DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
Division of HIV / AIDS Prevention

CENTERS FOR DISEASE
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Consultation on Public Health Issues Regarding Male Circumcision in the United States for the Prevention of HIV Infection and Other Health Consequences

Summary Report

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April 26-27, 2007
Summary Report

Overview

This meeting was convened in response to the three African clinical trials showing a protective effect of male circumcision on HIV acquisition by adolescent and adult men. While exciting to have another prevention tool available in the global fight against HIV, these trials were conducted with heterosexual men in countries with high incidence, generalized epidemics in Africa. It is not clear how to incorporate male Circumcision into the prevention efforts in the United States (US) where the epidemic profile is quite different from that in Africa, and where neonatal circumcision is very common. The purpose of this consultation was to discuss what could reasonably be adapted from the African trials, what the cost-effectiveness and potential protective impact may be in the US, and what additional information was needed to decide on possible domestic implementation strategies.

Thursday, April 26th

Welcome / Charge to the Consultants / And Recent WHO / UNAIDS Guidance

(b)(6)

Welcome

[redacted] MD (b)(6)
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) welcomed participants to the Consultation on Public Health Issues Regarding Male Circumcision in the United States (US) for the Prevention of HIV Infection and Other Health Consequences. He pointed out that the Centers for Disease Control and Prevention (CDC) was particularly interested in discussing issues related to the US, explaining that the interventions CDC implements in the field tend to be behavioral oriented. The effect size of those interventions is about 30% to 40% in reducing risk behavior. With regard to male circumcision, Dr. (b)(6) said that when an intervention reduces HIV incidence by 50% to 60%, it seems an obvious choice to use such an intervention. However, in digging below the surface, issues arise for that intervention that suggest perhaps it should not be used everywhere and for everyone. The World Health Organization (WHO) came out with recommendations that did not say, "Where there is heterosexual transmission, everywhere in the world this is an obvious intervention."

With that in mind, this meeting was convened to talk about the issues, particularly related to the US. The US does have behavioral interventions for small groups based on risk, race / ethnicity, and gender. The data on male circumcision is really related to heterosexual transmission. Does the US have a heterosexual epidemic? Not much of one; however, that does not mean they should not be thinking about this issue. Because there is a males having sex with males (MSM) epidemic in the US, the major question is: Are there enough data to say that male circumcision should be recommended to MSM? Dr. (b)(6) explained that CDC convened this meeting in order for its consultants to deliberate the role of male circumcision in comprehensive HIV prevention programs in the US and to offer input to CDC to assist them in answering the many questions involved, such as: Should it be recommended? Should it be paid for? If it should be done, who should pay for it?

In conclusion, Dr. (b)(6) expressed his gratitude to the consultants for traveling to Atlanta, particularly their overseas colleagues. He stressed that the best minds in male circumcision and HIV in the world were in attendance.

Charge to the Consultants and Recent WHO / UNAIDS Guidance

(b)(6) MD, Deputy Director
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) added his welcome to the consultants. He requested that those present introduce themselves, pointing out that a list of participants could be found in their notebooks. Following the introductions, Dr. (b)(6) delivered the charge to the consultants and reported on recent WHO / UNAIDS guidance.

The specific charge to the consultants was to review scientific evidence regarding male circumcision efficacy in preventing HIV and other adverse health consequences; review existing data regarding cost-effects of infant and adult male circumcision for disease prevention; and provide expert advice to CDC regarding needs for additional information, programmatic and policy steps, and recommendations that should be made by CDC. Dr. (b)(6) stressed that CDC was not seeking consensus. The expected outcomes of this consultation included: A report of the consultation, including identification of next steps (e.g., information / research needs) and community and partners; a manuscript in a peer-reviewed journal; an updated CDC Fact Sheet; and possibly CDC recommendations. While there is a CDC policy statement, the agency does not currently have a recommendation on male circumcision.

Dr. (b)(6) then reported on 2005 HIV / AIDS new diagnoses in the US among adults and adolescents by transmission category in the 33 states that have had long-standing name-based HIV reporting. There is about a three to one male to female ratio, with 28,000 male diagnoses reported in 2005 versus just under 10,000 female cases. Among men, two thirds were MSM with an additional 5% MSM who were also injection drug users (IDUs); about 13% IDUs; and 15% identified as having heterosexual risks. For women, the story was very different. Fully 80% of the women identified were identified as having heterosexual risks, with 19% identified as IDUs. This is a complicated epidemiology in the US, which will be a key factor for considerations going forward.

Another very striking aspect of the American epidemic is the racial disparity of HIV. With respect to rates of estimated new HIV / AIDS diagnosis cases per 100,000 population for adults and adolescents, by sex and race / ethnicity, Dr. (b)(6) pointed out that there are tremendous disparities between especially Blacks and also Hispanics and White populations. For Black women, the rate of HIV is 20-fold higher than the rate of White women. These important epidemiologic data must be considered for public health recommendations.

Dr. (b)(6) then reported on the WHO / UNAIDS Consultation on Male Circumcision and HIV Prevention from March 2007. This was the result of a series of meetings convened by WHO / UNAIDS over the last year and a half, since the first clinical trial data came out. There were 11 conclusions drawn from that consultation, as well a series of recommendations, which Dr. (b)(6) summarized as follows:

1. The research evidence is compelling. Male circumcision should be recognized as an efficacious intervention for HIV prevention, and as an additional strategy for prevention of heterosexually acquired HIV in men.

2. Male circumcision does not provide complete protection for men against HIV. It is not known if male circumcision reduces sexual HIV transmission from men to women. Male circumcision should never replace other known methods.

3. Correct communication and messages on male circumcision are critical. There is a need for careful, balanced information. Male circumcision should be discussed within the context of comprehensive HIV prevention, always in a culturally sensitive manner.

4. The social cultural context should inform male circumcision programming. There is a diverse history of male circumcision practices around the world and it is important to consider those as each individual country or region makes their recommendations. The US has its own unique history of male circumcision, which will be taken into consideration. Efforts need to be culturally appropriate, stigma must be minimized, and stakeholder consultations should inform the process.

5. Human rights, legal, and ethical principles must guide service delivery (e.g., informed consent, confidentiality, absence of coercion).

6. The gender implications of male circumcision as an HIV prevention method must be addressed. It is important to minimize the potential negative gender-related aspects of male circumcision programs.

7. Programs should be targeted to maximize the public health benefit. The benefit will be the greatest where heterosexual HIV transmission is high and male circumcision is low. There is insufficient evidence for MSM. Settings with high HIV and low male circumcision should consider scaling up male circumcision services for adolescents, young men, and, as indicated, older men. Countries should consider neonatal male circumcision. Monitoring and evaluation are required, especially of any untoward effects of these programs as they begin to roll out.

8. Health services need to be strengthened to increase access to safe male circumcision services. Circumcision is not a simple intervention. There have to be a needs assessments and systems development. Traditional practitioners should be engaged in many parts of the world that are currently and have for a long time provided circumcision services.

9. Additional resources should be mobilized to finance the expansion of safe male circumcision services. National plans are needed. Male circumcision should be made affordable (ideally free of cost to those who need it). Already bilateral and multilateral donors, including the US government, are planning to support male circumcision services as requested by countries. The US President's Emergency Plan for AIDS Relief plans to provide resources, as is the Global Fund for AIDS, TB, and Malaria.

10. Promoting circumcision for HIV-positive men is not currently recommended due to possible risks associated with transmission following circumcision of positive men. HIV testing is recommended for men seeking male circumcision; however, this is not a mandatory requirement.

11. Research is needed to guide program implementation. There is a lot to be done. This is a very complicated issue. Research needs include: Risk / benefits of male circumcision for male-female HIV transmission, MSM, heterosexual anal sex; male circumcision of HIV-positive men; effects on other STDs; and safer methods.

Dr. (b)(6) concluded that there were a number of key issues for the US to bear in mind going forward, including: The role of male circumcision in HIV prevention for men who have sex with men, which is the predominant mode of transmission in the US epidemic, accounting for two thirds of male transmission; the relative contributions of receptive and insertive anal sex; the role of male circumcision for men who have sex with women; the status of neonatal circumcision policy; what form recommendations should take; and reimbursement: who will pay for circumcision?

Why Consider Increasing Male Circumcision in the United States?

Overview of International Male Circumcision in HIV

(b)(6) **PhD**
(b)(6)

Sharing an illustration of Egyptian male circumcision from about 5000 years ago, Dr. (b)(6) reported that circumcision is one of the oldest and most common surgical operations in the world. It is believed that about 30% of men are circumcised globally. The predominant reason for this is religion. About two thirds of those circumcised men are Muslim, and about 1% are circumcised because they are Jewish. In the Jewish tradition, circumcision occurs around the eighth of life. In the Muslim religion, circumcision can occur at later ages. Often young boys or adolescents are circumcised. Religion is the main determinant of male circumcision globally, accounting for about two thirds of the circumcisions. Another main determinant is ethnicity. Ugandan adolescent boys undergo traditional circumcision, which is seen as a right of passage to manhood. Unlike in the US, in many parts of the world, circumcision is not undertaken neonatally. Instead, it is or was an integral part of progression to manhood. This is seen in many parts of Africa and other cultures such as Aboriginal, Mayan, et cetera.

While religion and ethnicity are large determinants for circumcision, secular changes are observed in circumcision patterns as well. The US is a good example of this. In the Republic of Korea, circumcision was unknown in the 1950s—no men were circumcised. Currently, around 60% of men are circumcised there. This is thought to be due to the US influence in South Korea, which introduced the practice, and it became the norm within just a few decades. However, the Republic of Korea does not circumcise neonatally on the whole. Instead, it is done in young boys around age 8 to 10 when they believe they can understand what is going on and know why it is being done.

With respect to male circumcision prevalence at the country level, Dr. (b)(6) pointed out that in the Middle East and North Africa circumcision is almost universal. Large parts of West and Central Africa also have a high prevalence of circumcision among non-Muslim and Muslim men. This is also seen in the Horn of Africa. In contrast, in Southern Africa circumcision tends to be less common. These are country level prevalences, but there can be a lot of variation within a country. For example, in Kenya where around 80% to 85% of men nationally are circumcised, there are two ethnic groups which traditionally do not circumcise, the main one being the Luo who live in Kisumu where one of the trials was carried out. The Asian picture is quite interesting. In the Muslim countries (Bangladesh, Malaysia, Indonesia) the majority of men will be circumcised because of their religion. In the Philippines over 90% of men are circumcised. The origin of why circumcision is so common in the Philippines is not clear. In North America, circumcision is fairly common, though less so in Canada than the US. Male circumcision is declining in Canada and Australia. In Europe, male circumcision is virtually unknown apart from those done for religious reasons. In the United Kingdom (UK) it was quite common in the early part of the 20th Century. However, in 1948, when the National Health Service came in, they did not fund male circumcisions and the prevalence dropped rapidly. In Latin America and most parts of Asia, circumcision is virtually unknown.

Turning to the epidemiology of male circumcision and different infections, Dr. (b)(6) reported that one of the earliest epidemiological studies was conducted in 1855 by British physician George Hutchinson. Dr. Hutchinson published a study in the *British Medical Journal* in which he looked at a series of his venereal disease or STD patients. He had 58 Jewish patients, of whom 19% were diagnosed with syphilis. Of his non-Jewish patients, 272 (61%) were diagnosed with syphilis. The remaining patients were diagnosed with gonorrhea: 47 (81%) Jewish and 107 (39%) non-Jewish. Hutchinson concluded that circumcised Jews were much less likely to contract syphilis than uncircumcised Jews. Thus, these associations have been seen for 150 years or so.

Fast-forwarding to look at how these hold up using more recent data, Dr. (b)(6) reported on a meta-analysis she and her colleagues conducted in 2006 of male circumcision and ulcerative STDs (e.g., Chancroid, Syphilis, HSV2). There were not many studies of Chancroid (7), but the ones they found all showed protective effects of male circumcision. There also seemed to be a reduced risk of syphilis among circumcised males. For HSV2, there was perhaps a borderline protective effective, but not very strong evidence that male circumcision protects against becoming infected with HSV2 virus. While the data have not been assembled as systematically for gonorrhea, in 1988 Steve Moses et al found five studies, all of which found a protective effect. Looking more recently, Dr. (b)(6) et al found about a dozen studies, for which the picture was quite mixed. Though they did not put these into a formal meta-analysis, it looks like weak or not very strong evidence about a protective effect of male circumcision on gonorrhea. The trials will provide a lot more rigorous information about the effects of male circumcision on some of these STDs.

For human papillomavirus (HPV), the data is a lot stronger. There is a meta-analysis of eight studies in press (*Castellsague et al, 2007 in press J Infect)* showing that the risk of penile HPV and related lesions is significantly lower in circumcised men (OR=0.56, CI 0.39-0.82). That ties in very well with observations about a reduced risk of penile cancer. There is good evidence of a highly protective effect of circumcision on invasive penile cancer. There is also some evidence of lower risk of cervical cancer in female partners of circumcised men (*Daling et al, Int J Cancer 2005, 116:606-616;* (b)(6) *et al, 2000 Pediatrics 2000, 105:e36)* (OR=0.42, CI, 0.23-0.79). This could also be of great public health importance.

With respect to the impact on urinary tract infections (UTI), there has been one meta-analysis; one small RCT in Turkey, which had only 35 boys per arm; four cohort studies, and seven case-control studies. The results of these are all very consistent and highly significant, showing about an eight to ten-fold reduced risk of UTI in the first year of life among circumcised boys. What is interesting is the way people interpret these kinds of data depending upon what kind of assumptions they make. One analysis concluded that six UTI can be prevented for every complication (0.2% complications) (*Christakis et al, Pediatrics 2000:105:246-249*). The meta-analysis concluded that nine UTI can be prevented for every 20 complications (2% complications) (*Singh-Grewal et al, Arch Dis Child 2005: 853-858*). The 2% complication rate was a lot higher than Dr. (b)(6) had seen in large series of neonatal circumcisions in the US and Israel. This is an area where more work needs to be done to try to pin this down better.

Concerning HIV, one of the first foci of attention was the map that was drawn using data from the late 1980s of Africa, published in *Scientific America*, 1996. This showed a strong correlation at that time between areas where men were not circumcised in Africa and where HIV was most prevalent. There was a striking correlation, but as every epidemiologist knows, correlation does not mean causation. There might have been any number of reasons why these two overlapped so well, for example to do with Muslim religion and perhaps different sexual behaviour practices. Nevertheless, it is rare to see such a striking ecological correlation. Looking at more recent data at the country level, the same correlation is still observed. The countries with the highest prevalence of HIV are in Southern Africa (Swaziland, Botswana, Zimbabwe, Zambia, South Africa) and they have a relatively low prevalence of male circumcision. Countries with the lowest prevalence of HIV, where HIV was still introduced in the 1980s but it has not taken off in the way it has in Southern and Eastern Africa (Cameroon, Angola, Ghana, Benin) have a very high prevalence of male circumcision. There are a few outliers, for example Uganda has a male circumcision prevalence of about 25% but a relatively low HIV prevalence for Africa of about 6%. That is likely to be due to the very strong prevention messages that have been coming from the government, non-governmental organizations, (NGOs), community level successful HIV prevention programming in Uganda over the last 15 years or so. Uganda could be a case where, despite lack of male circumcision, there have been very strong behavioral change programs implemented. Lesotho also sticks out somewhat. About half of men there are circumcised based on self-report, while clinicians there report that those men may not be completely circumcised—there might just be a slit versus a full circumcision. So, more data are needed on that.

The same general pattern is observed in Asia, although important to note is that the prevalence in Asia is a lot lower at about 2% male circumcisions. The countries with the highest HIV prevalence within Asia tend to be the ones with lower male circumcision prevalence, though there are exceptions. A perfect correlation would not be expected because there is a lot of transmission due to IDU, probably more men have sex with men, and there are different transmission dynamics. Still, in the countries where almost all men are circumcised (Indonesia, Philippines, Pakistan) the prevalence of HIV is very low. So, it is not worth reading too much into these kinds of ecological correlations, but it does offer an idea about potential impact.

One of the first strong epidemiological studies which highlighted the potential role of circumcision was a cohort study of men in Nairobi who had had contact with an HIV positive sex worker (*Cameron, et al., Lancet 1989: 2; 403-7).* They were followed up, with the investigators studying time to seroconversion. They studied four different groups of men. Men who were uncircumcised and had a genital ulcer disease (GUD) had the highest risk of seroconversion. Half of them seroconverted to HIV within about 40 weeks after contact with an infected sex worker. The next highest incidence was among uncircumcised men who did not have a GUD, of whom about 29% seroconverted. Men who were circumcised who had a GUD, had an incidence of about 15%. Men who were circumcised and did not have a GUD had the lowest incidence. This highlighted the potential importance of circumcision / uncircumcision as a factor and the potential importance of GUD, both of which have been found to be strong transmission factors associated with HIV.

Drs. (b)(6) and (b)(6) were involved in the Four City Study in sub-Saharan Africa in which they were trying to determine why HIV took off so much more rapidly in East African Compared to West Africa. Was it to do with different behavioural patterns, different networking, or different levels of STDs? What was going on to drive the epidemic so much more strongly in some parts of the continent than in other parts? The investigators undertook population-based surveys in four cities: Cotonou (3% prevalence), Kisumu (25% prevalence), Yaoundé (7% prevalence), Ndola (25% prevalence). What they found, much to their surprise, was that relatively few behavioural factors showed up as being important. In fact, it was Yaoundé in Cameroon where men were reporting the most number of sexual contacts. However, a few behavioural factors did show up as being more common in the Eastern African countries, for example: Early age at first sex, early age at marriage, and larger age difference between spouses. The two major factors seem to be lack of male circumcision and herpes or HSV2 prevalence, which prompted them to look more closely at both of these.

They went on to do a meta-analysis focusing on sub-Saharan Africa where HIV prevalence is so much higher than in the rest of the world and reviewing studies that looked at the association between male circumcision and HIV. All of the population-based studies they reviewed found that circumcised men were at about half the risk of HIV compared to uncircumcised men, adjusting for behavioural factors as well as they could. The effect was highly statistically significant overall, at about 50%. They then also looked at higher risk populations (e.g., STD clinic attenders, truck drivers, occupational groups). Here they saw an even stronger effect. These studies also adjusted for behavioural factors as far as possible. All of them found protective effects, and all but one were statistically significant. When combined, the effect is highly significant. These studies showed that circumcised men in these populations were at about a third of the risk of HIV compared to uncircumcised men. Their rationale for why men in high risk populations might be even more protected is that circumcision protects against some GUDs, and it is known that GUD is a risk factor for HIV, then there would be some indirect protection against HIV through being protected against GUD.

The Rakai data that confirmed this was from discordant couples who were followed where the woman was HIV positive and her partner was initially HIV negative. The couples were followed over time and the investigators looked at HIV incidence. There were 50 couples where the woman was HIV+, men HIV negative, and the man was circumcised. In none of these 50 couples did the man seroconvert regardless of the viral load. So, even at a high viral load in the women, none of the circumcised men acquired HIV during this study. This is in contrast to the uncircumcised men where, on average, the incidence was 16%, and highest among the couples where the woman had a higher viral load. This is quite strong evidence because it is among discordant couples where one can look directly at what is going on. Also using discordant couples, the Rakai team looked at male to female transmission of HIV. This study found from evidence that, where the man was HIV positive and the woman was negative, the woman was more likely to seroconvert if her partner was uncircumcised—so again, a protective effective on male to female transmission associated with circumcision. This provided the justification for conducting the trial of male to female transmission.

Dr. (b)(6) then turned to the biology for the rationale for why circumcision might work. In the uncircumcised penis, the inner foreskin is a thinly keratinized mucosal surface. This means that it might be more susceptible to minor trauma and abrasion compared to the penile shaft or the outer foreskin, which can in turn facilitate entry of pathogens. Secondly, the area under the foreskin tends to be a warm, moist environment, suitable for pathogen replication. This could be why an increased risk of GUDs and UTIs are seen among uncircumcised boys and men. In terms of HIV specifically, if there is an increased risk of genital ulcers in uncircumcised men that is going to increase the risk of HIV acquisition in itself through disrupted mucosal surface of the ulcer. Also immunologically there is a high density of HIV-1 target cells in the penis, and those in the inner foreskin are nearer the epithelial surface due to lack of keratinization there, so it is easy for the HIV virus to find those target cells (*McCoombe, AIDS, 2006 20 p. 1491).* There has also been further work (*Patterson Am J Pathol, 2002. 161 p. 867)* showing that the cells in the inner foreskin are more easily infectable with HIV than external foreskin or cervical tissue.

Pertaining to acceptability of male circumcision in non-circumcising communities in parts of Sub-Saharan Africa, Dr. (b)(6) shared data (b)(6) (b)(6) These were all done before the results of the trials were out; that is, before there was widespread knowledge the circumcision seems to protect against HIV. Already at that time, there seemed to be a high proportion of men (median about 60%) who said they would be willing to be circumcised if it could be done safely and at low cost. Women were also asked if they would favour circumcision of their partners, with a relatively high proportion of women saying they would. The main reasons why men and women seemed to be open to the idea of circumcision were that there was widespread perception that it would improve hygiene, reduced the risk of STI / HIV, enhance sexual pleasure, increase sexual desirability. The main barriers included cost, safety, and pain. Interestingly, cultural issues did not really come up as barriers. There is often a perception that circumcision is closely bound with cultural issues, but that does not really seem to pan out.

An area where more work is needed is the safety of male circumcision. Although, there are good data from large series of neonatal circumcisions in the US and Israel consistently showing complication rates are 0.2%-0.4%, which is mainly bleeding and infections. This would be considered low rates of complications. In the developing world, these figures are very different and quite alarming in some situations at 2.4%-20%. This is an area in which the global health field needs to be very active to ensure that safety is a top priority. In children in the developed world, the complication rate is 1.2%-15.5%. In adolescents / adults, the complication rate in the clinical setting is 1.7%-11% and in the non-clinical setting is 35%.

