporated into the whole spectrum of comprehensive prevention strategies including condom use and abstinence and faithfulness and other risk reduction, you know, needle exchange and everything else.

JAKE PETERS: You understand what I mean about the confusion? When the message comes out, when a statement is made and is spread out in the media as it was during the opening ceremony then as Melinda Gates stated it, people take that and they can become confused. Because they walk away with that message and they're genuinely confused. But if they –

RENEE RIDZON, M.D.: I think your point is understood.

KAWANAGO AGOT: Yeah. But [inaudible] last call on [inaudible] those who are working at the level to then make sure that our education messages are like homegrown. So that they address those issues at the local level because as we are educating people there is so many messages that are going to up and you know you can't stop you from to what the other people are saying. But [inaudible] that are operating at the local level to make sure that we make our messages be very clear in term of what circumcision can do and what it cannot do.

RENEE RIDZON, M.D.: Okay. Back microphone, please.

Jamual UNKNOWN: Thank you. My name is Jamual [inaudible]. I'm from south Africa. I would have loved to hear from the studies presented. You know some of the – explaining some of mysteries associated with the role of the first [inaudible]. Scientific you know because as far as, you know, I would agree that circumcision is quite beneficial but I don't think that there was no role of [inaudible]. You know number one to say we quite know that [inaudible] cells present in the foreskins are quite more susceptible to infection by HIV. But what, what is in the same breathe there is also lysosome produced by the foreskin which kills HIV. And this studies have not explain those mysteries that of what of the protective effects of the foreskin. I would have loved that to come out of your studies. And lastly, the question of the method of

conducting the circumcision itself. With guillotine method versus the dissection method which has not also come out of your studies as true. Which method was used and which one would be fit because as some speaker mentioned here earlier on that you know there is circumcision performed by African traditional healers of which mostly of those is the Africa I know. They are more of a guillotine, you know, kind of procedure followed as opposed to the dissection method. Thank you.

RENEE RIDZON, M.D.: Bertrand? Okay. We are going to allow five more minutes or less in questions so they need to be a single question and very, very, very short. Dr. Weaver?

MARIA WEAVER, M.D.: Hi, Maria Weaver, Johns Hopkins University and [inaudible] Sciences Program. We are conducting the third randomized trial of HIV prevention in negative men but we are also with Gates support conducting a complimentary study that looks at HIV positive men, safety, and STD effects. And looking at safety, STD and HIV effects on women. So, that will be that very complimentary. We are also looking at community aspect, community understandings of HIV acceptability among positive, negative women and men who don't want to be circumcised.

So it will be – this ties into the comments that were made by [inaudible] very nice talk by the previous speaker, both the need alls to look at women because in our observational data we see substantial reductions up to 50-

percent lower incidence among female partners of HIV positive men who were circumcised in our observational data. And we strongly believe that needed to tested again in randomized trials. So this isn't a question. It's just a little addition.

RENEE RIDZON, M.D.: Thank you. There are also some posters on male circumcision today if the audience is interested, they can see some of those too. Back microphone.

CAROLINE OMAN-MILLETT: Caroline Oman-Millett, Medical Research Council. I'm a social scientist so I'm interested in what the previous person said about circumcision. My question is did you research what the reasons were for choosing circumcision among the cohort. I think it's really important to understand norms surrounding male circumcision around genital hygiene and also about female genital hygiene and how partners negotiate about these kind of things. And also how possible results such as those from Orange Farm might influence in the future take up of male circumcision. I think we need a lot more research about these issues. So, my question is whether people asked prior to your study?

KAWANAGO AGOT: Yeah. We did, as I mentioned we did ask them the reason when they were opting for circumcision since this was elected circumcision and there was referral for enhancement of sexual pleasure. There was the report of genital hygiene. There was the report of reduction in STI and HIV as their reason for choosing but what we didn't do was do more

demographic followup on study on the issues around hygiene and so on and so forth. But that is being done by one of our co-studies in [inaudible] the one that was presented initially. So that is going on and we are hoping to get more rich data in terms of that.

RENEE RIDZON, M.D.: Front microphone, please.

NISHA HANNAN: My name is Nisha Hannan. I'm from Jamaica AIDS Support. Dr. Agot I'm very happy to see your face on the panel. One of my concerns about the entire conference is that whole structure of panels being primarily from the West, from people who are predominantly white, [Applause] [Laughter] talking to us about our bodies. And my question is this how can we roll out projects like these that tell us to tell men particularly black, what to do with their penis from research that is from a predominantly white and Western structure. [Applause] it's impossible. I work on the front lines of HIV/AIDS and we cannot get men to use a condom. In my work with women reproductive health trying to get them to get the – to tie their – to cut their – what's the name of that – [inaudible] doing vasectomies. Impossible. We are going to tell them now to have a circumcision. It's – what you are asking us to do and to think about must involve scientists from our cultures at the very start as leaders of the science, not as followers. Thank you.

[APPLAUSE]

RENEE RIDZON, M.D.: In the back, please.

ELIZABETH GOGOI [misspelled?]: Thank you very much indeed. I was very, very interested in listening to the speakers. I'm Elizabeth Gogoi from Kenya, Nairobi. What I would really like to say is that — to suggest is that we need to do research. Find out the perception of women, find out the perception of the elders, find out the perceptions of circumcisers, from the traditional healers who do this [inaudible]. Let's not ignore them. But also there are rituals that people follow when they are circumcising the young men. What does this issues — can we follow scientifically and [inaudible] to design acceptable methods of rolling out this program. Thank you.

KAWANAGO AGOT: Maybe just to say one thing is, Elizabeth, we — that is going on like my boss did a study in Bondo [misspelled?] that is actually looking at the traditional providers of circumcision and many of us [inaudible] is said I mean that acceptability studies also ask the women and a number of the women actually also preferred to have circumcised, not as many, but to prefer to have circumcised spouses or partners. And also agree to circumcise their children. Of course, the percentage is much lower but these have been asked in susceptibility studies and we have records for that. Of course, there is also in Kenya we have as Dr. Judy Brown that is also doing a lot of trying to incorporate teachings on HIV

prevention during the cultural circumcision ceremonies. So that is not just a normal circumcision ceremony, about growing up and that gets infused with the teachings on HIV reduction. 'Cause going on at the [inaudible] really is a neat thing going …

[END RECORDING]