Dr. (b)(6) concluded that approximately 30% of the global adult male population is circumcised, of whom 68% are Muslim; <1% are Jewish; and 13% are non-Jews / Muslims living in the US. Patterns of circumcision can change over time within a population according to secular norms. Male circumcision is associated with lower risk of UTI, HPV, invasive penile cancer, and chancroid. There is clear ecological, observational, and biological evidence of increased risk of HIV infection among uncircumcised men. There is evidence that acceptability of male circumcision in non-circumcising populations in Southern and Eastern Africa is already high and growing.

Results of the South African Trial

(b)(6) **MD, PhD**
(b)(6)

Dr. (b)(6) reported on the impact of male circumcision on the female-to-male transmission of HIV from the results of the Orange Farm intervention trial. Dr. (b)(6) interest in male circumcision began in 1995 in a study which tried to understand the heterogeneity of HIV prevalence in Africa. HIV prevalence is still high in places such as Senegal with 1% prevalence among adults, and other places such as Lesotho with 23%. In this study, they took into consideration a number of possible factors, including: Sexual behavior, sexual activity, and type of partners. Sexual behavior could not explain the heterogeneity. For example, in Cameroon, sexual behavior was about twice what it was in Zambia, although HIV prevalence was much lower in Cameroon than it was in Zambia. It looks like sexual behavior was the fueling force of the epidemic, but other forces could create either low epidemic or high epidemic with the same sexual activity. They found that male circumcision was a good candidate to explain, at least partly, the heterogeneity. In Cameroon, where sexual activity was higher, all men were circumcised. In Benin, all men were circumcised and there is a low HIV prevalence. In the two locations with quite high prevalence, Ndola and Kisumu, most men were not circumcised. In Kisumu, there was a mixture of circumcised and uncircumcised. It was clear there from the data that the prevalence among uncircumcised men was much higher.

They began to think about this, reviewed Dr. (b)(6) meta-analyses and other data, and concluded that they must prove the association between male circumcision and reduced HIV transmission. Even with all of the data available, nobody was convinced that male circumcision could be used as an intervention. Thus, they designed the Orange Farm RCT in 2001. The objective of this trial was to assess the effect of male circumcision on HIV incidence among young males. The location was South Africa in Orange Farm, which is an urban area close to Johannesburg. The local context for this study was suitable due to several factors. There was heterosexual spread of HIV, a high HIV prevalence (ANC data: HIV=31.6%), a male circumcision prevalence of 20%, a high median age of male circumcision of 17 years old, acceptability of the study (70% of uncircumcised males indicated that they would accept being circumcised if it would reduce the risk of getting HIV), and an important context of the trial is that it had very limited funding.

The study design was a randomized controlled intervention trial, for which approval was obtained through the University of the Witwatersrand Human Research Ethics Committee, authorization was granted by health authorities, and the ANRS scientific committee reviewed the study. Recruitment was from the general population among males in the age bracket of 18-24 year-old because that was an age where the HIV prevalence was quite low and the HIV incidence quite high. This was a good age from which to get good power without having to recruit huge numbers of subjects. Within that age range, they recruited those males who were uncircumcised but who were willing to become circumcised, who were in good health, living in the area, and who were accepting of being randomized with signed informed consent.

Following screening and randomization, participants in the intervention groups were offered to be circumcised within a week. Participants in the control group were asked to wait until the end of the trial before being offered to be circumcised. The follow-up was 21 months total, which is a short timeframe. After the screening, which took place in the first month, the three follow-up visits took place at the end of month 3, month 12, and month 21. The month 3 visit was designed to study the possible impact of male circumcision on HIV acquisition as a result of sexual activity during the healing period following circumcision or contamination during surgery. The sample size was calculated in order to get a power of 80% to detect a significant difference in the HIV incidence, assuming a reduction of HIV incidence of 50% in the circumcised arm.

The male circumcisions were performed by selected physicians who were general practitioners. For the procedure, a local anesthetic and post-operative analgesia were utilized. The technique used was the forceps guided method, using a standard protocol from Wits University Department of Urology to ensure that the three doctors performed the procedures exactly the same. The procedure takes approximately 30 minutes. This is not a blind trial, but the follow-up and evaluation were done blinded. For both arms, each visit was the same and included counseling (professional counselor), questionnaire (sexual behavior), blood sample tested for HIV (3 ELISA), clinical examination to check circumcision status because some of those in the intervention arm did not go for circumcision, treatment of GUD, and prevention of opportunistic infection.

The statistical analysis is somewhat complicated because time is continuous and the exact date of infection is unknown. We had to use a piecewise exponential proportional hazards model. This is a very simple model with duration between each period for each person, time independent covariates (background characteristics), time dependant covariates (sexual behavior, treatment of GUD), rates of infection / 100py); rate ratios (RR) of HIV incidence (RR with 95% CI), and easy implementation (Poisson log linear model, with duration between each period introduced as an offset so it is not so complicated).

At baseline, about 90% of the subjects were sexually active when recruited. Condom use at first sex was quite low at about 13% to 15%. The number of sexual contacts in the last 12 months reported by subjects was very low at 8 to 9 contacts. This was important because it was hard to believe that with such a low reported sexual activity in a population of young men from the age of 18-24, there was high transmission.

At the outset of the study, but Dr. (b)(6) was not optimistic about the results of a trial. He did not believe they would find anything, given that the time period was too short even to see the reverse because these young men could feel that they were now protected by male circumcision. He was also extremely afraid of having a lot of infections in the intervention arm because of sexual activity during the healing period, even if subjects were told not to have any sex during the first six weeks. Thus, he was very surprised by the results.

They had a planned interim analysis, although recruitment did take longer than planned. They had some adverse events (3.8% 60 / 1582), but no deaths. All adverse events were minor and were treated (e.g., bleeding, infections, swelling, pain, small cut in the penis, et cetera). The adverse events were very consistent with what has been reported by the two other trials, even if they do not use exactly the same classification. Loss to follow-up was 7.9% (Intervention: 6.8% versus Control: 9.7%). Despite all of the counselling and other efforts, they still had 69 HIV infections, with 20 in the intervention group and 49 in the control group. As a result, the HIV incidence ratio for the intervention group was 0.85 (0.55 - 1.32) / 100py, and for the control group it was 2.1 (1.6 - 2.8) / 100py, for a total of 1.5 (1.2 – 1.9) / 100py. The unadjusted RR was 0.40 (0.24 – 0.68) p=0.00059, meaning that there is a reduction of HIV infection in the intervention arm. This can be expressed as a protection (1-RR): 60% (32% - 76%), meaning the intervention prevented 6 out of 10 potential HIV infections. Comparing the South African Trial to the evidence from the observational studies, the South Africa trial is very consistent with what could have been expected. They also looked at the effect on HSV2, gonorrhea, and Chlamydia and could not really find anything. For syphilis, the power is too small to say anything. With regard to GUD, there is a major difference between the two other trials. In the Orange Farm Trial, they could not really find anything, but there is an important significant association with HSV2 status on blood samples and reported genital ulceration, with an odds ratio of 3.4 (2.1 – 5.3) p<0.0001.

The sexual behaviour between the two arms was compared. A higher number of sexual contacts were found among the intervention arm, although it is not clear why. Again, this was a very short period of time so the average was only 18 months. Thus, the significance of this is unknown. The effect of male circumcision is unknown. Men could be more at risk of infection because they are circumcised, because they are not circumcised—no one knows. Perhaps they could find this if they repeat some studies looking at the risk, because now the information is clear.

Further calculations resulted in the following:

Unadjusted RR
RR0: 0.40 (0.24-0.68) Protection: 60% (32-76)

Adjusted RR on time independent variables
(age, religion, ethnic group, alcohol consumption, recruitment period)
RR1: 0.38 (0.23-0.65) Protection: 62% (35-77)

Adjusted RR on time independent and dependent variables
(..., marital status, condom use, # of sexual partners, # of sexual contacts)
RR2: 0.39 (0.23-0.66) Protection: 61% (34-77)

Per protocol unadjusted RR (no dilution effect due to cross-over)
RR4: 0.25 (0.13-0.47) Protection: 75% (53-87)

Treatment received unadjusted RR (no dilution effect due to cross-over)
RR3: 0.24 (0.13-0.44) Protection: 76% (56-87)

This was the first RCT demonstrating a strong protective effect of safe male circumcision on HIV acquisition by males. That is still valid. Nothing can be said about the reduction of the female-to-male transmission. Regarding public health intervention, many things have been done since this study. The WHO recommendations have come out. Efforts are being made extremely rapidly at the agency, on the ground, and countries are really doing things. There is still a lot of operational research needed.

Since the trial, Dr. (b)(6) has been involved in additional studies. A modeling study was completed which was based on the results of the Orange Farm trial, and perhaps this should be repeated using the results of the two other trials. The modeling study suggests that over the next ten years in sub-Saharan Africa, male circumcision could avert 1.1–3.8 million new HIV infections, and 0.2–0.5 million deaths in men and women. In the ten years following that, male circumcision could avert a further 1.9–7.5 million new HIV infections, and 1.5–5.3 million deaths in men and women. A 2006 cost-effectiveness study in South Africa showed that doing three male circumcisions can avert one HIV infection in the next 20 years. The cost per HIV infection averted is estimated to be $181.

Results of the Uganda Trial

(b)(6) **PhD, MPH,** (b)(6)
(b)(6)
(b)(6)

Dr. (b)(6) pointed out that there are more than 40 observational studies that have found a significant protective effect of male circumcision against HIV acquisition in men. Biological studies have shown that HIV target cells are at high densities in human foreskin, and the inner foreskin is highly exposed to HIV by virtue of lacking a squamous epithelial layer. Of course, now there is a randomized controlled trial of circumcision from Orange Farm, South Africa, that has shown a 60% protective effect of circumcision in intent-to-treat analysis and a 76% protective effect in per protocol analysis. The normative agencies, a name someone gave, in this case to UNAIDS and WHO, have declared that male circumcision should not be actively promoted until the results from two additional trials are known. One is being conducted in Rakai, and Dr. (b)(6) presented an update on the other—an RCT of male circumcision in Kisumu, Kenya.

The hypotheses in the Kisumu trial included the following: 1) Circumcision will reduce HIV incidence among men aged 18-24 years by 50%; 2) Circumcision will result in less than a 2% rate of significant post-surgical complications requiring follow-up care; and 3) There will be no difference between circumcised men and controls in reported sexual behavior following the circumcision procedure. Investigators attempted to target moderate and high risk young men in Kisumu. They recruited bicycle transporters who had a reputation for being high risk, as well as car washers, football players, and people from STI clinics and VCT centers. Inclusion criteria were that: Men had to be uncircumcised, HIV negative, sexually active (defined as having had sex in the last 12 months), aged 18-24 years, residents of Kisumu District with no plans to move for at least the next 2 years, consent to participate, and their hemoglobin levels had to be over 9.0 grams per 100 ml or they would not be appropriate for surgery. Excluded were those men with the following: Foreskin covering less than half of glans, hemophiliac or other bleeding disorder, high prothrombin time index, other medical conditions contra-indicating surgery, and absolute indication for circumcision. The primary exclusion criterion was that men could have no absolute indication for circumcision. If they had, for example, phimosis, they were referred to another clinic. The circumcision procedure included the forceps guided method, which was the

same as in the Orange Farm Study. Serious infection and bleeding control measures were set up, as were emergency procedures. Fortunately, the provincial medical hospital was about 1 kilometer away from the clinic, so if they did have any emergencies, they were well prepared. Men were given explicit oral and written post-op instructions, and were followed-up at 3 days, 8 days, and 30 days after surgery. What likely reduced adverse events was that men were given the post-op instructions about wound care, highlighting the importance of the post-operative care component to any circumcision program. Adverse events were categorized by severity (e.g., mild, moderate, severe adverse events) and then by relationship to the study (e.g., definitely related, probably related, possibly related, not related).

Dr. (b)(6) reported that at initial screening, a total of 6686 young men came to the clinic. This is an indication of the acceptability of circumcision in this non-circumcising community. Of these 6686 young men, 8% did not meet at least one of the initial inclusion criteria, most reasons being: unlikely to reside in Kisumu, unwilling to undergo an HIV test, or not being completely uncircumcised. Of the 6159 men who met the initial criteria and were tested by double rapid tests for HIV, 5633 were HIV negative, 8% were HIV positive, 1% were discordant, and 91% were HIV negative. A post-test counseling group was created which included individual and group counseling, and free medical care and income-generating activities were provided to the HIV positive men.

Of the 5622 who were negative, about 20% (1100) were excluded based on the exclusion criteria, with more than half of those excluded reporting absence of sexual relations within the last 12 months, and others having an absolute indication for circumcision or a contraindication for surgery, a condition preventing sex, or having been treated for a medical problem (most for an STI), and not returning thereafter. Many men presented at the clinic because they were seeking treatment. They were treated, and although they were encouraged to return, once they were cured many did not return. Ultimately, 4489 men qualified to be enrolled. 38% of these either were not willing to accept one arm or the other, or simply did not return for enrollment. Thus, 2784 men were enrolled, with 1393 being randomized to the control or delayed circumcision arm, and 1391 being randomized to the treatment or circumcision arm. Enrollment was completed in early September, 2005. There were no real differences between the two arms at baseline in terms of demographics, physical characteristics, sexual histories, or laboratory results. Although there was a slight tendency for higher prevalence rates of STIs in the circumcision arm (29% vs 26% for herpes; 1.4% vs 0.6% for syphilis; 5.3% vs 4.0% for Chlamydia).

Regarding the study visits from randomization through 24 months, Dr. (b)(6) indicated that those randomized to the circumcision group normally underwent surgery within two days of being randomized. They returned to the clinic 3 days and 8 days post-surgery to check the wound, to answer questions about satisfaction and behavior since surgery, and to be counseled not to have sex or to masturbate for at least 30 days after the procedure. In most cases, the bandage was removed at 3 days. They were also checked again 30 days post-surgery. Men in both arms were tested for HIV one month and three months post randomization, and were asked a few perfunctory questions about their level of satisfaction in their sexual behavior since the surgery. Then at 6, 12, 18, and 24 months, they were tested for HIV using double rapid tests, and blood and urine were collected for STI diagnosis and for later immunological studies. If the person had urethral discharge or an ulcer, swabs were taken. Swabs were also collected for HPV studies. Any participant diagnosed with an STI is recalled to receive treatment, and all participants receive free medical treatment throughout the period of participation. At 6, 12, 18, and 24 months these men were also put through an extensive behavior questionnaire, which had also been administered at baseline. After 24 months of follow-up, those in the control group

were offered free circumcision right away, or they could wait until the results of the trial are known.

At the one month visit, follow-up was 92%. At the month 24 visit, 86% of all potential subjects for that visit actually presented for the visit. There was very little loss to follow-up. The trial was stopped on December 12, 2006 as was the Rakai Trial during the same Data and Safety Monitoring Board (DSMB) meeting because essentially they met the bound for stoppage. At that time, 87% of the Uganda trial had been completed. Follow-up for HIV status was incomplete for just 8.6% of all of the possible HIV status that still had not been completed. There were no differences at baseline between those who missed a visit and those who did not, although those who missed the visit were slightly better educated. The median duration of follow-up was 24 months, and 23 men withdrew from the study. There were 4 deaths that were unrelated to the surgery, 16 withdrew themselves, and 3 were withdrawn by the study team due to lack of cooperation and for being abusive to the staff. There was no differential loss to follow-up with respect to the study arm.

With respect to HIV sero-incidence, at the time of stoppage in the circumcision group, the two year incidence was 2.1%. In the control group it was 4.2%. That was significant at the 0.0065 level. At the time of the stopping rule, the level they had to meet was .002, so they easily met the stopping rule. The risk ratio was 0.47. The effect of circumcision really starts being demonstrable at the six-month visit, with twice as many HIV seroconversions compared to the circumcision group. That was a pure intent-to-teat analysis. For those who had seroconverted through month 6, the team reanalyzed the samples taken at baseline by PCR. They found that at baseline, 3 individuals who were allocated to the circumcision group and 1 who was allocated to the control group were infected or HIV positive at baseline. There were also 5 seroconversions at month 3. They were all confirmed seronegative by PCR at baseline, and 2 were positive at 1 month and 2 were negative, and there was one for whom they did not have a sample. Adjusting then for the PCR analysis, the picture of HIV seroconversions using the PCR result were as follows:

	M0	M1	M3	M6	M12	M18	M24	Total
Circumcision	3	4	0	4	3	0	8	19
Controls	1	0	3	9	18	7	9	46

AT baseline, or M0, 3 of the individuals in the circumcision group and 1 in the control group who had been labeled seroconverters in the intent-to-treat analyses actually were infected at baseline. Removing those who were positive at baseline, the incidence in the circumcision group is 1.866 / 100py, and in the controls it is 4.097 / 100py. This is highly significant. The relative risk in that group then was 0.41, or a protective effect of 59%.

In terms of adherence to treatment, 1334 circumcision procedures completed (95.9% of the expected circumcisions). In the treatment arm, 69 were not circumcised within six weeks (representing 5.0% crossover) and 16 men crossed over from control to circumcision arm (1.1%) because they went outside the clinic and sought circumcision elsewhere. So, they can be considered cross-overs as well Adjusting for these cross-overs, or thinking of an as-treated analysis, the relative risk becomes 0.45 (95% CI: 0.27, 0.76). But if the adjustment for the non-adherence to treatment and exclude the 4 participants confirmed to be HIV positive at baseline, the relative risk is 0.40 (95% CI: 0.23, 0.68) or a 60% protective effect.

With respect to data from the clinical signs and symptoms of STDs, there was an almost 2-fold difference in the incidence of GUD in the control group compared to the circumcision group. So, the relative risk of GUD was 0.56. For urethral discharge there was no difference. For genital warts, there was a very large difference with a relative risk of 0.14 or a protective effect against genital warts of about 86%. In terms of the lab results for STIs at follow-up, comparing the 2-year incidence in the circumcision versus the control group, there are very few syphilis cases, so no significant difference. Markedly, there were no differences in trichomonas, gonorrhea, or Chlamydia infections. Also remarkable is that there was no difference at all in HSV2. Thus, circumcision seems not to have a protective effect against HSV2 acquisition, but does have a strong protective effect against GUD. In terms of the 2-year HIV rates and the risk ratios by baseline HSV2 status by study arm, men who have HSV2 at baseline are at about twice the risk of seroconversion over the next 24 months (1.91 risk ratio). That is, if an individual had HSV2 at baseline, he would be at twice the risk of seroconverting, but there is no difference in the relative risk of HIV serioconversion by study arm. While circumcision does not seem to have a protective effect against HIV2, there is this story of GUD.

To summarize the results in the strict intent-to-treat analysis, the relative risk was 0.47. When that analysis is modified to take into account the serovonverters at baseline, the protective effect is 0.41. In the as-treated analysis, also taking out those who are positive at baseline, the risk ratio is 0.40 or a protective effect of 60%. That probably reflects the more true protective effect in this population. Then the investigators adjusted for baseline variable differences, and the results were virtually identical. That changed the results by about 1%.

Safety was an important component of the study. There were 27 adverse events in 26 individuals, which represents a 1.7% rate of definitely, probably, or possibly related to the procedure, including: 10 delayed healing or partially disrupted wounds (0.7%), 6 post-operative wound infections (0.4%), 4 bleeding episodes (0.3%), 7 (0.5%) other events. The other adverse events included: 2 excessive swelling, 1 anesthetic reaction, 1 excessive pain, 1 pubic abscess related to surgical tape, 1 case of folliculitis, and 1 participant reported erectile dysfunction. The 1 case of erectile dysfunction was classified as possibly related because at follow-up, they discovered that the man had entered the trial and wanted to be circumcised because he already had erectile dysfunction and was hoping that circumcision would cure him. Antibiotics were used sparingly, only for 7 of 9 cases with delayed healing, 6 of 6 wound infections, 2 of 5 bleeding cases, and 3 of 7 other complications.

The surgical outcomes were excellent based upon interviewing the men. In terms of level of satisfaction, 99% of were very satisfied, 0.5% were somewhat satisfied, 1 client was somewhat dissatisfied, and 0 clients were very dissatisfied. Notable is that at 30 days post-op, 5% of 1286 participants reported having had sex since their circumcisions, while 99% of men had resumed work (83% within 3 days). At 90 days post-op, 65% reported having resumed sexual intercourse. The men were asked whether their partners were satisfied. Based on the men's reports, 92% said their partners were very satisfied with the outcome, 5% were somewhat satisfied, 2% were somewhat dissatisfied, and 0.3% were very dissatisfied. There was one woman who said she was very dissatisfied, although they have not tracked her down yet. Disturbing was that despite the very vigorous counseling against having sex before 30 days (or fully healed), 5% engaged in sex before that 30-day visit.

Regarding risk compensation, or disinhibition, at baseline about 14% in both arms had been abstinent. That went up slightly at the 6-month visit and then remained stable, going up slightly in the control group, and remaining stable or going back to baseline in the circumcision group. In terms of change between the baseline and the 24-month visit, there was no difference in the two arms. There was a tendency by the 24-month visit for the controls to be engaging in slightly less risky behavior. That is a trend observed across five measures (e.g., consistent condom use, unprotected sex, last sex with casual partner, two or more partners in the previous month). Condom use went up dramatically after baseline, so counseling seemed to be doing some good. There was no change between the two study groups in terms of their condom use across the visits, but by month 24, there was a significant difference with the control group actually using condoms more than the circumcision group. Similarly, unprotected sex in the previous six months dropped rather markedly after baseline, hopefully due to counseling. There was no difference in the change across the two arms over the time period of follow-up, but again at month 24, the control group was engaging in less unprotected sex than the circumcision group. The pattern for last sex with a casual partner is about the same, although there is no difference on this measure at month 24. The same pattern was observed for two or more partners in the previous six months, with difference in the change between the two arms, and slightly less risky behavior in the control group by month 24.

In summation of the behavioral results, from baseline to the 6 month visit, both groups reported safer sexual behaviors in absolute terms. The gains at 6 months were basically sustained over all 24 months of follow-up, except for sexual abstinence in the circumcision group, which returned to the baseline level at month 24. There was little difference between the treatment groups in the patterns of behavior change from baseline, with the exception of greater than partners. Circumcised men reported more risky behavior at month 24 for unprotected sexual intercourse and consistent condom use: unprotected sex (51% vs. 46%); consistent condom use (36% vs. 41%). The bottom line essentially is that there is no sexual disinhibition in the circumcision group. They do not start engaging in more risky behaviors than they did at baseline. In fact, they engage in less risky behavior. The control group essentially reduced their risk behavior slight more than the circumcision group. One of the reasons for the control group reducing their risk behavior more than the circumcision group may be that they are in a circumcision trial, they are hearing about the possible protective effect of circumcision the entire 24 months they are in the trial, and they feel less protected than the circumcision group.

Dr. (b)(6) concluded that the HIV intent-to-treat analysis showed a protective effect of 53% (95% CI: 0.22, 0.72), the HIV as-treated analysis showed a protective effect of 60% (95% CI: 0.23, 0.68), and no behavioral disinhibition was observed. However, as noted, circumcised men engaged in somewhat more risky behavior than controls at 24 months. In terms of safety, related adverse events were 1.7%, which is comparable to some Western data. With regard to STIs, there was no difference in HSV2 incidence, no difference in HIV incidence in those with HSV2, and GUD was more frequent in uncircumcised men. The picture of GUD and HVS2 incidence and risk of HIV infections needs to be sorted out.

Results of the Rakai Trial

(b)(6) (b)(6), MSc
(b)(6)
(b)(6)

Dr. (b)(6) reported the results of two RCT of male circumcision for HIV prevention in men and women in Rakai, Uganda. One of these was a National Institutes of Health (NIH) funded trial of circumcision in HIV negative men to prevent acquisition of HIV, and the second was a Gates funded trial of circumcision in HIV positive men and effects in women. The primary study endpoints were HIV incidence (NIH in males; Gates in females) and safety of surgery in both infected and uninfected men. The secondary study endpoints were STD symptoms, STIs (although assays are incomplete at this time), behaviors during follow-up to look for disinhibition, and issues of acceptability. The study setting was the rural Rakai District of Southwest Uganda on the Tanzania border. This study differed from the other two African trials in that it was nested within a 14,000-person cohort, so it is widely dispersed in 50 rural communities, with decentralized enrollment and follow-up and a centralized surgical facility where the surgery and immediate post operative follow-up are conducted.

The trials were integrated by screening 6808 men. If those men had abnormalities or other indications or contraindications to surgery, they were excluded. If they had temporary issues (e.g., genital infection, anemia, et cetera) they were treated and later re-screened. If the men were HIV positive (997) they were enrolled in the Gates trial and randomized either to immediate circumcision (496) or delayed circumcision (500). If they were HIV negative, accepted VCT, and had no abnormalities they were enrolled in the NIH trial. 5000 men were enrolled who were randomized at 2474 into the intervention group and 2522 into the control group. That disparity in numbers randomized reflects the decentralized enrollment of this trial.

Dr. (b)(6) first described the NIH trial of male circumcision and HIV acquisition in HIV negative men, which was published in *Lancet* in early 2007. Eligibility criteria were that the men had to be HIV negative, uncircumcised, aged 15-49 (which differs markedly from the other two trials), accept VCT and learn their results, provide written informed consent, have an Hgb > 8 gm/d, and have no penile abnormalities. They were randomized to immediate circumcision (intervention arm) or delayed circumcision for 24 months (control arm). HIV infections were detected by two separate EIAs with Western Blot confirmation. If the Western Blot was indeterminate, PCR was also done. For all HIV seroconverters, the last antibody negative sample was tested by PCR (Roche Amplicor 1.5) to detect infections in the serological window period.

The circumcision surgery was performed by trained medical officers in properly equipped outpatient theaters. A sleeve circumcision procedure, under local anesthesia, was used. This also differs from the other two trials. Surgery on average took about 20-25 minutes, and men were observed for 30-60 minutes postoperatively. Because participants were enrolled from this wide geographic area, those who lived at a distant from the surgical theaters were kept in dormitories over night to monitor them and to be able to do post operative follow-up the next morning. The schedule of follow-up visits for the intervention arm were on Day 1 (within 48 hours post operation) and at Week 1 (5 –9 days post operation). For both study arms, the follow up visits were at Week 4 (4-6 weeks post enrollment), Month 6 (± 2 months post-enrollment), Year 1 (± post -enrollment), and Year 2 (± 2 months post-enrollment). Information was obtained at baseline and each follow-up, including: Interview on sociodemographic characteristics,

behaviors and health; serum for HIV, syphilis, and HSV-2 serology; penile swabs for HPV detection; urine for trichomonas, gonorrhea, or Chlamydia; penile examination to confirm circumcision status and to detect pathology; and swabs of GUD if present.

The statistical analysis was first an intent-to-treat analysis where men were just allocated to arm of randomization and crossovers were ignored. Second, an as-treated analysis was done of circumcised versus uncircumcised men, irrespective of arm of randomization. Crossovers were allocated to actual circumcision status. Two statistical procedures were used. The first was a person-time analyses where HIV incidence / 100 py was calculated for each follow-up interval and cumulatively over 24 months. Then the incident rate ratios (IRR) were calculated of HIV in intervention versus control estimated with exact 95% confidence intervals (CI) and Poisson multiple regression. Second, time-to-event analyses were done using the conventional Kaplan-Meier time-to-detection curves generated from enrollment to visit of HIV detection, and hazard ratios (HR) were estimated.

In terms of characteristics at enrollment, there was good comparability of age and marital status, very similar distributions of reported number of sex partners (including non-marital partners), and very similar reported uses of condoms. There were no differences, so randomization ended up producing comparability. With respect to the trial profile, 4996 men were enrolled (Intervention 2472; Control 2522). The reason that was less than 5000 is because some men double enrolled under false names, equally in both arms. That was detected and their second enrollment was excluded. Regarding crossovers, 146 (5.9%) men in the intervention arm did not return for surgery within six months, which is similar to what was observed in Kenya. Of the controls, 33 (1.3%) men received surgery outside of the trial. There were quite a number of deaths. By the 6-month follow-up, there were 3 deaths in the intervention arm and 8 in the control arm. By the 12-month follow-up, there were 4 deaths in the intervention arm and 5 in the control arm. By 24 months, there were 8 deaths in the intervention arm and 4 deaths in the control arm. Overall, the mortality was 4.5 per thousand in the intervention arm and 5 per thousand in the control arm. None of that mortality was related to trial participation. It is comparable to the mortality observed in negative men of this age group in the cohort. There is a major difference in the health setting of these different trials, and this rural population appears to have a higher mortality risk in this young age group.

This investigation was monitored by the same DSMB as monitored the Kisumu trial. The trial was closed on December 12, 2006 after a second, but unscheduled interim analysis showed efficacy (nominal $\alpha = 0.0215$). Approximately 73% of person-time anticipated had been accrued at closure. What is very important for the interpretation of the analysis is that because of the early trial closure, only 44% of men had the opportunity to complete the second year of follow-up. Retention rates were consistently ≥ 90% at all visits.

In the analysis of HIV incidence by study arm, within each follow-up interval, at 0 to 6 months, the intervention had a lower incidence than the control, but it was not statistically significant. Between 6 to 12 months, there is a marked decline in incidence in the intervention and a very slight decline in the control, and the incidence rate ratio is 0.35 and borderline. By 12 to 24 months, there was change in the control, some continuing drop in the intervention, and the rate ratio is .25 which was significant. It is probable that the reduction in incidence observed in both arms, but specifically the control group, partly involves self-selection. Men at higher risk become infected earlier, leaving the surviving population at lower risk. In these data at least, there clearly is an aggressive decline in incidence over time in the circumcised men (p for trend = 0.014). That decline over time in the circumcised men was highly significant. There was no significant decline in the control arm. When an interaction term was done for follow-up time and

treatment arm, that interaction term was borderline significance. IRR declined progressively during follow up (time-by-study arm interaction p = 0.054).

Concerning cumulative HIV incidence at 0-24 months using the Poisson person-time analysis, the incidence rate was 0.66 in the intervention arm and 1.33 in the control. The incidence rate ratio is 0.49 (0.28- 0.84). This was highly significant, and is why the trial was stopped. Unadjusted, the intent-to-treat efficacy was 51% (95% CI 16-72%). After adjustment for baseline characteristics it remained at 51% (95% CI 19-71%). Because there was good comparability at enrollment, adjustment made no difference. The As-treated efficacy was 55% (95% CI 22-75%). There is a bias in the Poisson analysis. The bias arises because they did not have time, given the early trial closure, to complete the second year of follow-up. However, it was within that second year that the maximum efficacy was seen. The Kaplan-Meier estimates are not biased by that reduced opportunity for follow-up in the second year. Essentially, out 24 months, the Kaplan-Meier intent-to-treat efficacy was 57% (95%CI 25-76%) and the as-treated efficacy 60% (CI 30-77%). Thus, the three trials are arriving at very similar estimates of efficacy despite differences in age groups, populations, locations, et cetera.

Pertaining to HIV incidence in subgroups, 6 men (3 in the intervention, 3 in the control) reported no sex partners in the interval that they became infected, although they did report sexual activity at other intervals. The data for these 6 men have been studied carefully, they have been re-interviewed, and it appears to be just misreporting. However, with men reporting 2 or more sex partners at an interval, there is a consistent reduction in incidence in the intervention compared to the control, and the incidence rate ratio is much lower for those with high risk sexual behavior. Looking at it by men reporting no extramarital partners or extramarital partners, in those reporting extramarital relationships, the differential between study arms is much more marked and the incidence rate ratio is much lower. This is similar to what Dr. (b)(6) reported in the observational studies, that the high risk men appear to have higher protection from this procedure than lower risk men.

STI symptoms were self-reported at each visit (e.g., GUD, urethral discharge, dysuria). Rates of STI symptoms were assessed per 100 visits, cumulatively over 24 months. For GUD, as in Kisumu, there was a marked reduction in the intervention versus the control with a prevalence rate ratio of 0.53 (CI 0.4-06). However, no impact was seen on urethral symptoms of discharge or dysuria. In addition, the investigators looked at syphilis prevalence by arm and found that it was about 4% in the intervention and 3.7% in the control over 24 months. No impact was observed in syphilis seriology. The team is currently assessing how much of the reduction in HIV incidence associated with circumcision might be due to the reduction in the prevalence of GUD and the effect of GUD as a cofactor for HIV. The incidence in men without genital ulcerations who were circumcised was 0.63 and in the control it was about 1.06. The circumcision effect was 0.60. If the man had genital ulceration, in the circumcised the incidence rate was 1.8. If he was a control and had GUD, it was 6.3. Again, the stronger protective effect of circumcision is seen in men with this risk factor than men without. The other thing that emerges is that the difference in incidence associated with genital ulceration is about 3-fold in the intervention arm and almost 6-fold in the control arm. What they think is going on, although they have not yet quantified it, is that circumcision is having two separate effects. One is that by removing the vulnerable foreskin, HIV target cells are removed. The second is that it is reducing GUD as a potential cofactor for HIV acquisition, but it may also be mitigating the effects of GUD on HIV acquisition.

In terms of behaviors during follow-up, no differences were observed in number of sex partners at the first follow-up or second year follow-up by study arm. Consistent condom use was very similar in the first follow-up. In-consistent use was somewhat higher in the intervention than the control arm at that time, but out of 24 months, condom use was identical in both arms. All men received very intensive health education repeatedly at every visit throughout the study and they responded. As with Kisumu, an increase was seen in safe sex behaviors between baseline and follow-up, hopefully as a response to the education. One thing they found very puzzling was that alcohol use with sex, which in this population is a risk factor for HIV, was more common in the controls than the intervention arm at all follow-up intervals. How to interpret this is not clear.

With respect to acceptability, pre-trial surveys were administered and 60% of men said that they would be willing to accept circumcision. Among those men who were enrolled from the cohort, 45% of eligible enrolled in the trial. Among the controls who became eligible for circumcision two years after follow-up, over 80% accepted circumcision. Most acceptability studies in Africa suggest high acceptance by men and women for hygiene, HIV / STI prevention and sexual pleasure. Acceptance of neonatal circumcision was also high.

Turning to the trial supported by Gates, Dr. (b)(6) indicated that the endpoints for HIV positive men were safety, STI effects, and behaviors. For women, they were HIV / STI acquisition and behaviors. The trial design was to enroll HIV positive men, uncircumcised, aged 15-49, with a CD4 >350, and no penile abnormalities. They were randomized to immediate circumcision or circumcision delayed for 24 months. Through the cohort, these men were linked to their female partners. The idea was to identify discordant couples and then to assess male-to-female HIV transmission within those discordant couples.

The DSMB for the Gates Trial closed enrollment on December 19, 2006, a week after the NIH trial was terminated all together. However, they recommended continued follow-up. This is an on-going trial, so current data are limited. The surgical complications contrast HIV positive to HIV negative men. Moderate to severe events were 3.6 (13) in the positives and 3.4 (78). There really was no difference in complication rates by HIV status. In terms of whether early resumption of sex might affect complications, in men who resumed sex before healing was certified, 16.8% of the HIV positive men and 13.9% of the HIV negative men experienced complications. In those who resumed sex after healing, 4.7% of the HIV positive men and 6.6% of the HIV negative men experienced complications. Wound healing by 30 days post-surgery was 71.2% in the HIV negative and 80.7% in HIV negative men. That difference is significant, so it appears that HIV positive men have slower wound healing than HIV negative.

GUD in the HIV positive men, cumulatively over 24 months, was 10% in the intervention and 15 in the control, with a rate ratio of 0.64 (0.45-0.85) in the intervention and 0.53 (0.43-0.64). The reason this is important is because it is known that if a positive man has an ulcer, he is going to be more highly infectious to his wife. This protective effect against GUD afforded by circumcision will hopefully translate into female reduced acquisition.

With respect to male to female transition, this trial profile is extremely complicated. 997 HIV positive men enrolled, of whom 497 were placed in the intervention arm and 500 were placed in the control arm. In the intervention arm, 380 were married (77%) and 302 spouses (79%) enrolled. In the control arm, 360 were married (72%) and 255 spouses (71%) enrolled. Enrolled in the intervention arm were 127 (42%) male positive / female negative discordant couples, while the control group had 112 (44%). For the interim analyses, only those couples where the husband and wife were enrolled at the same visit were selected out, which dropped the numbers. The bottom line here is that if male positive / female negative discordant couples,

concurrently enrolled, who had at least one follow-up (70 such couples in the intervention arm and 54 in the control arm), the female acquisition rates over 24 months were 16 for the intervention arm and 8 in the control. The incidence rate ratio was almost doubled, but nowhere near significant. Obviously, the investigators and the DSMB were very worried that they may be doing harm. They were instructed to determine why they might be seeing a higher transmission rate in wives of circumcised men. What may explain this is early resumption of sex more than 5 days before healing was certified compared to couples who resumed sex either after healing was certified or within about five days of certification. These men are only seen at 30 days to certify healing, so when they see a healed wound, it has preceded that visit of observation. Only 12 people resumed sex early, but there were 3 sero-conversions, 25% transmission rate. Among those who delayed resumption of sex, the transmission rate was 9.3% which is what would be expected in discordant couples over a six month period. The delayed sex groups had very similar transmission rates to the control group. These investigators do not have enough follow-up beyond six months to be able to say anything about possible long-term benefits or harms to women. That is going to take more follow-up time. Of concern at this point is that it is unclear whether they will have the power to address the question of female acquisition. There really needs to be a multi-centered study in discordant couples to address that issue. The female benefit or risk is a critical question that must be addressed.

Regarding policy implications, it can probably be said that all men, regardless of HIV status, must abstain from sex until complete wound healing is certified to avoid surgical complications. Second, HIV positive men most definitely have to abstain from sex until complete wound healing to avoid infection of female partners. Significant reductions are not seen in HIV negative men. Follow up of female partners is too limited to assess possible reduced male-to-female transmission. In all three trials, with respect to male acquisition, significant reductions in HIV are not observed in negative men for the first six months. It only emerges subsequent to that. There is information on women only for that first six months. It is hoped that benefit will emerge, partly based on the observational data that Dr. (b)(6) reported, and also based on the marked reduction in genital ulceration being observed in the HIV-infected men.

Discussion

- With regard to shedding that takes place after circumcision, an inquiry was posed with regard to whether someone who is "healed" after surgery continues to shed. If so, could the shedding possibly be a factor in the continued possibility of transmitting the disease. Dr. (b)(6) responded that they had criteria for healing (e.g., a well-formed scar, no scabs, et cetera). While he said he could not answer the question, in the continuation of this trial, they will see those circumcised men at much more frequent intervals post-operatively, closely examine the wound, take swabs to determine if HIV shedding can be detected, and take blood because another concern is that the stress of surgery could increase the uremia in the positive men. They do not have that revision to the protocol approved yet.

- An inquiry was posed regarding what types of incentives and / or other on-going benefits were used to enroll / retain participants. In addition, from the view of an anthropologist, a question was raised with respect to what the implications were to the business of incentives in relationship to the impact upon the study. Dr. (b)(6) responded that men who were circumcised received a $15 equivalent for the time they had to take off work and trouble they went to. For each subsequent visit, it was a $1.50. That is the routine IRB approved compensation. That was equal in the intervention and the control arm for those who were circumcised. Dr. (b)(6) responded that all three trials provided free medical care throughout the follow-up. The Ugandan trial provided $4.30 per visit (300 shillings), which is equivalent

to about a day's work for this population. Clearly, if subjects are given too much it can be perceived as coercive. The Ugandan investigators and IRBs were very sensitive to this. The greatest attraction to the trial seemed to be the free circumcision and medical care. There is no question that in that setting, safe male circumcisions are very important. Men can obtain circumcisions elsewhere, but they may not be safe.

- A question was raised regarding whether there was a difference in incidence of infection when the procedure was the sleeve circumcision versus the clamp, pull, cut. Dr. (b)(6) responded that the results are remarkably consistent across the three trials. There was little difference in safety and adverse events and almost no difference at all in incidence. Dr. (b)(6) added that they did see somewhat more complications in the Rakai Trial than in the South African and Uganda trials. However, he was not clear whether they could ascribe that to the surgical procedure so much as the conditions under which these people live. In Rakai, men will return to agricultural work shortly after surgery. When investigators look at the timing of infections, most occurred a week or more post surgery and this is believed to be secondary contamination of the wound because these men are working in the fields. He did not believe it to be a procedure issue.

- It was noted that Dr. (b)(6) could not have experienced worse timing for a technical difficulty and an "oops" than when a photograph of a penis was on the slide. It is the "oops" factor that will make it difficult to push this.

- Dr. (b)(6) data seemed to suggest that there were more infections in the HIV infected people who were circumcised. With that in mind, an inquiry was posed regarding whether they knew anything about the T4 cell counts in those people, and whether it was primarily in people who were more immunologically impaired that the infections occurred post circumcision. Dr. (b)(6) responded that they did not see more post operative infections in the HIV positive versus the HIV negative men. All of these men had CD4 counts above 350, so they should not have been seriously immuno-compromised. If they became immuno-compromised, they were started on antiretrovirals.

- Dr. (b)(6) was congratulated for opening up the field outside of HIV when she mentioned syphilis, chancroid, and UTI. These are all bonuses that are realized with a permanent procedure. No booster procedures are required. Along the same lines, reflecting on the work in Cameroon, twenty years later the results are the same. In the meantime, 20 years and millions of lives have been lost. Every time a new report has come out over the years, everybody says, "We need more evidence." But, people are dying. Fooling around with vaccines where the virus is one step ahead of the vaccine and will still be is foolish. This "vaccine" is not going to be one step ahead of it because it is a permanent "vaccine." Along the same lines, the comment Dr. (b)(6) started with was problematic. He seemed negative about 50% to 60% protection; however, there are vaccines given to children that begin with 60% protection. That is pretty potent protection, especially when it is multiplied where cases are not going to be transmitted more. For 20 years, there has been 60% protection with circumcision. Stop fiddling!

- In each of the studies there were individuals who decided not to be circumcised. With that in mind, an inquiry was posed regarding what kind of data were available on their risk profile and after the study was stopped, what the magnitude was of the uptake of circumcision among this population. Dr. (b)(6) responded that regarding those who were in the intervention group but chose to remain uncircumcised, some were better educated and more mobile. Most of them simply left the district, generally for work. There did not seem to

be much self-selection and the numbers were small. The magnitude of uptake after the trial was stopped can only be reported anecdotally. There has been a marked increase reported by not only hospitals within the Rakai district, but also around the country. This actually presents a major public health problem. There is now a demand and if it is not met by skilled practitioners, it will be met by practitioners who may provide substandard surgery or post operative follow-up and none of the intense post operative education provided in the trial. At least for Africa, movement must be rapid because the "horse is out of the barn."

- Related to acceptability, all of these studies began with the premise that men had to be willing to be circumcised if they were thus randomized. A question was raised about how many "no" responses investigators had to go through before they got to a "yes" and whether there was any insight into the reasons people did not want to get involved. Dr. (b)(6) responded that in Orange Farm, they do not really know the answer to this question because they did not actively recruit. Information was in the community. Dr. (b)(6) responded that in Kisumu they do not know the reason because no one ever said "no." They say, "Yes, I really want to, but I have to help my father build a new house. I'll be back in two weeks" and then they do not return. The investigators believe the main reason are time away from work and that they will have to go through pain. Dr. (b)(6) responded that because the Rakai Trial was within a cohort, they do know about the population who was eligible to enroll who decided not to. Of those who were eligible, 45% did enroll. Most men who decided not to wanted to wait to see if it worked or feared pain or complications.

- In applying the results of these three trials to the US, and the charge of this workshop, two observations were made. According to Dr. (b)(6) slide, 15% percent of infections among men in the US are ascribed to heterosexual contact. Most epidemiologists would most generously describe that as an upper bound of a range, the true central value of which is lower because there is a disincentive to report homosexual activity and / or drug use in many of the source data for those statistics. On other hand, there appears to be no experimental evidence of the protective effect of male circumcision against infections among women. There is some observational data. It would seem that without data on MSM and protective effect for women, the potential maximum upper bound of its impact in the US would be a 50% to 60% percent prevention rate among 10% of infections among men who are heterosexual. Dr. (b)(6) responded that this was why the consultation was convened. A small proportion of identified cases of men in the US are attributed to heterosexual transmission. CDC needs guidance from the consultants on the value in the US and what an appropriate public health recommendation might be.

- It was noted that in communities, a vaccine is an injection or inhalant that teaches the body's immune system to fight future infections. Since this is a procedure, it was suggested that it not be referred to as a "vaccine" as it will be confusing to communities.

- An inquiry was posed regarding what condom use was at baseline, what community acceptability was with respect to condom use, what condom uptake was for people who were in the intervention or outside the intervention following the trial, and whether condoms were provided post trial or whether people had a way of obtaining them. Dr. (b)(6) replied that, similar to what was observed in Kisumu, in Rakai there was an increase in consistent condom use. Consistent use was around 14% at enrollment. During follow-up it went up to 19% percent at 24 months. It was even higher earlier in the follow-up. Consistent condom use is complicated. It is seldom observed in marriage. It is mainly observed in casual relationships. There is not much meaning for a population level consistent condom use. Substratification by those having casual affairs must be done. Among those people, 60%

are now reporting that they are consistently using condoms. The Rakai Trial does provide free condoms and has a social marketing scheme that provides very cheap condoms. Condom use has gone up markedly, particularly among the young.

- A question was raised regarding whether post trial there was an increased community level interest in circumcision. Dr. (b)(6) responded that overwhelmingly this occurred. There is a lot of media coverage and all communities and trial participants were informed of the results. There was a huge surge in demand that cannot currently be met. Dr. (b)(6) added that he did not know what the consequences of the trial were on circumcision demand in the Orange Farm study. Dr. (b)(6) indicated that there have been reports in the Kisumu community that there is 3-fold increase in people going to the provincial hospital and to other clinics seeking circumcision services. In the Uganda clinic, after December 12th people were asking us for services, but there is no funding to provide them. The team has conducted some training sessions. They recently put the word out that they would like volunteers who would like to be circumcised and people flooded in. They now have a project to treat STIs and doing VCT for non-trial participants who are asked if the clinic could offer circumcision whether they would like it—93% say they would.

- A question was posed regarding whether, in any of the trials, the investigators discussed the possible ways they were at risk for HIV in terms of any of the people in the trials having sex with men. Dr. (b)(6) responded that they did ask men about having sex with men. Of the 2800 men, 4 said that they had sex with men. During the follow-up, 6 additional men said they had. The true rate is not known. It is a highly stigmatized behavior that is actually illegal. People can be arrested and are often tortured for it. Dr. (b)(6) indicated that in Orange Farm, 2 or 3 men reported having sex with men. Dr. (b)(6) agreed that it is very difficult to get this information from interviews. They see vanishingly small reports and these are usually people who are incarcerated, for example. What is known is that rectal gonorrhea is not seen in either gender. There are very strong cultural taboos against anal sex, so the presumption is that this is very rare.

- An inquiry was posed regarding future plans to address the potential for those who are not well trained or well qualified offering / performing the procedure. Dr. (b)(6) responded that they have an NIH grant to conduct post trial surveillance among trial participants. They have submitted a grant for additional support to scale up circumcision, conduct training, conduct needs assessments, and a variety of other activities. They are doing their best to acquire the resources. The problem is that the closure of the trials is relatively recent. However, it is gearing up.

- In the Orange Farm study, there was evidence that a sizeable proportion of people were switching arms. A question was posed regarding the extent to which that phenomenon was seen across the studies and what the implications would be for reporting findings. Also of concern was behavioral disinhibition. One of the three articles actually stated that there is evidence for behavioral disinhibition depending upon how that is defined, yet all three of the studies seemed to report significant results at various times that suggested that people in the circumcision arm were reducing their risk behavior at a slower rate than the controls, or reported higher numbers of sexual contacts, and higher rates of unprotected sex at various points in the study. Is this a semantic issue? Is more conceptual clarity required about the adverse potential changes in behavior as a result of circumcision practice? What role might behavioral science play in future trials? Dr. (b)(6) replied that the Orange Farm Trial had the highest rate of crossover. They know that some refused to be circumcised. They were disappointed by the high rate of crossover. Dr. (b)(6) added that the Uganda Trial found

that risk behavior did decrease by virtue of being in the study. They think this is due to vigorous counseling. Obviously, disinhibition is a big risk. People must be counseled that it is not fully protective. Another way to think about it is that circumcision offers a great opportunity to access a population that is often not accessible in East and Southern Africa that does not go to health facilities. When they present for circumcision, it is an opportunity to council them, treat their STIs, give them VCT, et cetera. Circumcision cannot be a standalone surgical procedure. It must be integrated with all of the other prevention strategies aside from just the biological protective effect of circumcision.

- In the NIH trial, an inquiry was posed regarding whether any subset analyses were done based on age to determine if there was any difference in older versus younger men. Dr. (b)(6) responded that they did and there was protection in all ages, not statistically significant because it was not part of the subgroup. The oldest age had the highest protective efficacy. They do plan to do a number of pooled analyses that will address such issues.

- There appeared to be greater effect in higher risk groups. A question was raised regarding whether that was attributed to the concurrent effect on other STIs or to other factors. Dr. (b)(6) responded that it is a fascinating observation. He did not know of any other example in epidemiology where people at the highest risk received the most benefit from protective factors. It could be mediated by GUD. The investigators speculate that it may analogous to what was observed in the highly exposed but uninfected commercial sex workers in Nairobi, for example. The argument is that the only unkeratonized vulnerable mucosa left after removal of the foreskin is the urethral meagis, so it is a very small target. They could get self-infectious inoculums of HIV that could induce local immunity and give an even higher level of protection in those who are highly exposed and getting those repeated inoculums. There would be less protection in men who were not highly exposed because they would infrequently encounter the virus. They have discussed with immunologists whether they could test this hypothesis by looking for a mucosal immune responses. At this point, they do not know how to do this. The commercial sex worker data are very persuasive.

- In terms of the timing of this effect, in the data that were presented it appears that this really kicks in after 6 months and perhaps increasingly after that. With eye toward thinking about recommendations ultimately in the US and elsewhere about timing of this procedure, a question was raised regarding whether they should be thinking about this in terms of having people circumcised before they initiate intercourse so that there is a full year before exposure. Dr. (b)(6) responded that the messages have to be to abstain from sex until the wound has healed and practice safe sex thereafter always. His team has looked at infection rates by resumption of sex before healing. Higher incidence is seen in those who resume sex early, but it is not significant because the proportion of the population doing that is quite small.

- It was noted that there are two separate issues. One is waiting to resume sex until wound healing, which is probably an easier message to get across. Second, there is the broader issue of when maximal effect is actually reached. These messages also have to be carefully crafted.

Overview of Domestic Male Circumcision

(b)(6) **MD**
(b)(6)
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) reported Africa / US differences in HIV and male circumcision, HIV epidemiology in the US, male circumcision in US, risks of male circumcision, male circumcision and female-male HIV transmission in US, MSM willingness to be circumcised, male circumcision and other health outcomes, and policy and payment issues.

With respect to key Africa / US differences in HIV and male circumcision, HIV prevalence in Africa trial countries is 6-19%, while in the US the adult prevalence is 0.4% (*NHANES* 2002). Male circumcision prevalence in the Africa trial settings is 10-25%, while in the US overall it ranges 70-80%. HIV transmission risk groups in the Africa trial countries are primarily heterosexual, while in the US risk is primarily in MSM. The sexual transmission epidemiology is a critical difference. Heterosexual men are at risk as the insertive partners, with good clinical trial data evidence now that male circumcision is protective for them. However, MSM are at greater risk as receptive partner, for which there is reason to believe that there is little to no protection.

In 2005, of the HIV / AIDS cases diagnosed among male adults and adolescents in 33 US states with confidential name-based HIV infection surveillance, 67% were attributed to male-to-male sexual contact and 13% were attributed to injection drug use. Approximately 15% of cases were attributed to high-risk heterosexual contact and 5% attributed to male-to-male sexual contact and injection drug use (~28,000 cases). Most (80%) of the HIV / AIDS cases diagnosed among female adults and adolescents were attributed to high-risk heterosexual contact, and 19% were attributed to injection drug use (~9,000 cases). High risk heterosexual male cases make up 11% of the total transmission in these 33 states.

With respect to diagnosis rates for HIV / AIDS cases among male adults and adolescents residing in 33 states with confidential name-based HIV infection surveillance, for male adults and adolescents, the rate (HIV / AIDS cases per 100,000) for non-Hispanic blacks (127.6) was nearly 7 times higher than for non-Hispanic whites (18.5) and more than twice as high as the rate for Hispanics (57.6). The distribution of risk factors for HIV infection differs by race / ethnicity. From 2001 through 2005, of white (not Hispanic) men with AIDS, 72% had been exposed through male-to-male sexual contact, and 12% had been exposed through injection drug use (IDU). Of black (not Hispanic) men, 45% had been exposed through male-to-male sexual contact and 24% through IDU. Of Hispanic men, 53% had been exposed through male-to-male sexual contact and 24% through IDU.

Referring to National Health and Nutrition Examination Survey (NHANES) data from 1999-2004 regarding male circumcision in the US, Dr. (b)(6) reported that 6174 men were interviewed about circumcision status and sexual behaviors. The overall prevalence of circumcision was 79%. By race / ethnicity, in non-Hispanic whites prevalence was 88%, in non-Hispanic blacks prevalence was 73%, and in Mexican Americans prevalence was 42%. In these data, circumcision was not associated with sexual behaviors. Importantly, there were similar rates of circumcision among those who reported male-male sex. Comparisons of sexual behaviors were limited to 4872 boys / men (1,397 uncircumcised and 3,475 circumcised) who reported having had sex. The mean age of sexual initiation did not differ by circumcision status (16.7 years in

uncircumcised men and 16.9 years in circumcised men, p = 0.3), or the percent of men who had ever had a male partner (3.4% in uncircumcised men and 4.9% uncircumcised men, p = 0.07). The median number of lifetime sex partners was 5.8 (95% CI 5.1-7.6) in uncircumcised men and 7.0 (95% CI 6.1-7.8) in circumcised men; the geometric mean was also similar (6.8 in uncircumcised versus 7.5 in circumcised, p = 0.1). In men born in the US from 1940-1979, circumcision increased, more in non-Hispanic blacks and Mexican Americans than non-Hispanic whites. Circumcision decreased significantly in those born in the 1980s (84%) compared to those born in 1970s (91%).

Dr. (b)(6) referred to another survey on male circumcision rates in the US, the National Hospital Discharge Survey (NHDS), which is a national probability survey that has been conducted annually since 1965. In 1999, 65.3% of male newborns born in hospitals were circumcised. A more recent update in 2003 shows that decreased to 55.9% (Kozak LJ. *Vital Health Stat* 2006). It is important to note that NHDS may underestimate procedures not coded and circumcisions performed after discharge. MHDS is based on ICD-9 coding, so these may be miscoded, undercoded, or not recorded.

From that same data source, Dr. (b)(6) discussed changes in racial and regional patterns of infant. In 1999, 65.3% of all male newborns born in hospitals were circumcised. While the overall percentages of circumcised infants have remained relatively unchanged throughout the past two decades, ranging from a low of 60.7% in 1988 to 67.8% in 1995, different patterns emerge when these estimates are further examined by race and geographic region. For most of the past 20 years, proportionately more white newborns received circumcisions than did black infants. Between 1980 and 1990, white infants, on average, were 13% more likely than black infants to be circumcised. By 1995, this percentage difference declined to about 7% - 68.6% of white infants compared to 63.9% of black infants. Currently, circumcision rates for black and white infants are about the same. In 1999, the latest year these data are available, 65.5% of white newborns and 64.4% of black newborns were circumcised. These findings compliment the accumulating and extensive body of knowledge pertaining to the medical benefits and risks of circumcision.

Newborn circumcision rates, however, have continued to vary greatly by geographic region. Over the past 20 years, proportionately more babies in the Midwest received circumcisions than did newborns in any other region—76% of infants born in 1980 and 81% of those born during 1999. In the South, circumcisions also increased, from about 56% in 1980 to 64% in 1999. However, the most notable change occurred in the West where newborn circumcisions dropped from 62% in 1980 to 37% in 1999. This latest available figure for the West represents over a two-fold difference (2.2) when compared with circumcision estimates for the Midwest. This dramatic decline, in part, reflects the increased birth rate among Hispanics who have been shown in several other studies to be less likely to receive circumcisions than other white and black infants. In the Northeast, the circumcision rates in 1980 compared to 1999 were about the same at 67% and 66%, respectively.

Referring to Dr. Thomas Wiswell's data pertaining to the percentage of male infants not circumcised during the neonatal hospitalization who were circumcised during the first year of life, Dr. (b)(6) reported that during the 8-year study period, 138,597 boys were born in US Army facilities, of whom 76.9% were circumcised during the neonatal period. The neonatal circumcision frequency rate significantly increased during the period 1985 through 1992 (P < .0001). The annual rates represent boys born during those specific years who underwent the procedure. Of the 32,072 uncircumcised boys, there was a steady, significant increase in the proportion who were subsequently circumcised during the first year of life (P < .0001). The

largest increment occurred in the year following publication of the 1989 American Academy of Pediatrics (AAP) statement. Boys younger than a year of age made up approximately 20% of all children who were circumcised after the newborn period, while those 1 through 12 years of age made up the majority of the remainder.

Turning to the risks of neonatal male circumcision, Dr. (b)(6) reported that in combining two large datasets for a total of more than 230,632 circumcised male neonates (Wiswell TE *Pediatrics* 1989, Christakis DA *Pediatrics* 2000), the overall complication rate of 0.2%, including-bleeding (0.08-0.18%) and infection (0.0008-0.06%) during hospitalization. It is important to note that this is a medical record review during the hospitalization, so it does not report on subsequent complications. Another US report of 5521 circumcised male neonates (Gee WF *Pediatrics* 1976) reported an overall complication rate of 2.0%, including bleeding (1.0%) and infection (0.4%). Uncommon / rare complications include phimosis, penile adhesions, inclusion cysts, fistulas, meatitis, and injury to the glans. Referring to the recently reported African Clinical Trial data for risks of adult male circumcision, Dr. (b)(6) noted the adverse events in Kisumu there were 1.7% adverse events, including bleeding (0.4%), infection (0.4%), wound disruption (0.3%), swelling (0.1%) (Bailey RC *Lancet* 2007). In Rakai, there were 3.0% moderate adverse events and 0.2% severe adverse events: infection, hematoma, wound disruption, herpetic ulceration (Gray RH *Lancet* 2007). In Orange Farm, 3.8% of complications were pain (0.8%), swelling or hematoma (0.6%), penile damage (0.3%), infection (0.2%), delayed wound healing (0.1%) (Auvert B *PLoS Med* 2005). Important to note is that there are differences in how complications were defined and / or ascertained, for example, the inclusion of pain in the Orange Farm data may have in part attributed to the overall higher overall observed complication rate there.

Looking at data on female-male transmission and transmission of HIV in the US, Dr. (b)(6) reported on a prospective study of 758 heterosexual men (non-IDU) in New York City of whom 41% were circumcised and 14 of whom were seroconvertors. This study focused on genital ulcer disease, so there may have been some over-enrollment of uncircumcised men. The crude relative risk of HIV-1 seroconversion among the non-circumcised was 4.1 fold higher with a p-value of .04, so significantly higher in the unadjusted data. Accounting for chancroid and other STD and risk, the adjusted odds ratio is 3.5; that is, a 3.5 higher odds of HIV infection in uncircumcised men. The confidence intervals do include 1 and the p-value is .11, so that was not statistically significant. Overall, 758 heterosexual men with no history of injection drug use completed the study; HIV-1 seroconversion occurred in 10 of 344 (2.9%; 95% CI, 1.4% to 5.3%) men with a genital ulcer and in 4 of 414 (1%; CI, 0.2% to 2.5%) without a genital ulcer (relative risk, 3.0; $P = 0.05$). In a multiple logistic regression analysis, those men with chancroid and a new sexually transmitted disease during follow-up each had about three times the risk for HIV-1 seroconversion (P 0.04). (Telzak EE *Ann Intern Med* 1993)

Lee Warner conducted a cross-section review of clinic records of heterosexual, non-injecting, black male patients attending Baltimore STD clinics 1993-2000. Of these patients, 87% were circumcised. Among all visits (n=40,571), circumcision was not significantly associated with HIV prevalence [2.5% vs 3.3%, aOR = 0.88 (95% CI 0.75-1.05)]. However, among visits with known HIV exposure (n=394), circumcision was associated with reduced HIV prevalence [10.2% vs 22.0%, aOR=0.42 (95% CI 0.20-0.92)]. Similar to the earlier observational data, the control trial data, there was apparently a stronger protective effect in those at higher risk.

In recent data from Ellen Begley regarding willingness to be circumcised among MSM in the US, 415 men were interviewed at gay pride / minority gay pride events in 2006. Of those interviewed, 80% were circumcised. Among the uncircumcised, 70% were a racial / ethnic minority. Of those who were uncircumcised, 54% said they were willing to be circumcised if shown to reduce HIV risk, while 15% said that they were unsure (Begley E *14th CROI* 2007).

Pertaining to male circumcision and other outcomes, Dr. (b)(6) reported that the lack of male circumcision is also associated with: balanoposthitis; phimosis; infant urinary tract infection HPV transmission; penile cancer; chlamydial infection (although there is not consensus on this), and cervical cancer in female partners of uncircumcised men. It appears that genital ulcer disease lowers the risk of syphilis, chancroid, and HSV-2 infection (Weiss *Sex Transm Infect* 2006).

Turning to policy issues, Dr. (b)(6) focused on the AAP's Neonatal Male Circumcision Policy Statements and the evolution and impact of those. In 1971, there was what was taken as a fairly negative statement that there was "no absolute medical indication for routine circumcision." There was some indication of declining circumcision rates following that statement. In 1989, there was what was taken as a more positive statement that said, "circumcision has potential medical benefits and advantages as well as disadvantages and risks." Again, there was some evidence of male circumcision rates increasing following that. In 1999, what was interpreted as now a neutral stance that there are "potential medical benefits; however, these data are not sufficient to recommend routine neonatal circumcision." With this neutral stance, although evidence is declining, there was evidence of declining circumcision rates with that. In 2005, the 1999 neutral statement was re-affirmed following the report of the Orange Farm data.

With respect to the issues of financing and reimbursement, in a 1995 study from the US, information was reported on how neonatal male circumcision is paid for / reimbursed: private insurance (61%), Medicaid (36%), parents self-payment (3%) (Mansfield CJ *J Fam Pract* 1995). In 1997-2000 study of a Nationwide Inpatient Sample, a very large database, controlling for other demographic and socioeconomic factors, it was shown that male neonatal circumcision significantly associated with having private insurance (Nelson CP *J Urol* 2005). Since 1999, and again related to the AAP neutral stance, 16 states have eliminated Medicaid payment since it was deemed "not medically necessary" (Natl Conf State Legislatures 2006). At this point, this is being played out state by state with advocates who do not think Medicaid should pay for circumcision, and also due to tight Medicaid budgets.

Dr. (b)(6) concluded that there is compelling evidence that male circumcision reduces female-to-male HIV transmission. Different in the US context are lower HIV and higher circumcision prevalences, primarily MSM transmission, and unlikely protection for higher-risk receptive sex among MSM. It is also important to note that some racial / ethnic minorities have a higher prevalence of HIV, lower male circumcision prevalence, and relatively more reported female-male transmission; and greater potential for benefit. There is evidence that the risks of male circumcision may be lower for neonates, and also that the costs are lower. There is lower female-male HIV transmission risk among circumcised men in US. There is some demonstrable willingness to be circumcised among MSM in the US. There are other health benefits of male circumcision. Important for the discussions of this meeting are financing and policy matters.

Evidence on Male Circumcision and HIV in MSM

(b)(6) **MD**
(b)(6)
(b)(6)

Dr. (b)(6) reported on published longitudinal data pertaining to the association of lack of circumcision with HIV risk in MSM; recent unpublished data from three studies in men on prevalence of male circumcision, association of lack of circumcision and prevalence of HIV, acceptability of partner circumcision, and attitudes toward participation in a circumcision trial; and population attributable risk.

The HIVNET vaccine preparedness study (*JAIDS* 2005;39:82-89), was a longitudinal study of risk factors for HIV among HIV negative MSM, women with sexual risk, and injection drug users (IDU). Investigators did an analysis on a subgroup of MSM enrolled in six US cities (e.g., Boston, Chicago, Denver, New York, San Francisco, Seattle). Volunteers were enrolled and were followed over 18 months, with semi-annual visits. During the semi-annual visits, men were asked questions about risk behaviors. The risk behavior data collected at follow-up was collected prior to the participant recognizing whether they had acquired HIV infection in the interim, because the HIV test was done at that visit and they returned 1-2 weeks later for their test results. They were also asked a variety of demographic variables at baseline, as well as self-reported circumcision status. All men received risk reduction counseling, provision of condoms, and linkage to prevention services throughout the trial.

Before presenting data on the trial, Dr. (b)(6) reviewed the issue of attributable risk. Attributable risk is useful when considering the strength of the association between the risk variable and the outcome variable (in this case the variable is lack of circumcision and the outcome variable is acquiring HIV infection). Another important component is the prevalence of that exposure. For exposures that are common, that may drive an epidemic; whereas, risk factors that are uncommon may contribute less to the overall rate of infection in that particular population. Attributable risk combines information on increment in risk and prevalence of exposure; estimates the potential proportion of new infections hypothetically avoided by eliminating that exposure in given population; and is helpful in understanding factors that contribute most heavily and should be targeted for interventions. Although, what is known is that oftentimes, if there is an intervention with one risk factor, other risk factors may change. Therefore, there is no guarantee that in intervening with this particular risk factor there would be a magnitude of effect on the population. Nevertheless, attributable risk is beneficial in terms of prioritizing types of interventions to use in prevention strategies.

With regard to the baseline characteristics of MSM who were enrolled in the HIVNET vaccine preparedness study, Dr. (b)(6) reported that overall about 75% were white, 12% were Latino, approximately 7% were African American, and other racial / ethnic groups were approximately 5%. A third of the men were 35 years of age or less, which means that two thirds were over the age of 35. About 40% were college educated, 30% had private health insurance, and nearly 85% were circumcised. This is similar to other populations of US men. With respect to independent risk factors for HIV infection in the population, in order of population attributable risk, having a larger number of HIV negative male sex partners was a risk factor to which more than a quarter of the infections could be attributed. Part of what is going on there is that when men have multiple partners, all of whom they think are HIV negative, some of them actually are not HIV negative and may have acute infection and be more infectious. This was a factor

investigators believed was very important to try to accommodate in counseling messages. Substance abuse population attributable risk was approximately 28%, while having no private health insurance carried a population attributable risk of approximately 18%. Being the receptive partner with partners who had unknown HIV status or who were HIV positive, in combination, accounted for about 25% of the total number of infections. Being the receptive partner is the independent risk factor for HIV infection. There is no question that being the insertive partner is a risk factor, but it is not an independent risk factor in this particular analysis. Although, being the receptive partner for oral sex with ejaculation with an HIV positive partner was an independent predictor in this population. Thus, lack of circumcision was associated with a doubling of risk of HIV acquisition in this population. However, because 85% of the men were actually circumcised, it only accounted for about 10% of the new infections.

In subsequent analyses, investigators attempted to tease out the mechanism by which lack of circumcision was causing an increased risk of HIV acquisition. They were not able to sort out any interaction with any of the risk or demographic variables (e.g., unprotected insertive anal sex, self-reported STDs, the city in which they enrolled, race / ethnicity, age, substance use). They may have failed to find interactions for any of a variety of reasons, including sample size limitations because it was a relatively small population who were uncircumcised, insensitivity of the measure because these were self-reported circumcision status and STDs, and inaccurate reporting of sexual risk practices. This is not always an intentional issue, but asking people to go back six months and report all of their risk activities can sometimes be an inaccurate endeavor.

Dr. (b)(6) then reported on a cross-sectional survey conducted by colleagues from George Washington University, in which they enrolled nearly 500 MSM in New York City who were immigrants from Brazil (146), Columbia (169), or the Dominican Republic (167) (Reisen; unpublished). Based on the self-reported circumcision status of the participants, the overall circumcision rate was substantially lower (25%) that in a US-born population, as would be expected. Overall, 27% were HIV positive and 11% were of unknown HIV serostatus. A caveat with all of the unpublished data is that initially, it looked as though there was also a doubling of risk in the association of lack of circumcision with HIV serostatus in a prevalent cohort of the cross-sectional cohort. However, when investigators subsequently did some sub-group analyses, they found that there was no association of lack of circumcision and HIV infection in either the group from Columbia or the Dominican Republic, only in the Brazilian group. What that means is unclear, and investigators continue to analyze the data.

Questions that have arisen are: Will gay men want to be circumcised? How will that affect sexual desirability and social interactions? These investigators asked circumcised and uncircumcised men enrolled in the trial what their overall preference was for circumcision status in their sexual partners. The vast majority of circumcised men either wanted a circumcised partner or had no preference for whether their partner was circumcised. The majority of uncircumcised men did not care. In the group of uncircumcised men who did care, there was a slight tendency to prefer an uncircumcised partner.

Dr. (b)(6) then turned to a study of MSM sentinel surveillance in four Andean cities (J Guanira, J Sanchez; unpublished data). These investigators have undertaken an elegantly performed sentinel surveillance in these four Andean cities (e.g., three in Peru, one in Ecuador). They recruited sexually active adult MSM who reported anal sex in the last six months and who also reported some high risk sexual activity (e.g., exchanging sex for drugs, money, or services; inconsistent condoms with an HIV positive partner, STD, or that their last sexual encounter was unprotected). They excluded men who were known to be HIV positive, so these are only men

who believe they are HIV uninfected or believe that they are HIV uninfected or do not know their HIV serostatus. They conducted HIV and STD screening, collected data on risk behavior, and asked a host of questions about the participants' willingness to participate in future prevention trials (e.g., vaccines, pre-exposure prophylaxis, or circumcision).

The circumcision rate overall in all of the cities is about 4%. In each city, the rates were 5.5% in Lima, 0.7% in Arequipa, 4.9% in Guayaquil, and 2.5% in Ica. So, circumcision is a very uncommon practice. While the HIV epidemic in MSM is often thought of in terms of occurring throughout the Americas because it is the predominant mode of acquisition through most of the Americas, the circumcision rates are quite different geographically.

These investigators also looked at HIV prevalence by circumcision status. They found that in Lima and Guayaquil, there was no apparent difference between HIV prevalence in the circumcised versus the uncircumcised group, with an overall 15% HIV prevalence in the group who did not know that they were already HIV infected. If they restricted their analysis to men who stated that they were the insertive partner 50% or more of the time over the last five years, there is an association. Overall, there is a decrease in the circumcised group (7.7%) compared to the uncircumcised group (13.3%). Thus, there is some evidence of association in their cross-sectional data. They also did a multivariate analysis to look at risk factors for prevalent HIV cases in this group of men, restricting the analysis to men who reported being insertive 50% or more of the time. This was a sample of 1363 MSM. The adjusted odd ratio in this sample was 0.35 for being circumcised. Again, circumcision was protective in the range of the other observational and intervention trials. This particular analysis controlled for age, syphilis, and sexual risk at last sexual encounter.

Investigators asked if men would be willing to participate in a circumcision trial. There were some differences by city, but overall about 70% stated that they would be willing to participate in a circumcision trial (all men versus those who were predominantly insertive). Investigators also asked men what issues would affect their willingness to participate and if they were very concerned, concerned, or not at all concerned on a variety of factors. In the *very concerned group*, men were most concerned about risks associated with undergoing surgery. They were also concerned that following circumcision, their partner might insist that condoms not be used in the sexual encounter. They were somewhat less concerned about the waiting period necessary following surgery, and less concerned about being rejected by friends or family or their partners not wanting to have sex. In the *concerned group*, everything had some concern in the 20% to 30% range. There was a substantial group who were not concerned about the period of abstinence, rejection of family or friends, or that their partner might not want to have sex. For issues of trial participation there was very little concern (e.g., having to be tested for HIV frequently, having appointments over a 12-month period, having to give blood samples). Thus, most of the concerns focused on surgery and behavioral disinhibition that might occur.

Turning to a study of prevalence of male circumcision at the San Francisco City Clinic, Dr. (b)(6) reported that these investigators have looked at data from 1996-2005 in over 58,598 men who have been clients at the municipal sexually transmitted disease clinic. When participants present, they self-reported age, race / ethnicity, and sexual orientation. Of the population, about 54% are white, 19% are Latino, 16% are African American, 10% are API, 58% are heterosexual, and 36% are gay / bisexual. The age distribution includes those born in 1950s (14%), 1960s (32%), 1970s (37%), and 1980s (10%). Overall, 56% have been circumcised. In that population, over this 10-year period, there has not been an association of circumcision status with HIV serostatus.

In terms of the rate of circumcision by birth cohort and race / ethnicity, there has been an increasing rate of circumcision from the earlier part of the century, particularly in the 1930s and 1940s up through the 1960s, and then a substantial decline within each birth cohort. The rates have been highest in whites and African Americans in this particular population, with the lowest rates in Latinos and Asian / Pacific Islanders. Interesting was that in this population, MSM had a lower prevalence of circumcision than heterosexual men. However, it is difficult to tease apart all of the issues of age, race / ethnicity, and sexual orientation.

Returning to the issue of attributable risk, Dr. (b)(6) indicated that if this risk reduction was found to be replicated in other studies, and that there was a doubling of risk with lack of circumcision, what would be expected is that in populations which are highly circumcised (e.g., much of the US population not including the immigrant population) is a fairly low attributable risk. About 10% was observed in the vaccine preparedness study. However, in populations where circumcision is much less prevalent, the potential impact on the population could be very high all other things being equal.

In conclusion, Dr. (b)(6) indicated that additional data would soon be available from other large longitudinal studies (which are collected circumcision data at baseline and are collecting HIV infection risk at follow-up) to confirm the association of lack of male circumcision with HIV risk in MSM: HPTN 039 (herpes suppression); and STEP study (HIV vaccine). There are many other studies collecting information about circumcision status and risk of HIV acquisition. They certainly want to turn to those studies to understand something about whether this protective effect of circumcision holds up in these longitudinal studies. The prevalence of male circumcision is high in the US, but is decreasing. There are especially vulnerable populations where rates are substantially lower, particularly Latino populations and Asian / Pacific Islander populations in the samples presented. Thus, the population attributable risk could be substantial in populations with low rates of male circumcision, if these associations hold up once people are circumcised.

Evidence of Adverse Outcomes in Male Circumcision

(b)(6) **MD**

(b)(6)

Dr. (b)(6) indicated that he as presenting during this consultation in order to share a different perspective of male circumcision. He said he would argue that for the last 150 years, circumcision has been a procedure in search of an indication, and that infant circumcision may not be a good idea for a number of reasons (e.g., anatomy, physiology, complications / pain, ethics / consent, human rights).

With respect to the anatomy, prepuce is present in all males and females in primates and mammals. It has been present for 65 million to 100 million years. Prepuce is an integral part of the penile skin system, about 22% to 33% of the overall length of the flacid penis. There is adequate mucocutaneous tissue to cover the entire shaft of the penis during erection. It is also a pentlaminar structure—it has five layers. The outer epithelium is stratified squamous epithelium; the dermis, which is underneath that; the dartos, which is a layer that contains smooth muscles and elastic tissue that allows the skin to fit snugly around the penis itself; the lamina propria is just underneath the mucosa, with a high concentration of fine-touch neuroreceptors; and the mucosal epithelium. It is also a junctional tissue, which means that it is

the interface between skin on the outside and mucosa on the inside. It is there to keep the moisture in and contaminants out. Other examples of that are the eyelids and lips, both of which have a very high concentrations of fine-touch neuroreceptors at the junctional areas. The junctional area in the foreskin is the ridge band. By contrast, the glans is a neurologically "dumb" organ. With the highest concentrations of fine-touch neuroreceptors, the prepuce should be the most sensitive portion of the penis. The function of the foreskin is to keep glans moist and contaminants out. Rather than thinking of the foreskin's function being to protect the glans, it may be that glans exists to stimulate the foreskin.

In terms of physiology, Masters and Johnson (1966) is often quoted. This is actually only a paragraph in their book titled, *Human Sexual Response*. Methods not described in any detail at all with respect to who they tested, how they tested them, or how they arrived at the results. It was never submitted to peer-review. Subsequently, there have been some case reports and case series of men circumcised as adults, in which there are anecdotal reports of loss of sensation and / or gain of control. There have been several survey studies in the last four to five years, which surveyed adult males before and after circumcision. Subjects were men with penile problems who were undergoing circumcision for medical indications, of whom 27% to 64% reported no improvement. They also reported decreased erectile function, decreased penile sensitivity, and difficult insertion at the time of coitus. Sex was reported as being worse after surgery by 20% to 38% of these men. The shortcomings of the surveys included the small number of subjects, low response rates (44%, 46%), unvalidated survey tools (although these have been validated in the last year), short follow-up (12 weeks), subjective measures, expectation bias, and impaired health and health measures. Often, those with impaired health will often rate their health as being higher than a healthy person would rate their health if they were in that impaired state.

Intravaginal ejaculation latency was measured indirectly in a survey by O'Hara and O'Hara of women who had sexual relations with men with and without foreskins (*Br J Urol*, 1999). They found that the women experienced premature ejaculation with circumcised partners, and more vaginal comfort, sexual response, and ability to tolerate prolonged intercourse with male partners who were not circumcised. Since then, there has been a multinational study by Waldinger et al. which found no difference between countries except that the Turkish men had the shortest latency (*J Sex Med*, 2005). Richardson and Goldmeier found in Londoners that Islamic Londoners had a higher rate of premature ejaculation (*J Sex Med*, 2005). Kim and Pang found shorter latencies following adult circumcision (*BJU Int*, 2007). Perhaps the decreased contact time contributed to the effects found in the RCTs.

Three studies have used objective measures, the most recent of which was published in March 2007, although Dr. (b)(6) indicated that he had not had an opportunity to review the full study at this point. Bleustein et al (*Urology*, 2005) looked at 125 men referred to a urologist with and without erectile dysfunction, and measured three locations. They found lower thresholds in normal males, but those differences were not statistically significant when adjusted for age, diabetes mellitus, and hypertension. Sorrells et al (*BJU Int*, 2007) looked at the Semmes-Weinstein Monofilament Touch-Test Sensory Evaluators. This study included 91 circumcised men and 69 normal men (e.g., uncircumcised). Investigators did penile mapping of 17 locations in normal men and 11 locations in circumcised men. The difference is that there are locations on normal men (e.g., uncircumcised) that are not there on circumcised men. On the circumcised men, they measured the pressure threshold on the ventral and dorsal scar. The findings were that the glans of the circumcised penis had higher fine-touch pressure thresholds, the circumcision scar is the most sensitive portion of circumcised penis, and portions of penis removed by circumcision are the most sensitive parts of the penis.

The most common complications include loss of the foreskin, with the highest concentration of fine-touch nerve receptors and nearly all of the fine-touch neuroreceptors in the penis removed at the time of circumcision (100%), infection (1%-3%), bleeding (1%-9% from a trial actively looking for bleeding to determine whether Vitamin K made a difference), meatitis / meatal ulcers (20%), meatal stenosis (5%-8%), phimosis / hidden penis (1-2%), subcutaneous granuloma (5%), apnea / ALTE (4%), retained Plastibell® ring (1.6%), poor cosmetic outcome resulting in circumcision revision (1%-2%), balanitis (16%), adhesions (30%), and skin bridges (2%). Looking at these numbers, it does not make sense for the overall complication rate to be reported as 1%. Other complications that have been reported in the medical literature include: septicemia, meningitis, fascitis, Fournier's gangrene, staphylococcal scalded skin syndrome, scrotal abscess, osteomyelitis, septic hip arthritis, tetanus, herpes simplex infection, empyema, hair strangulation, total denudation of the penis, glans amputation, penile amputation, urethral fistula / iatrogenic hypospadias, loss of penile shaft skin, skin necrosis, scrotal laceration, penile edema (not at the time of the surgery, but in adolescence and early adulthood), multiple pyogenic granulomas, acute obstructive uropathy, acute urinary retention, ruptured bladder, abdominal distention, acute renal failure, urinary tract infection (primarily in Israel), penile ischemia, pneumothorax, pseudoparaphimosis (with Plastibell®), pulmonary embolism, unilateral leg cyanosis, gastric rupture, myocardial injury, erythma multiforme, urine advancing in SQ fascial plains, and death.

Also the horizon is that, especially in the US, community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) may become a major issue. It has been known for about 15 years that circumcised newborn males are more susceptible to staphylococcal skin infections. There have been three to four studies on that. CA-MRSA in newborn nurseries affect predominantly males. The only study so far to look at MRSA and the rate of risk for those circumcised and those not circumcised was recently published. This new evidence suggests that circumcised newborn males were at a 12 times greater risk for CA-MRSA infection (Nguyen et al. *Infect Control Hosp Epidemiol*, 2007).

Concerning behavioral impact, two studies from Toronto found that circumcised males cried longer and louder when vaccinated four to six months later. The researchers believed that it may have long-lasting effects on the pain responses and / or perception. This has also been observed in children who have malignancies. It is been found that if these children receive adequate anesthesia with their first procedure, pain control is easier with subsequent procedures. Cansever (1965) conducted psychological testing on five-year-old Turkish boys both before and after their had their circumcisions, and found that they had a fairly profound psychological impact. Several studies have found that there are differences for preferred sexual activities and number of partners impacted by circumcision, while other studies have found this not to be the case. Imprinting of newborns was demonstrated by Jacobsen's group in Scandinavia with respect to what happens with perinatal events and how it affects behavior as adults. That has not really been studied as it relates to circumcision. Whether circumcision results in post traumatic stress disorder has never been studied either.

Newborn circumcision is painful. Topical and local anesthetic decrease the pain, but it is still very painful. Looking at cortisol levels at baseline compared to cortisol levels with anesthesia, there is still substantial increase, which does mean it is still very stressful. Pain-relief practices are not consistent with AAP guidelines on treating pain in neonates. The guidelines state that neonates should be treated in the same way older children and adult males, which is with general anesthetic. Dr. (b)(6) said he would make the case that neonatal circumcision is less expensive because inadequate pain relief is provided.

In terms of ethics / consent, autonomy should be respected. Everyone should be able to have control over their own body, make decisions for themselves, and not have others make decisions. This is the basis for informed consent. Concerning bodily integrity, men should have a security of person that someone should not be able to remove healthy pieces of one's body without the person's permission. The AAP Committee on Bioethics recognizes that newborns cannot give consent because they do not have the capacity, so proxy consent from parents is relied upon. They also say that proxy consent should only be used in situations of clear and immediate medical necessity (e.g., disease, trauma, or deformity). Given that the healthy, normal foreskin is not diseased, traumatized, or deformed, and the AAP has never recommended circumcision, it is not medically necessary. In this case, based on AAP guidelines, proxy consent of parents is probably not applicable. For non-essential treatment that can be deferred without loss of efficacy, male circumcision should wait until the child's consent can be obtained. The physician must act in child's best interests because the child is their patient, not the parent.

Dr. (b)(6) and two of his colleagues who are attorneys composed (b)(6) regarding why they believe that parental consent is invalid. The reasons include lack of a compelling reason; newborns are a vulnerable population requiring additional protections; it fails both best-interests test and substitute-judgment test in terms of overall risks and benefits; disclosure standard is higher for procedures performed for non-medical indications; disclosure has little impact on parental decision making; and parental rights are only invoked when parents want to do something that is not in their child's best interests. Moving to human rights, newborn circumcision is medical violence inflicted for non-medical reasons. It violates the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) guidelines on involuntary restraints. Neonatal circumcision is intentional, deliberate, and causes severe pain. It is performed by physicians licensed by the state.

The last two items can lead to making a definition of newborn circumcision as a form of torture—not a strong argument, but a possible argument. The Universal Declaration of Human Rights says that "everyone has the right to life, liberty and security of the person." The Convention on the Rights of the Child says that no violence, injury, or abuse, should occur while the child is under the care of a parent or legal guardian, and that all effective and appropriate measures should be taken with a view to abolishing traditional practices prejudicial to the health of children. This is usually thought of in terms of female circumcision. What is somewhat disturbing is the number of similarities between female and male circumcision: both are performed on non-consenting minors; they are done for cultural and religious reasons; they are justified by spurious medical reasons; they are believed to enhance marriageability and sexual performance; they are believed to control sexuality; some studies have suggested that female circumcision reduces the risk of HIV; and this is also an important sources of income for practitioners.

The US has the highest rate of heterosexually transmitted HIV among developed nations and the highest rate of circumcision among Western nations, and Blacks have the highest rates of HIV and circumcision. To put this into context regarding the HIV studies in Africa, Dr. (b)(6) acknowledged that while the investigators did the best job they could, these three RCTs all suffered from selection bias, lead-time bias, expectation bias (participants and researchers), attrition bias, length bias, improper randomization, and early termination. Early termination may have amplified any lead-time bias. They all have four major ethical deficiencies: 1) It was known before the studies were initiated that even with the most extreme positive results, circumcision would be less effective and more expensive than other proven therapies (e.g.,

condoms, aggressive STD surveillance, and treatment); 2) HIV-positive participants were not informed of their status, placing their partners at risk; 3) Participants did not have truly informed consent and were coerced into participation; and 4) Equating the results with that of a "vaccine" is the worst form of hyperbole. These three RCTs do not apply to the US, given that they were performed on adults not infants, the prevalence is much higher in Africa, the HIV virus strain in Africa differs from that in the US, and sexual mixing patterns are radically different in Africa.

Bailey et al correctly stated in *Lancet* (2007) that "circumcision does not offer full protection from HIV acquisition." The closest intervention to that is a condom. There is not much on the comparison of circumcision to condoms in the literature. It has been said that it is like comparing the rhythm method to oral contraceptives, and that it is not a matter of preventing HIV but a matter of delaying (Garenne, *PLoS Med* 2006). It is also a tradeoff of opportunities. For every circumcision performed in Africa, 2500 to 3500 condoms would not be available because resources are limited. To be competitive with condoms or aggressive STD treatment, circumcision would need to cost $1.50. If condoms can provide nearly complete protection, it is not clear what additional value circumcision adds. Perhaps efforts should be focused on condom use instead because it is more cost-effective.

Dr. (b)(6) concluded that the circumcision experiment has been performed in the US and it has failed to protect against HIV infection, STDs, penile cancer, or cervical cancer. If it really worked, there would have been a marked reduction in these illnesses compared to other countries of similar socioeconomic status.

Discussion

- A participant thought that Dr. (b)(6) presentation was quite disturbing, stating that there was a lot of verbiage and not very much documentation. Dr. (b)(6) has written on this and he should explain some of data he has presented. Two aspects should be addressed: 1) his statistical methodology; and 2) his clinical observations. Dr. (b)(6) did a meta-analysis on HIV and circumcision that was published a number of years ago in which he concluded that circumcision in Africa had nothing to do with HIV. He said it increased the prevalence of HIV. One member who has done some studies in the US responded to this article in the same journal and pointed out that Dr. (b)(6) used faulty and invalid methods to arrive at erroneous conclusions. Similarly, there was a major study with HPV in the *New England Journal of Medicine* that showed that HPV was three times more common to culturate on uncircumcised than circumcised men. Dr. (b)(6) did another meta-analysis on this issue and concluded that there was no relationship between circumcision and HPV. The office of the *New England Journal of Medicine* article just finished a reply to Dr. (b)(6) in which they pointed out Dr. (b)(6) had three major statistical methodological errors in his studies, and had these errors been corrected, the true relationships of increased prevalence would be recognized. The other issue relates to his clinical observations. Dr. (b)(6) published an article a number of years ago showing the high incidence of penile abnormalities in circumcised males. The problem was he was the sole observer as to what constituted a penile abnormality. This is a subjective observation. In the other study, he recently mentioned high incidence of urethral stenosis. Again, he was the only observer of what that was. The interesting thing about Dr. (b)(6) studies is that he could not do a control group using uncircumcised males as controls because he said he did not have enough uncircumcised males in his population.

- Dr. (b)(6) responded that in the stenosis study, they did have a control group of men who were circumcised, so this is an untrue allegation. Admittedly, the study he published on the HIV meta-analysis was prior to returning to obtain his Master of Science in Biostatistics, so he did make a few mistakes. Fortunately, some biostaticians from the UK picked up on that and re-analyzed the data. They noticed the same trends that Dr. (b)(6) did, that for high risk men, circumcision makes a greater difference. In the general population group, it did not seem to make a difference. For women, circumcision status of their partners seemed to make even less of a difference. Regarding HPV, one of the major issues they ran into with the study published in the *New England Journal of Medicine* is that they had a sampling bias that did not sample the shaft of the penis in the men in that study. Subsequently, there has been a large study conducted at the University of Washington in which investigators found that a little more than half of the HPV on circumcised men is only found on the penile shaft. So, what happened is that the *New England Journal of Medicine* study would miss probably half of the circumcised men who had HPV. They tried to make an adjustment for that using meta-regression techniques. Dr. (b)(6) indicated that he had read the letter to the editor and has responded to it. Both will soon be published. For the HIV meta-analysis, Dr. (b)(6) relied on the same techniques as Tom Wiswell used in his meta-analysis of UTI and male circumcision.

- It is known that sexuality changes in the course of a person's life, so when they discuss groups such as MSM, they are placing individuals in fixed categories. People may have certain patterns with partners. With that in mind, a question was posed to Dr. (b)(6) regarding what the data could tell them about which US population might benefit most. She was also asked to discuss whether it is known what population of men in the US are exclusively insertive and what population of men are intermittently insertive.

- Dr. (b)(6) responded that this is not yet known. Presumably the mechanism by which it would act would be in men who are the insertive partner. They were not able to tease that out with their dataset. Their Peruvian partners seemed to find more of an association. There are so many other risk factors that also may be modulating the impact. In terms of being exclusively or intermittently insertive, she did not think this was known because it can change over time. It can be practice related, relationship related, and there are issues with substance use that may also influence whether people are more exclusively intsertive, receptive, or both. The majority of men in her studies have engaged in both practices, which is what makes it difficult to tease out how much of the contribution is from being the insertive partner, because the receptive partner overwhelms that association. It must be somewhat if they believe the association with circumcision.

- It was noted that the heated discussions they were observing would have to be face increasingly with the anti-circumcision movement. In most studies, complications are reported as .2% to 2%. Because their contact information was included in the notebook they received for this consultation, this participant cautioned everyone that they may see some consequences of that. Truth is and good scientific data are important to defend themselves. Adult circumcision will impact not only pediatric, but also adult circumcisions.

- Dr. (b)(6) responded that the complication rates reported depended upon the method of how it was collected. Database studies usually are about ten times lower than the ones where they actively followed circumcisions prospective for complications.

- Since this debate has arisen and the incredible findings from African have gained attention, this participant has begun to discuss it as a risk reduction approach when compared with condoms. With that in mind, referring to Dr. (b)(6) comments about various types of behaviors among gay men, this participant pointed out that there are many opportunities for promoting condom use. The participant wondered if these investigators had asked any questions about receptive oral without ejaculation, et cetera. In the whole context of risk reduction, education, and counseling, particularly with young gay men who are moving into how they are going to negotiate their lifelong sexual behavior within committed relationships, it seemed like an important area to consider.

- Dr. (b)(6) responded that what is clear with any of the biomedical prevention efforts is that they have to be paired with counseling and risk reduction because none of these are 100% protective. In their study, they asked about receptive oral sex with ejaculation because the risk is so much higher. They were surprised to find that it was an independent risk factor if a person knew their partner was positive. They did not ask about without ejaculation because the risk would have been presumably so much lower.

- With the calculation of the attributable risk, the sum was greater than 100%. Dr. (b)(6) was asked to comment on how to interpret attributable risk when the sum exceeds 100%.

- Dr. (b)(6) responded that it is not parsing out 25% of the infections were only do to X, and 15% were only due to Y. She thought where it helped the most, because these are all calculations, was with what the relative contribution is to the infections. What they could say was that the majority of infections were occurring due to having many partners, having unprotected receptive anal sex, and substance use. Lack of circumcision in her population was a relatively minor contributor to new infections.

- An inquiry was posed regarding whether there are studies in the US context of women with HIV, or women at high risk, that queried reliably the circumcision status of their primary or other partners from whom they may have been infected. Dr. (b)(6) responded that he was not aware of any.

- It was noted that problematic with respect to data on Latinos, rarely are there any analyses of acculturation and that impact on sexual practices. It is hard to evaluate. All Latin American countries have less than a 20% circumcision rate, so it is one of the most vulnerable groups. This calls into question the validity of all data for which that is not factored in.

- Dr. (b)(6) replied that those data were undergoing continued analyses by the investigators, so she did not have the details of other measures beyond what she presented. However, she acknowledged that there were valid points.

What is the Potential Cost of Male Circumcision and the Impact on HIV Transmission in the US?

(b)(6) PhD, (b)(6) MPH
(b)(6)
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) pointed out that once the findings from the African trials became available, CDC began analyses, through models, to better understand the potential costs and effects of circumcision in the prevention of HIV in the US. She stressed that while the findings she would be sharing were preliminary and unpublished, they suggest the potential costs and impact of circumcision among MSM and newborns on HIV prevention in the US. She first discussed CDC's analysis of the potential impact of circumcision on a population of MSM in a large urban area, and then described their analysis of the potential impact of circumcision on a newborn male's lifetime risk of HIV.

The key question of the analysis of MSM was: If some proportion of uncircumcised MSM chose to become circumcised, what would be the effect on the number of new HIV infections among MSM over time? What costs would be incurred or saved? This was an analysis of the effect of circumcision on a population, in contrast with the newborn analysis, which focused on the effect on an individual. They used a dynamic, compartmental model, initially developed at Imperial College in London in collaboration with CDC, to determine the costs and effectiveness of chemoprophylaxis among an urban, MSM population. The model includes a pool of 327,000 MSM as of 2005, among whom 61,600 (19%) are HIV infected. The males are 13 years old and older. There are two sexual activity levels: low-risk and high-risk. Of these men, 70% fall into the low-risk category and 30% into the high risk. The classes are distinguished by the annual number of sex partners. Those in the low-activity class have 3 partners per year on average, while those in the high activity class have 20 partners per year on average. The likelihood of infection among serodiscordant couples, based on estimates from the published literature, varies both by sexual activity class and by disease stage of the HIV infected partner. The model was validated against the number of MSM and HIV prevalence among those MSM over time in one large, urban, US city.

With respect to how CDC approached the protective effect of new adult circumcisions among MSM who choose circumcision, first they assumed that 79% of MSM are already circumcised. That assumption was based the proportion of US males ages 14 to 59, who reported being circumcised on the National Health and Nutrition Examination Survey (NHANES) conducted in 1999-2004. These data recently were published in the journal *STD*. They assumed that MSM are as likely to practice acts of insertive as receptive sex, and that circumcision protects against the insertive acts only. CDC believes that this is a conservative assumption. Some reports suggest that MSM are more likely to report performing insertive sex. They also assumed that circumcision confers 50% efficacy for insertive acts. However, each act of unprotected receptive sex has nearly 5 times the probability of HIV infection as does each act of insertive sex (e.g., .27% risk compared with .06%). Ultimately, in their calculations, circumcision only reduced the likelihood of infection from serodiscordant partners by 13.5%.

To show the effect of an increase in circumcisions, they made some base case assumptions about the percentage increase in circumcisions, participation by activity class, and behavioral disinhibition. For the base case comparison, they assumed a 15 percentage point increase in circumcision among MSM over 5 years, with about 7500 MSM choosing circumcision in each of those 5 years. However, in an alternative analysis, considering that there might be much less uptake, they looked at a 5 percentage point increase in circumcision over 5 years, or about 2500 men year. In the base case model, men of both activity classes were equally likely to choose to be circumcised. In two separate analyses, they modeled a disproportionate number of low-activity class men and a disproportionate number of high-activity class men choosing to be circumcised. That among those who chose circumcision, about 90% would come from the low activity class. Then they flipped that and assumed that perhaps they were successful in targeting high risk men, and that among those circumcised, 90% were from the high risk group. In the base case model, they modeled no behavioral disinhibition. In the alternative analysis, they assumed that all men who chose to become circumcised increased their number of sexual partners by 25%. Although circumcision in CDC's model occurs over a 5-year period, from 2006 through 2010, they estimated the number of new HIV infections that would occur for both the same 5 year period and also for a 10-year period, from 2006 through 2015.

The results are expressed as the expected number of HIV infections prevented and the proportion of HIV infections prevented, for the base case and alternative scenarios, and for 5 and 10-year periods. In the absence of circumcisions or additional interventions, another 19,000 cases of HIV would be expected in this group from 2006 to 2010 and another 36,000 cases would be expected from 2006-2015. The base case scenario indicates that 410 infections, or 2.2% of those expected, would be prevented in 5 years; 1192 (or 3.3%) of those expected in 10 years would be prevented. The first comparison scenario replaces the assumption of a 15 percentage point increase in 5 years with a more modest 5 percentage point increase. Instead of assuming that the low and high-risk MSM would be equally likely to choose circumcision, they assumed that the newly circumcised would be primarily (90%) from the low-risk group. Then they assumed that 90% would be from the high-risk group. They also examined the impact if, after circumcision, men increased their number of sex partners by 25%. In CDC's model, that not only eliminated the benefits of circumcision, but also it increased the total number of new infections.

CDC also studied the cost of adult circumcision. $5,544 was the estimate from the National Inpatient Survey. All costs reported in these analyses have been adjusted to 2006 dollars. They obtained another cost of $3,849 (approximately $4,000) from a managed care organization where adult circumcision is performed in an outpatient surgery center. For the initial analysis, they used the higher cost. Lifetime HIV treatment costs of $328,611 were assumed, which was recently reported by Bruce Schackman and others. This estimate was discounted to the time of infection. Dr. (b)(6) reported program costs, number of infections prevented, HIV treatment, and net costs for each scenario and for 5 and 10 year periods. For the base case scenario, and over a 5-year period, the program costs were $190 million, 410 infections were prevented, treatment costs were $124 million, and net costs were $66 million. Over 10 years with 1192 infections prevented, new circumcisions are saving money from HIV treatment costs averted, and the estimated savings are $144 million. Dr. (b)(6) pointed out that the program costs remain the same regardless of the analytic horizon for cases prevented, because in both scenarios, all the circumcisions are performed during the first five years. Program costs are lower when there is a 5 percentage point increase in circumcision rather than a 15 percentage point increase because many fewer men are being circumcised. For all scenarios at 10 years, circumcision appears to be cost saving or at least roughly equal to program costs. In the US, life-saving medical interventions are not typically held to the standard

of being cost-saving. Based on life-saving interventions that are recommended in the US, it is typically expected that up to $50,000 or even $100,000 will be paid for a quality-adjusted life year saved.

With regard to the cost per HIV infection prevented and the cost per quality-adjusted life years saved for scenarios where the net costs were not negative, or in other words where circumcision was not cost saving, CDC assumed 24 years of survival after HIV infection, and that each infection prevented results in 6.3 quality-adjusted life-years saved. For the base case/ 5 year scenario, the net cost is $66 million dollars, with 410 infections prevented. That equals $161 million per infection prevented, or $26,000 per quality-adjusted life year saved. The 5 percentage point increase / 5 year net cost of $34 million equals $333,000 per infection prevented and $53,000 per quality-adjusted life year saved. The low-risk / 5 year net cost of $122 million equals $539,000 per infection prevented, or $87,000 per quality adjusted life year saved. For the low-risk / 10 year scenario the net cost is $1 million, or $1,500 per infection prevented or $235 per quality adjusted life year saved. Assuming slightly lower program costs of $4,000 per circumcision, the program costs for a 15 percentage point increase in circumcision decline from $190 million to $137 million, while those for a 5 percentage point increase in circumcision decline from $66 million to $48 million. One additional scenario, low-risk / 10-years, becomes cost saving all for the scenarios where there are net costs, the cost per quality-adjusted life years varies between $5,000 and $48,000.

Based on the assumptions included in this model, CDC's analyses suggest that circumcision among MSM will have a relatively small impact on the number of new infections over time, unless they are very good at getting lots of high-risk MSM to participate, but that it could be another important addition to the other interventions available. The results suggest that circumcision would be cost-effective over 5 years at an efficacy of about 14%, due to the rather low costs of circumcision and high costs of treating a case of HIV. The results also suggest that circumcision may be cost saving over a period of 10 years, which may help to build a case for the public financing of circumcision. This strategy would generate best results when performed among highly active MSM. A fairly small amount of behavioral disinhibition would override the benefits of circumcision, but this is probably the case with many interventions.

Dr. (b)(6) then reported on the preliminary analysis for newborns with respect to the costs and effects of circumcision for HIV prevention in the United States. The research question was: By how much can circumcision reduce lifetime risk for HIV and the expected lifetime cost of HIV? (b)(6) and (b)(6) in CDC's surveillance branch, have recently calculated the lifetime risk of HIV among all males in the US and by race / ethnicity. These data come from 33 HIV name reporting states and are based on the age of diagnosis for men diagnosed in 2003 and 2004. There is a wide disparity by race / ethnicity. There are also some large disparities noted in the proportion of men circumcised in the US, also broken down by race / ethnicity, from recent NHANES data. They also looked at HIV mode of transmission for men diagnosed in 2003 and 2004. The predominant mode of transmission remains sex with men for all racial and ethnic groups, but there are still large differences by group.

For this analysis, CDC initially assumed that the lifetime risk of heterosexually-acquired HIV for circumcised males would be half that of uncircumcised males. In a separate analysis, they additionally assumed that the lifetime risk of MSM-acquired HIV for circumcised males would be 86.5% that of uncircumcised males. Based on the prevalence of circumcision among each racial / ethnics group, from the NHANES data, they calculated lifetime risk for HRH-HIV and MSM-HIV for circumcised versus uncircumcised men. Then they summed the total lifetime risk of HIV from HRH, MSM, IDU, and other for circumcised versus uncircumcised men. Assuming

that circumcision provides 50% efficacy for HRH-related HIV, circumcision may reduce lifetime risk by 9% to 13%, depending on race / ethnicity. Assuming that circumcision provides 50% efficacy for HRH-related HIV and 13.5% for MSM-related HIV, circumcision appears to reduce lifetime risk by about 20% across racial and ethnic groups.

They also looked at the costs of neonatal circumcision. According to the National Inpatient Survey, adjusted to 2006 dollars, the cost appears to be about $678. They used the same lifetime HIV treatment cost as they did in the MSM analysis. The average age of HIV infection was assumed to be 36 years. Based on that, they discounted lifetime HIV treatment costs to the time of birth in order to compare them to circumcision costs. Lifetime HIV treatment costs at the time of birth were $113,381. In terms of total lifetime risk of HIV among uncircumcised and circumcised men, by race / ethnicity, when circumcision confers 50% efficacy for HRH-HIV, and multiplies it by the lifetime cost of treating HIV, this generates the expected lifetime cost of HIV by race / ethnicity. The difference in expected lifetime treatment cost between uncircumcised and circumcised males ranges from $102 to $1,134, and that can be compare to the $678 cost of circumcision.

Dr. (b)(6) concluded that neonatal circumcision appears to decrease lifetime HIV risk by about 10% if the efficacy for HRH-related transmission is 50%, and by about 19% if efficacy for MSM-related HIV is 13.5%. Reductions in expected lifetime cost of HIV may partially or entirely offset circumcision costs.

The results from these preliminary analyses suggest that circumcision could be beneficial in the US and it could be cost-effective, and even cost saving. However, some very important questions remain. A better understanding is needed of the efficacy of circumcision among MSM, which MSM would be likely to choose circumcision, and how their behavior might change after choosing circumcision. It would also be helpful to understand more about current circumcision prevalence among men who are already infected with HIV. The assumption is that the efficacy seen in the African trials will endure. In CDC's models, it endures for 10 years for MSM and over a lifetime for newborns. This is a key assumption that would be important to try to validate.

Cost of Circumcision in US Newborns and Adults

(b)(6) MD
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Dr. (b)(6) reported that in their analysis, HIV was not the most important determinant of cost. The most important determinant of cost savings was the cost of newborn circumcision versus the cost of adult circumcision and the fact that about 7% to 10% of uncircumcised infants will be circumcised later in life for other medical reasons, mainly recurrent infections and mechanical problems with foreskin retraction. He pointed out that HIV was not the main point of his presentation. Instead, it pertained to the other preventive health benefits of circumcision. He reminded participants that they heard objections earlier in the day to the use of the term "vaccine." Having practiced pediatrics for over 50 years, using this term did not bother him. He was using it in the sense that it is a preventive health measure that has significant protective benefits to the child's health.

With respect to circumcision, Dr. (b)(6) said that there are 11 evidenced-based benefits of circumcision that have been proven in multiple studies over the past 20 to 30 years, including improved hygiene and the prevention of penile cancer, balanoposthitis, phimosis / paraphimosis, UTI, HPV infections, HIV infections, cervical cancer, chlamydia infection, penile dermatoses, and valid urine specimen. To get a valid urine specimen on a baby with a 104 degree fever, a tube must be inserted either through the bladder or the urethra. In the case of a circumcised infant, there is good data that the urine is sterile. Avoiding catheterization in a baby with a high fever is important. Prevention of HPV may be the greatest cost benefit in the US rather than HIV. Recent multi-national studies published in the *American Journal of Epidemiology* showed a two-fold increase in chlamydia infection in uncircumcised males. In newborn infants in the US, where the quality of circumcision is good, the risk of surgical complications rare (0.2 - 0.6%) and is usually minor. The figures of 1% to 9% are in undeveloped countries.

With respect to the history of circumcision, Dr. (b)(6) referenced to passages from the Bible. The Old Testament Genesis, Chapter 17, states, "God said to Abraham, the covenant between me and you and your offspring to follow which you shall keep: throughout the generations every male among you shall be circumcised at the age of eight days." The New Testament, Luke, Chapter 2, Verse 21 states, "And when eight days were completed for the circumcision of the child, his name was called Jesus, the name given by the angel before he was conceived in the womb." The Muslims circumcise as well. However, the great majority of circumcisions in the US are not for religious purposes. Jewish circumcisions make up 2% to 3% of the circumcisions in the US, with 95% of the circumcised males in the US being neither Jewish nor Muslim.

Dr. (b)(6) reported on the origins of American circumcision from 1850-1915, indicating that there were some extremely observant clinicians around the turn of the century or before, when there was an emphasis on cleanliness. Circumcision was a middle to upper middle class procedure because "cleanliness is next to Godliness" and also these clinicians realized that penile cancer, cervical cancer, syphilis, and local infections were more rare with circumcision. Open minded Americans / immigrants were freed from rigid old world social / class order and were interested in a new life and new ways. Dr. Peter Remondino (1846-1926), a prominent San Diego physician, did a lot of the pioneering studies. He wrote a book titled, *History of Circumcision...*(1891). He already knew much of what is being discussed currently (e.g., HPV, penile cancer, et cetera). In 1891, Dr. Remondino wrote, "Repeat attacks of herpes preputialis [HPV] and some consequent point of induration are looked upon as starting points for the cancerous affection of the prepuce."

Cancer of the penis studies in the US began at Memorial Sloan Kettering Institute in New York City (Dean, A.J., *J UROL* 1935;35:252). Dr. Dean did a wonderful study in which he had 120 cases of penile cancer. The average age was 50 years (24-81 years), 22% were less than 40 years old. None had newborn circumcision. This was in New York City where about a third of their population of cancer cases were Jewish. He noticed that and stressed that none of his 120 subjects were Jews, although a "large proportion of the patients at Memorial Hospital are Jews and Jews have no racial immunity to epidermoid cancers in other parts of the body."

In 1973, Dagher said that "Despite overwhelming evidence from urological surgeons that neoplasm of the penis is a lethal disease that can be prevented by removal of the foreskin, some physicians continue to argue against routine neonatal circumcision in a highly emotional and aggressive fashion" (Dagher et al, *J. UROL* 1973;110:79). He had 156 cases, of whom 1/3 died, and none of whom were circumcised.

Field Marshall Erwin Rommell, known as the "The Desert Fox," during World War II invaded North Africa before going to Europe. North Africa is full of deserts and the soldiers could not wash. Someone once wrote an article called "Circumcision in the Sand" with the idea being that in desert areas, it is a major problem for sand to get under the foreskin. The military took notice of this because these men could not do anything other than stay in sick bay soaking their penises in gentian violet solution. In a book written about surgery in World War II, in the urology section, it is stated that, "Hospital admissions for paraphimosis, phimosis, balanitis, and condyloma acuminata during 1942-1945 totaled 146,793. Had these patients been circumcised before induction, this total would probably have been close to zero" (Medical Department, U.S. Army, Surgery in WW II: Patton, *JF – Urology.* 1987. p145). There have been 12 very good studies (1987-2007) showing that uncircumcised males are at ten times more likely to get a severe UTI the first year of life. Electron microscopic studies have been conducted which show that bateria, *e. coli*, with tentacles on it stick to the foreskin and climb up into the kidney. With regard to the HIV / AIDS epidemic in Africa, there have been 20 million deaths and 40 million have been affected.

There are over 40 HIV acquisition studies (1987 - 2007) in addition to the three RCTs, which show that uncircumcised males are at two to four times the risk of contracting HIV. In a multi-national study, investigators cultured uncircumcised males for HPV and found it three times more likely that an uncircumcised male is going to carrying HPV on his penis. HVP is responsible for cervical and penile cancers. There is a high incidences of penile cancer in South America where they do not circumcise. Diego Rivera (1886-1957) was a Muralist / Communist who was quite sexually promiscuous. According to some reports, he had a tight foreskin as well. He went to Russia, where he was irradiated and had a really bad radiation. He died a miserable death from penile cancer at age 71. There are 8 studies (1932 - 2000) showing that uncircumcised males are at 20 times greater risk of penile cancer. He and his colleagues conducted a study with 91 invasive penile cancers, 89 of whom were uncircumcised. The two who were circumcised had much milder disease. Twenty times greater risk is probably being very conservative. It is probably closer to 100 times greater risk. Eva Peron (1919-1952) died at age 33 from cervical cancer. Women are at high risk to get cervical cancer if they begin sexual activity at an early age and have multiple uncircumcised partners. She was a street waif who was sexually active at a very young age. She had multiple partners, working her way up the military right up to Juan Perone. That is a typically history of someone who dies young of cervical cancer. HPV did it to her.

A multi-center (5) case–control study found that the female partners of uncircumcised males are more than twice as likely to get cervical cancer. The same multinational study showed that a woman was twice as likely to get chlamydia infections if their male partners were uncircumcised (Castellague *Am J Epidemiol* 2005). HPV and chlamydia are probably the most important sexually transmitted diseases in the US. There are 3 million cases per year of HPV. From the standpoint of America, these disease are much more important than HIV.

Dr. (b)(6) pointed out that King Louis XVI (1754-1793) married Marie Antoinette when she was 15. He had terrible phimosis. He could not have sex. She wrote to her mother that he could not have sex, but it was too painful because he could not retract his foreskin. At the age of 22, he was circumcised. After that they sex and children, which was good. He lost his foreskin, but a few years later he lost a more important part of his anatomy when he was beheaded at age 39. Local problems include balanoposthitis, phimoses / paraphimosis, genital hygiene, and penile dermatoses (2000). Uncircumcised men are at three times the risk of having one or more of these.

With respect to sex, over the past five years, five very good studies were conducted that have shown no significant difference in sexual function changes after adult circumcision. This makes sense. The sexual act is very complex. It begins in the brain, goes down the spinal cord, there are hormones, et cetera. Viagra® works on a very complex enzymatic system. Dr. (b)(6) said he did not believe that a small piece of foreskin was what made someone a good performer, when sex is such a complex act. There is no evidence of that.

Dr. (b)(6) (b)(6) (b)(6) (b)(6) has pretty good cost data. It probably now costs twice as much, but at the time of the study, the circumcision cost assumptions were as follows:

Circumcision Cost Assumptions		Circumcision Net Lifetime Cost Savings	
Newborn circumcision	$ 200	Initial Cost	
Circumcision Complications	$ 150	Neonatal Circumcision	$ 200.00
Outpatient UTI	$ 150	Circumcision Complications	$ .75
Inpatient UTI	$ 2,200		
Balanoposthitis/phimosis	$ 150	Treatment Cost Savings	
Postneonatal circumcision	$ 2,000	Outpatient UTI	_ 15.92
HIV	$ 45,198	Balano/phimosis	_ .66
Penile cancer	$ 7,500	Postneonatal circumcision	_ 108.00
		HIV	_ 57.39
		Penile cancer	_ 1.35
		Total cost savings	_ 182.57
		Total Lifetime Cost	**$17.43**

At the time of this study, HPV and chlamydia were not considered because the investigators did not know about them at the time. If these were factored in, the costs would be much higher.

A cost effectiveness study of circumcision for HIV in Africa was conducted by Kahn in 2007. His subjects were 1000 men from Orange Farm, South Africa. He concluded that circumcision could prevent 300 cases of HIV over 20 years and would save $2.4 million. Throughout sub-Saharan Africa, circumcision would save over $5 billion over 10 years (Kahn J, et al PLoS Med 2007;3:e517).

Dr. (b)(6) concluded that the best time to perform a circumcision is in the newborn period, within the first month of life. Regardless of what people say about newborns being so fragile, Dr. (b)(6) thinks they are very tough and that a human is never going to be tougher than during the newborn period. The newborn period is a window of opportunity, given that newborns are adaptable and programmed for stress; they are resilient-intense, with rapid reaction quick recovery; and they have high levels of "stress hormones" (e.g., epinephrine / norepinephrine, cortisol, thyroxin, and testosterone at levels as high as a young man). So, they are very well protected. It is easy to do a circumcision in a newborn. Adept pediatricians can do a newborn circumcision in under two minutes. Local anesthesia should always be used in a newborn, never general anesthesia. Any deaths associated with circumcision are likely to have been the result of general anesthesia. Post newborn circumcision is more complicated than in newborns: sutures are required; there are fewer experienced operators; the practitioner is more likely to use general anesthesia; healing is slower; and it is ten times more expensive. As

parents are hearing about HIV and circumcision, they are beginning to present with 3 and 4 years old boys to have them circumcised. Dr. (b)(6) stressed that this is a "different ballgame." The risks are greater, the cost-benefit ratio changes, et cetera. Therefore, it should be done in the newborn period.

Discussion:

- A participant was troubled by one assumption Dr. (b)(6) made in her cost calculation regarding disinhibition. There are data showing that people who might choose to get an adult circumcision would want to sustain the benefit and might be more likely to use condoms for insertive anal intercourse. It would seem that the inverse assumption could just as easily be made as the assumption of disinhibition. It was not clear how she arrived at the 25% and why she did not make the inverse assumption. It seems that a person that concerned with their sexual safety, who would have this operation, would indeed take extra measures when having insertive anal sex.

- Dr. (b)(6) responded that they were simply trying to be very conservative. It seemed like for any intervention they tried to model, that question about behavioral disinhibition arises. They tried to explicitly incorporate it into the model. They were really aiming at a threshold analysis of how much disinhibition it would it take before the benefits were eliminated. She said the point was well taken and it would certainly be wonderful if the reverse turned out to be true.

- Dr. (b)(6) was asked whether she could provide a side-by-side comparison of the cost effectiveness of needle exchange in preventing transmissions by injection drug use. This seems somewhat marginal in its effects compared to something like needle exchange that the US has not even begun to tackle. This participant stressed that they must not lose focus on the larger picture and the interventions they could be using, but are not. That would mean a lot in terms of harm reduction. This individual was also struck by Dr. (b)(6) comment about Uganda because that was an anomaly. Her theory was that the anomaly was based on the fact that there was an intensive prevention campaign going on, which was so much less invasive and yet apparently very effective. In terms of the sense of controversy, all of the issues (e.g., religious, cultural, et cetera) must be taken into account in that there are other ways to achieve what they are trying to get at.

- Dr. (b)(6) replied that the question of comparing circumcision to other cost effective interventions was a good one. CDC has not done that yet, except in a very limited case when they tried to compare it to chemoprophylaxis in this same population. The results were roughly the same. It does appear that on a population analysis, using conservative assumptions, the effect is not so large. However, it seems promising if used along with all of the other interventions available. It seems like it potentially could be quite cost effective, even though there is not a large impact, given that the cost of circumcision is so relatively inexpensive. Some of it will depend on the assumptions that are made about the long-term effeminacy. If circumcision does turn out to be efficacious over a person's lifetime, that is very good news.

- Regarding the analyses on MSM, there was an assumption that the effect was just carried through the insertive partner. This participant's sense of the state of the art was that it is not actually known whether this is a valid assumption. While clearly CDC wanted to be conservative, this participant wondered if any additional modeling was done that might have

included an effect mediated both through the receptive and insertive partners and if so, what that showed.

- Dr. (b)(6) responded that they did play with efficacy values a little. They felt that perhaps the 14% was fairly conservative. Based on some data they heard about from some observational studies, they considered whether the efficacy might not be higher and might be equal to that which was seen in the African trials, more like 50%. This model is still under development. When CDC started doing their dynamic model and incorporating a 50% efficacy, considering the levels of circumcision that the US has, the model starts early on in the mid 1970s. They were not generating an epidemic. With that level and an efficacy and amount of circumcision in the US, they were not getting very good results. They do still have work to do.

- A participant suggested that in working with some of the investigators from the three trials, looking at the partner data, CDC might consider plugging in a scenario in which there is efficacy associated with being a receptive partner as well as an insertive partner. It seemed that with what CDC did, efficacy was mediated only through an insertive partner. The jury is still out on that, particularly with respect to MSM. Since most MSM probably move back and forth in terms of roles, it might be useful. Regarding newborns, this participant wondered whether anybody had modeled what the costs might be if the current trends of declining male circumcision in newborns continue and policies do not change, where they might be in 10 years.

- Dr. (b)(6) responded that this is a good point. They have not done this yet, but they could model that.

- Dr. (b)(6) said he thought a lot of the business about circumcision decline was not true. There was a study recently published by Nelson in the *Journal of Urology* that shows a steady, slow increase. There was a 12% increase from 1989 to 1999 in newborn circumcision. The major differences have been in immigrants. Hispanics in California do not circumcise. More than half of the births in California currently are Hispanic. If their rate is zero and everybody else was 100%, there would still only be a 50% rate in California. The major change in various parts of the country is because of the Hispanic population. Circumcision is still increasing in the Midwest where the rate is probably 90%. There are various factors, one of which is religion. Christian Fundamentalists almost all circumcise, so in the "Red States" there is a very high rate. Just the opposite will be found in areas where the anti-circumcision groups are very active. In these areas, there are secular religious people who are not circumcising. In the US today, there is more chance that a Christian Fundamentalist in Kansas will be circumcised than a Jew in Berkeley.

- It was noted that no study has shown male circumcision has a protective effect against Chlamydia. The study Dr. (b)(6) cited is about the partners of uncircumcised men, which shows that it is the partners of uncircumcised men who have higher risk of Chlamydia than the men themselves. The impact models that have been done around African populations try to build in some secondary effect on partners, so as prevalence of circumcision goes up in the population of men, then the prevalence in the men goes down, which results in a secondary drop in prevalence in women. With that in mind, and inquiry was posed regarding whether there was anything that could work in that way with MSM in the US.

- Dr. (b)(6) responded that CDC did model that, although she did not show those results. Direct and indirect preventions were modeled and the number of indirect preventions continues increase over time, so that looks promising. The infections prevented in the first model represented all infections, including among partners.

- With respect to receptive and insertive intercourse among MSM, a participant stressed that it is extremely important not to assume that these would be equal. There is considerable evidence which shows that men do vary in terms of their preference for the insertive and receptive rolls. This is particularly important in studying African American and Hispanic men to understand that there are very different prevalences of insertive and receptive behavior. This is even more important with regard to bisexually active men who might engage in certain same sex acts. It would be useful to make a different assumption of 25%, versus 75%, or some variability in those proportions, to determine how the estimates differ. Assuming equivalence is a major problem, particularly with high risk men of certain ethnic groups for whom the model will be used.

- Dr. (b)(6) replied that she appreciated the comment on the assumption that half of men are equally likely to engage in both sorts of acts. CDC will think about how to incorporate this. She requested that the participant provide her with further information about the data on this.

- While Dr. (b)(6) enthusiasm about circumcision was appreciated, especially in terms of the potential effects for Chlamydia, one problem is that AAP will make up its own mind. They have changed positions about circumcision at least twice in the last 25 years. Part of the dilemma is receiving mixed messages from the AAP.

- Dr. (b)(6) responded that he was the chairman on the (b)(6) (b)(6) In the period between 1989 and 1999, all media questions came to him. He has written (b)(6) (b)(6). The main problem was that the AAP made a terrible statement in 1971 by saying there are no valid indications for circumcision. They had no reason to do this and they spent 35 years covering up that statement. It is very difficult to get a positive statement out of the AAP. Dr. (b)(6) stressed that this was his personal opinion.

- Surgical fees for the adult male represent a fairly small portion of the costs that were built into the CDC's model. In adult males in Chicago, the average cost is $205. That would make approximately 95% the other types of fees. With that in mind, an inquiry was posed regarding whether CDC built institutional localities' fees into the model (e.g., a service center versus an inpatient OR versus a clinic) and different types of anesthesia fees.

- Dr. (b)(6) replied that CDC struggled to obtain data on adult male circumcision costs. Even in the National Inpatient Survey, this information was very limited. She checked with a local urology group with a large practice in Atlanta who told her that their surgeon's fee is $550 and the outpatient surgery center fee is $900. It may well be that there is some variation. It may also be that they are not considering their costs fully.

- It was noted that what a physician bills and receives are two different things. The Medicare reimbursement fee, which is what one receives, is different from what one charges. Private insurers make up to about 135% percent of that. That still is a fairly small proportion of the $4,000 to $5,500 billed. In a hospital setting, the hospital fees combined with general anesthesia fees may very well be $4,000. In a future in which this is being considered as a

potential avenue for risk reduction, there may be other incentivization options. CDC should take these issues into consideration in the model as they move forward.

- Dr. (b)(6) pointed out that (b)(6) has a very sophisticated cost accounting system, so they capture everything. A lot of times people ask what something costs, but (b)(6) will not give all the costs. They may give the surgeon's fee and someone else's fee, but this does not include overhead because it is not captured (e.g., anesthesia standing by, operating room, et cetera). (b)(6) came up with a figure of $3,700.

- Dr. (b)(6) pointed out that the way the model is constructed, it does not differentiate between a receptive act and an insertive act. It merely applies the 13.5% efficacy to the situation in the populations. It is a very good question, but it is complex to include in the model. In the African situation, with half of the population insertive and half receptive, if there is something very effective to minimize the risk of the insertive population, in one generation of transmission, this can have a very big effect. If the population is doing both, and with a relative minority of the risk through insertive, even by greatly reducing the insertive risks, that same kind of indirect effect is not realized.

- In the modeling assumption, the 50 / 50 was striking; whereas, in all insertive / receptive sexual acts, there is 50% insertion and 50% reception. In terms of the people who differentially engage in one or the other, this is not necessarily the same that holds true. This can make a lot of difference because it depends on who does what with whom as with everything about HIV transmission. While the modeling presentation was enjoyable, as with any modeling discussion, the "Devil's in the details." It all depends on inputs and the sensitivity of those inputs at the place where everyone is least sure of them to change in sliding the scale one way or another. Also striking that was not in the model was the age and cohort effects of this rapid change, which with all due respect, is in fact observably changing in newborns. There are some very good reasons. There was a structural intervention against newborn circumcision in the form of cutting out Medicaid reimbursement for it in 16 states, including California. That is just one example. Also, the prevalence, both of infection and of circumcision, differ substantially by race / ethnicity. As a consultant trying to apply and use modeling data, more is needed. Granted, only so much can be done in one presentation, but other aspects are important to know such as how sensitive it is to variation to input, particularly on the inputs which are known to vary more than the assumptions, and on others which are uncertain.

- With respect to the 16 states that do not pay for circumcision, Dr. (b)(6) said that there again are the activist groups that have lobbied against circumcision, who get a receptive audience because the focus on the money that can be saved. Now that there are known to be multiple benefits, this sets up two qualities of care. That means that a poor baby born in California or any of the other 15 states where Medicaid will not pay, will not be circumcised even if his parents want it because they cannot afford it. He has some anecdotal material from four areas. In the US, it is socially advantageous to be circumcised. If a male is uncircumcised in the US, it generally means he is poor or foreigner. In Europe it is the opposite, where it is socially advantageous to be uncircumcised, because being circumcised means that a male is a Muslim or a Jew. The anecdotal cases indicated that because California will not pay, poor people scrounge to raise money to have their children circumcised so that nobody makes fun of them or knows they are poor or foreign. That is a terrible thing that has occurred with the 16 states.

- An inquiry was posed regarding why CDC cut off the MSM cost effectiveness at 10 years. Others have done the same thing, but in retrospect this was a mistake. In the observational data, looking at the relative risk of HIV by age, there are protective effects going out to highest age they could look at, which was 50, associated with pre-pubertal circumcisions. It seems that it is likely to provide lifelong protective effect. There is no particular reason why the protective effect should wane with age.

- Dr. (b)(6) replied that they could model it out further. (b)(6) who worked most closely with the dynamic model, felt that there were too many assumptions, that too many things change about age and sexual behaviors over time, and that they were really on "thin ice" beyond 10 years. However, she was sure that using the assumptions they did in the model, the effects would continue further out and that there would be a lot more indirect benefits.

Risk Communication and Disinhibition

(b)(6) **Ph.D.**
(b)(6)
National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention
Coordinating Center for Infections Diseases
Centers for Disease Control and Prevention

Dr. (b)(6) reported on HIV Risk Behavior Disinhibition and Risk Communication based on observations from a Phase III HIV vaccine efficacy trial. He pointed out that it is unclear how these data may inform circumcision programs and trials targeting MSM in the US. However, given that the data upon which he was focusing for this presentation were collected from MSM in the US, who may in many ways be similar to MSM who might participate in circumcision programs and trials, it was likely that these data would have some value.

With regard to the background, Dr. (b)(6) indicated that at the time CDC was preparing for the VaxGen trial in 1998, there were ethical concerns expressed about the possible increase in HIV risk behavior that may be related to undue optimism among participants that trial participation may confer some level of protection against HIV infection. These concerns stemmed from the Hep-B trial experience in 1980 where, subsequent to the final immunization, placebo recipients were more likely to become infected, suggesting that placebo recipients may have assumed they were protected and thus increased their risk behavior. In the context of HIV vaccine trials, there have been reports from Phase I and II trials that participants in these trials also increased their risk behaviors. Seroincidence studies in preparation for vaccine trials have found that the motivations among MSM for participating in trials were a huge proportion endorsed protection motivation from HIV as a reason for participating in trials, despite the fact they may have been randomized through a placebo or may have received a product that is not efficacious. Of course, increased risk behavior in the context of the trial was of concern because it would lead to increased infection. There was also a concern among trial sponsors that such infections would constitute a research-related injury and justify sponsor provision of treatment. These concerns are apparent today with regard to biomedical interventions as illustrated by the recent article titled, "Risk Compensation: The Achilles Heel of Innovations in HIV Prevention" (Cassel et al, 2006).

Different terms have been used to label the phenomena of increased risk behavior as a result of trial participation including (e.g., risk behavior disinhibition, behavioral enhancement, and risk compensation). It is likely that more attention is needed here for a variety of reasons. For the purposes of this presentation, Dr. (b)(6) indicated that he would use the term "behavioral disinhibition." Generally, behavioral disinhibition is thought of as an "increase in risk behavior associated with a preventive / therapeutic intervention, with potential mediators being perceived efficacy, decreased perception of risk, and perceived assignment status." Dr. (b)(6) revised the standard definition to "an increase in risk behavior or an attenuated decrease in risk behavior attributable to a preventive or therapeutic intervention." Graphically, these definitions can be easily conceptualized by first considering a trend line that represents what might be expected in an observational cohort of MSM followed over 36 months. Initially, there is some decrease in risk that then creeps up but remains below baseline during the follow-up period. With the standard definition, risk behavior initially decreases from baseline and then gradually increases over time (perhaps because of decreasing perception of HIV risk) and eventually surpasses that reported at baseline. The revised definition includes this obvious increase as a component; however, it also includes an additional possibility—the attenuated downward slope relative to the decrease that might be expect to be observed over time.

There are many constraints to evaluating potential behavioral disinhibition within the context of an efficacy trial. Efficacy trials are generally randomized, double blinded clinical trials, the simplest having two arms: 1) an experimental arm where participants receive a formulation; and 2) a contrast arm where participants receive a placebo or an earlier generation product. The endpoint efficacy is calculated by comparing the incidence between groups. The optimal design for evaluation behavioral disinhibition within the context of a clinical trial would be to include a third arm who, in the case of HIV vaccine, would not receive an injection. While behavioral disinhibition is often of great concern with regard to HIV prevention trials, cost and logistical issues preclude including such a control arm in an RCT. Because behavior is not the primary endpoint of interest and efficacy is, it is unlikely anybody will be willing to fund such a trial. Alternatively, disinhibition can be addressed in trials by including variables that may be theoretically related to disinhibition, and by conducting quasi-experimental research that includes contrast cohorts, although these present many logistical challenges and there are many threats to the internal validity of such a design.

The Phase III HIV Vaccine Efficacy Trial, VaxGen Vax004 Trial design was a randomized, double blind placebo-controlled trial, with two thirds of the participants randomized to vaccine and one third to placebo. There were 5108 participants, 308 of whom were women. Participants were predominately MSM, although high-risk women were also enrolled. There were 61 sites in the US, Canada, and the Netherlands. The trial commenced in June 1998, was a 3-year trial, and was completed in October 2002. The vaccine was (rgp120): B(MN) / B(GNE8). The product was administered in 7 doses over 30 months at 0, 1, 6, 12, 18, 24, 30 months. HIV counseling and testing were provided every 6 months and were based on the CDC client-centered model. Overall, no efficacy was demonstrated in MSM. However, a lot has been learned about conducting trials in the US among MSM, and a lot about prevention using this rich data.

Men who presented to the trial were asked why they were interested and motivated to participate. Most men endorsed altruistic motivations for participation: Help find an HIV vaccine (99%), help the community (98%), obtain current information on HIV(75%), reduce risk behavior (56%), get protection from HIV (46%), receive free testing (34%), financial reimbursement (14%), and receive medical care (9%). Over half joined the trial to reduce their risk of infection. Of concern with regard to the potential for disinhibition and trial-related harm associated with

HIV infection, was that almost half reported that they were joining the trial to gain some protection from HIV, despite being informed that some participants would be randomized to placebo and that the vaccine may not be efficacious.

With respect to the extensive risk behavior analyses, which were published in 2005, the dependent variables included: MSM having unprotected anal sex, and unprotected anal sex with HIV positive partners. The independent variables included: Time (study visit), HIV status / retention (uninfected, infected, LTF), demographics, perceived vaccine efficacy and treatment assignment, and protection motivation. Generalized estimating equations were used to analyze the risk behavior data over time. Dr. (b)(6) summarized the omnibus statistics for the effects related to unprotected anal sex and unprotected anal sex with HIV positive partners. For unprotected anal sex, there were effects related to visit, race, age, and perceived assignment. Furthermore, there were age by visit, and race by visit interaction effects. For unprotected anal sex with HIV positive partners, there were effects related to visit, age, and perceived assignment. There was no behavioral effect related to perceived efficacy of the vaccine.

In terms of the proportion of MSM who reported engaging in unprotected anal sex over time by the HIV status / retention variable, men who became infected were more likely to report engaging in unprotected anal sex than were those who remained uninfected and those who were not retained in the trial. Each group reported a decrease in unprotected anal sex from baseline to 6 months. Men who became infected returned to baseline levels at 12 months and did not significantly differ from baseline for the remainder of the trial. Infected men were followed under an infected participant protocol and dropped out of this particular protocol. Those who remained uninfected and those who were lost to follow-up remained below baseline throughout the trial or until being lost to follow-up.

Pertaining to the main effect on unprotected anal sex by consistency of perceived assignment (vaccine versus placebo), there are several points of interest. Unprotected anal sex for men perceiving assignment to vaccine was higher at baseline. This suggests that this is not a trial-related effect on HIV risk behavior because the data reported at baseline covered a retrospective period before participants were enrolled. It may indicate something unique about those men perceiving assignment to vaccine rather than a trial-related effect. There are diverging slopes for men perceiving assignment to vaccine and placebo at the 12-month visit. This pattern might be anticipated when considering the Hep-B vaccine trial experience (e.g., one might expect men perceiving assignment to vaccine to increase their risk behavior, and those perceiving assignment to placebo to decrease their risk behavior). However, the lack of a significant interaction effect does not support that this pattern is a trial-related effect.

Regarding the age by visit interaction effect for unprotected anal sex, both groups reported the same level of risk at baseline. However, younger men decreased less substantially at 6 months and returned to baseline a 24 months; whereas, older men reported less unprotected anal sex at 6 months and remained below baseline throughout the trial. It was found that a change in unprotected anal sex over time was associated with race / ethnicity. Relative to men in other ethnic groups, black men reported substantial decreases in unprotected anal sex from baseline to 6 month follow-up and maintained lower levels of unprotected anal sex throughout the trial. Not too much can be read into this because most of the men in the trial were white, so the N's for non-white men are low. Only 180 African American men enrolled in the trial completed their 36 months of follow-up. The appearance of an increase in unprotected anal sex among Asian men from baseline to 30 months was not statistically significant.

With respect to data from the non-trial participant cohort, Dr. (b)(6) reported that at 6 of the 61 sites, an additional cohort was enrolled in a quasi-experimental design approach. They were followed for 18 months. The vaccine trial participants decreased their risk somewhat, but increased over time. The non-trial pattern represents the revised definition of disinhibition—the attenuated downward slope of behavior relative to a non-trial participant group.

This dataset has been very valuable in terms of thinking about HIV prevention among MSM. There has been concern in the last five years that in the US, there has been a resurgence of the epidemic among MSM. Thus, CDC was interested in how they might exploit these data to learn more about contextual related factors to risk using individual level variables. They did this by borrowing a method from biology, cluster analysis, which is often used for taxonomy development. Cluster analysis determines similarities and difference among groups without imposing undue assumptions on the data. The challenge, however, is to determine what variables to use in the clustering procedure. The clustering schema that CDC used was based upon an individual-level hierarchical approach using contextual variables related to risk behavior, organized by the proximal / distal nature of these variables to the risk behavior. Demographic variables were considered to be most distal to HIV risk behavior, followed by drug use, and then sexual partnership variables. Partnership variables included both the numbers of partners and proportion of partners by serostatus to provide a more complete representation of partnership context. No assumptions were imposed on the data. Eight demographic / risk clusters were identified and men were distributed fairly equally across clusters (range 3%-19%), with the exception of older high risk MSM. Clusters were given descriptive names that captured the essence of each group. These eight clusters were: 1) White non-drug users; these had primarily HIV negative partners; 2) Older high risk men; these had an extreme number of partners (e.g., hundreds of partners in the last six months); 3) Younger party goers (using amphetamines and hallucinogens); 4) Older Viagra® users, 5) Men of color, 6) HIV negative men in primary discordant relationships with HIV positive partners, 7) Older popper users, and 8) Older low-risk men with primarily partners of unknown HIV serostatus.

In terms of unprotected anal sex over 36-months by demographic / behavioral contextual group, regarding the mean unprotected anal sex, there was significant variation with regard to the proportion of men in each cluster reporting unprotected anal sex at baseline. Unprotected anal sex decreased from baseline to 6 months and increased slightly thereafter. At 30 months, unprotected anal sex was statistically equivalent to baseline, but was below baseline levels at 36 months. Older high risk subjects reported the highest amount of unprotected anal sex. Primary discordant partners, generally regarded as attractive candidates for vaccine trials, reported the least amount of unprotected anal sex. The younger party crowd reported the second highest amount of unprotected anal sex. White non-drug users reported unprotected anal sex that fell below the average across all clusters. Older Viagra® users reported rates of unprotected anal sex that were above the mean. Older low risk subjects reported less unprotected anal sex, which is more typical of stereotypic perceptions of sexuality among older men. Older popper users reported higher than average rates of unprotected anal sex. Men of color hovered about the mean of unprotected anal sex over time, which was perhaps a surprise given the high incidence rates reported among young men of color by various researchers (e.g., Valleroy et al).

Considering the HIV incidence by cluster, the observed HIV incidence over 36 months was 2.9% / 100 person years. Point estimates and confidence intervals by cluster were as follows:

- Older high risk men had an annualized seroincidence of 6.6%, which is somewhat counter intuitive because there is always discussion about the young age effect among MSM in HIV prevention.
- The younger party crowd had the second highest point estimate at 4.9%.
- Older popper users were 3.6%.
- Men of color were 3.0%.
- Men in primary discordant relationships had the lowest incidence at 1.8%, who are often candidates for clinical trials because it is perceived that they are at such great risks due to their discordant partnership.
- Older low risk men were next, with a point estimate of 1.9%
- White non-drug users at 2.2% fell below the trial incidence.
- Older Viagra® users had a point estimate at 2.6%, just below the trial incidence.

If only individuals were enrolled in the higher incidence clusters (e.g., above the incidence for the trial) the incidence would be 4.% versus 2.% for those falling below the incidence observed during the trial.

Dr. (b)(6) concluded that high levels of risk behavior / incidence underscore the challenges of behavior change and the need for alternative approaches to HIV prevention, such as circumcision and other strategies. High risk individuals join trials seeking protection from infection. The risk behavior observed in this trial did not increase beyond baseline. Thus, there was no evidence of the standard definition of behavioral disinhibition. There is possible evidence of an attenuated decrease decline in slope as evidenced by the non-trial participant data. Risk behavior related to perceived assignment, while not a disinhibition effect, is probably illustrative of selection bias of HIV risk individuals motivated to decrease their risk and who would present to circumcision programs, vaccine trials, or other types of prevention trials. Behavior change is related to age and race. Heterogeneity among risk clusters, with regard to both behavior and incidence, suggests a need for diverse approaches to: recruitment strategies (outreach, messages, venues), enrollment criteria to maximize the incidence of the cohort enrolled, retention / compliance strategies, and risk reduction counseling. Generalizing these data to domestic circumcision programs / trials is problematic, although these data may be useful. The men who participated in this trial may be very similar and very interested in circumcision trials. Will a harm reduction strategy among high risk MSM result in circumcision program and trial participation? It is not about the desire to increase risk behavior, but rather the desire to decrease risk associated with existing behavior. However, often in thinking about disinhibition, these men are presumed to want a product so that they can go out and increase their risk behavior. Dr. (b)(6) does not think that is what is going on. MSM may not be that motivated to decrease their risk behavior, as evidenced by the behavioral trends which did not decrease that much, but they are motivated to decrease the risk associate with their current risk behavior. He thought this was more likely what they would see. There may be differences in the US in the demand for *product* versus *procedure.* Regardless, monitoring must be done of program and / or trial-related perceptions and behavior in circumcision studies in the US. In addition, personal risk reduction plans must be developed that include circumcision, annual or semi-annual HIV counseling and testing and client-centered strategies specific to the individual's risk context. Those may be many as indicated by the cluster analysis.

Ethical, Religious, and Cultural Issues

(b)(6) **MD**
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Dr. (b) indicated that while he was asked to speak on ethical, religious, and cultural issues, he did not plan to discuss religious and cultural issues. He thought these were well-covered by earlier presenters. Therefore, the issues he covered were the problems associated in attempting to weigh the benefits and risks of circumcision, challenges in obtaining informed and voluntary consent for circumcision, the issue of justice / fairness in setting public health policies, evidence-based public health policy and how all of the data may get translated into policy, and implications for future prevention trials.

There are, and will be more, disagreements in attempting to weigh the benefits and risks of circumcision. Yet, weighing risks and benefits is fundamental to public health and public health policy. As a number of the presenters recognized, data will be extrapolated from three very rigorously designed, very well carried out RCTs. However, it is extrapolating, which can be done in many different ways. First, the data will be extrapolated from the research setting where there is excellent quality control, as well as top grade counseling and education programs to real-world settings, to real world where someone may simply receive a procedure and little or no counseling. Moreover, the populations in the US are different, with different baseline prevalence and different modes of transmission. There are interesting issues pertaining to absolute versus relative risk, and whether the relative risk is the same across different populations, or in fact whether the intervention might be more effective in higher risk groups. There will be a great deal of legitimate scientific disagreement with respect to how to take data obtained in these three clinical trials and other supporting non-RCT data to different settings. There should be standards for how extrapolations are made and for what is too much to extrapolate. It is very rare that there are three RCTs exactly on the research question, with the intervention population under study. Thus, there is always extrapolation to some extent. There are standards for how much is too much extrapolation and what is legitimate, which must be kept in mind. There is an approach to this which says, "We're not going to promote, or suggest, or even consider an intervention until we have perfect data, until we have the definitive RCT or two or three RCTs in the setting we want, with the exact intervention population. We can't extrapolate from other data." That may be going too far because delaying while waiting for perfect data carries risks, particularly in an infectious situation such as HIV.

There are also issues related to selection and weighting of endpoints. Dr. (b) pointed out that during the day, there was a great deal of discussion regarding HIV conversion as an important endpoint. It certainly is a key issue in Sub-Saharan Africa. Dr. (b)(6) presentation reminded them that there are other endpoints that may be equally, if not more important, in the US neonatal situation. Some critics of circumcision are going to raise other issues that were relegated to footnotes in some of the presentations. Any evidence that people may have increased high risk sexual behaviors (e.g., disinhibition) over the optimal to some people is an absolute horror in and of itself and they will weigh that much more heavily than all of the other endpoints. Even worse, some people will say that another endpoint is not being considered, which is not disinhibition that is related to high risk sexual behaviors, but which is extra-marital sex even if it is safe sex. There are people for whom having sex outside of marriage is such a grave moral harm, they will argue that it should be a primary endpoint that outweighs all of the other endpoints. The other issues that will arise is that it is at least theoretically possible, even if

not practically possible in the real world, to achieve benefits by alternative means. People who have a fervent belief in abstinence as an HIV prevention mode may take this position. These are important issues that will likely complicate the discussion beyond the already complicated discussion they heard throughout the day.

With respect to perceptions of risks and benefits, scientific evidence may be contested / rejected by the public as evidenced by childhood vaccination research and policy. Despite the fact that these are three rigorous, well-designed RCTs of the highest standard of clinical evidence; however, many people in the world will not be swayed by that as much as they will be swayed by anecdote, rumor, and / or misinformation. For a lot of people, the impact of a rare but dramatic complication, even if it is anecdotal or urban legend, may actually account for more than the data of these very carefully designed studies. There are many reasons for that, but one certainly is if a rare but dramatic adverse event happens, there is an individual attached to that who has a story and a face. When preventing cases of HIV, as with any prevention measure, no face can be put on an individual. That makes a difference in terms of the perception of some members of the public.

Regarding informed and voluntary consent, obviously undue influence must be avoided. Someone used the word "coercion" earlier, which implies forcing someone to do something physically against their will. What is of greater concern in the medical arena or research area is undue influence where someone makes a choice to enter a clinical trial or to receive an intervention, but they are so heavily influenced by something else, it is not really a voluntary decision. But often, in some of their other "prevention hats," they try to bring social pressure to bear on individual decisions about risk (e.g., seat belts, car seats, preventing teen drinking). They try to bring into play persuasion and peer pressure. However, there is a fine line between persuasion and peer pressure versus undue influence. Consideration must be given to what the dividing line is between legitimate use of community norms to persuade people to do what is good for them versus undue influence. This will be particularly charged because circumcision is a private matter.

Concerning children, either neonates or young children, there is a complicated set of competing rights or ethical considerations of parents to make decisions for children, for children to be protected from serious harms, and for children to choose different values from their parents' values. In the US, parents are given incredible latitude to make decisions for their children because it is believed that parents, in general, act in the best interest of their children. Most policy and case law in the US is really not about children, but instead is about parental rights to control their children and do what they think is best for them. This is the starting point in the US. Some other ideas are actually more recent and it is not clear how they will play out. Balanced against that is that parents get to do what they think is best for their children given their cultural, personal, or religious beliefs. There is also the notion that children have to be protected from serious harms from even well-meaning parents. A classic example is Christian Scientist parents who do not vaccinate their children for measles in the middle of an epidemic. In such a case, the state can intervene. Another issue mentioned in passing earlier in the day was that of waiting for the child to reach an age where he can make a decision himself. If it is a decision upon which people differ, the child may choose a cultural / social identity that differs from his parents and may not want the kinds of social benefits that accompany traditional circumcision. Thus, when thinking about children, there are three differing ethical guidelines which must be kept in mind when considering policy.

With respect to justice and fairness, justice is a slippery term. No one is against justice and no one is for unfairness, but it is difficult to know what people mean by that. An issue that is important in public health policy regards whether a policy is targeted to high-risk groups where the most cases will be averted, or which is targeted at a much broader universal level even though many people in the larger population are actually at very low risk. When the policy of routine universal HIV testing in the prenatal periods was put into place, a map could be drawn of where the cases of maternal to child transmission in the US occurred. They were clustered in neighborhoods that broke down along racial and poverty lines, and in many other ways. However, rather than testing only women at high risk, it was recognized that this would be perceived as discriminatory, unfair singling out of certain groups because of where they lived or the color of their skin. Even though, from an epidemiological standpoint, it was clear they would be testing many women at very low risk, a universal policy was instituted. The balance between fairness in terms of not treating people differently in ways that may be discriminatory, versus targeting scarce resources where they will have the most cost-effectiveness is a tension. Another issue that will arise is that when talking about a surgical procedure, even if it may be minor, some individuals may be asked to accept the risk and inconvenience of that intervention primarily to benefit others (e.g., partners or so there is the sense that everyone is being treated fairly).

There are some challenges to evidence-based policy. It is critical to clarify what is known, what is not known, and what is genuinely uncertain and needs to be studied. That is the first step. While it is not easy, it is easier than the next step, which is making public policy. Everyone must recognize the public policy may be (probably will be) based on non-empirical considerations. Many of the forces that drive pubic health policy in the US and other countries will be driven by cultural, religious, and personal beliefs and may not be susceptible to empirical data. It is probably inevitable and evidence-based proponents may not like it. However, it is important to try to distinguish as best they can where the data would push them if they did a solely data-driven analysis (keeping in mind how that is interpreted, categorized, and designed is all value-based) from what the policy is. These may be very different.

Dr. (b) stressed that he was arguing for intellectual honesty and also because it is better in the long-run from a policy point of view, to keep these separate. The best example of that is from a number of administrations ago when Dr. David Satcher was Surgeon General. He was asked during a press conference to comment on the administration position regarding needle exchange for injecting drug users. Dr. Satcher's response was, "As a scientist, I want to say that it is absolutely clear what the scientific data show. Best we can tell, the data show that it reduces transmission of HIV. As an appointee in this administration, I have to say that the policy of this administration is that we will not fund, condone, or support needle exchange." He was honest about it and he made it very clear that whatever the data were, the policy was different. That is more honest and better in the long-term than those who make unfounded data claims. There are people who, to reach a conclusion they want to reach, will make unfounded empirical claims. If empirical data that are considered rigorous by good mythologists are going to be rejected, reasons should be provided that are understandable to people who may not share the same cultural or religious beliefs. For example, in certain religious traditions males are expected to be circumcised and it does not matter what the medical risks or benefits might be. That may be fine for certain political jurisdictions, families, religions, congregations, et cetera. But when setting public policy in a non-theocratic state, reasons should be offered for rejecting empirical data that is understandable to people who do not share those beliefs.

A looming issue pertains to the ethical issues in conducting the next generation of HIV prevention trials given these three well-designed studies in the literature RCTs. It is clear that there remain many gaps in the evidence base, and that it would be nice to have some RCTs of circumcisions of populations in the US to fill in these gaps. There are also implications of these three RCTs for any other HIV prevention trials. If there are going to be female-based, female control HIV prevention, the next generation of vaccine studies, et cetera, consideration must be given about what to do about circumcision. There are a number of ways to take circumcision into account for prevention efforts. First, there is clearly a covariate to be accounted for in designing analyses. Second, participants in a clinical trial must be provided with the information that is now known. This is certainly true when conducting a prevention trial in a resource-poor country with very high HIV transmission rates where participants cannot make an informed decision to enroll in that trial without knowing about these three studies. Some people would argue that a clinical trial needs to go further. That is, in addition to providing information to participants and collecting information for the analyses, access must be facilitated to reduce barriers to local access to circumcision. This may be as simple as making an arrangement with the local hospital to refer people who enter the trial and want to be circumcised to get that done outside the trial. If referrals are made to other sites, consideration must be given to what obligations trial investigators have to check on the quality of care at those sites (e.g., training, complication rate, wound care, et cetera). Dr. (b) predicted that there will be pressure to say that it is unethical to carry out an HIV prevention trial, certainly in Sub-Saharan Africa, that does not include circumcision as a background intervention in both arms of the trial just as counseling and condoms are now provided. The implications of that are profound in terms of sample size. Before concluding that this should be done, there is a complicated analysis to work through. This is not simple because different ethical principles that seem to make sense, pull in different directions.

There are also competing ethical guidelines. Dr. (b) said he begins with the idea that a prerequisite for conducting an ethical trial is that it is relative to the health priorities of the study population being studied. Thus, if conducting a trial in a country that does not have circumcision and offering that as part of the trial, are the results of that trial truly applicable to the country and the population being studied? If not, is it ethical to use them to answer questions that are really relevant to other people? The question being asked must also be relevant to the entire period of the study. What is likely to occur, similar to what happened when Highly Active Anti-Retroviral Therapy (HAART) became more affordable and more widespread, is that a study may be planned in a country where circumcision does not exist; however, in the course of doing the study it may become more available, people may get it outside the trial, and then there will be increasing pressure to provide it as part of the study. The other issues that will drive demands to include circumcision as background treatment in both arms of a prevention trial are ethical precepts to minimize risks to trial participants (45 CFR 46), to not withhold effective care (Helsinki Declaration), and to conduct research efficiently. If a small clinical trial will realize the same results all things being equal, that is better than a much large, more expensive, longer clinical trial. If circumcision in included in both arms, it will increase sample size dramatically.

In terms of approaches to prevention trials, Dr. (b) suggested giving consideration to testing a new intervention in participants who cannot or will not use the proven prevention methods (e.g., people who cannot or will not use condoms like commercial sex workers; people who have religious / cultural / other objections to circumcision) without providing circumcision. This would probably require a multi-site trial. He discouraged studies that say there is a "window of opportunity" to get a prevention trial done before circumcision becomes widely available in a country. It will become available before the trial can be finished. He also suggested thinking about what the Europeans have called "large, simple, multi-site trials" in other prevention areas

(e.g., European studies on hypertension, hypercholesterolemia, secondary prevention in myocardial infarction). The Europeans have done huge, large, simple trials in which they enroll thousands of patients but collect much less data on each patient to make the trial more efficient. They have added a new intervention versus placebo on top of best available and sustainable current therapy. This is standard in cardiology trials now.

Dr. (b) concluded that ethical issues are unavoidable. They will arise sooner or later. If they are not addressed in the planning stage of new prevention trials, they will transpire during the trial.

Discussion and Public Comment Period:

- With respect to not misconstruing data when reporting results if it goes against what one wanted it to be, Dr. (b)(6) cost-benefit analysis was striking in that she used a 25% disinhibition figure when the available data presented by Dr. (b)(6) showed much less disinhibition and, in fact, showed something contrary to disinhibition referring to it as the attenuating slope the other way. If assumptions are going to be built based upon evidence, it would be good to actually build them on evidence currently available. If this is the best evidence available, it is not clear why they are making up data at 25% disinhibition. Is it to produce an outcome that is certain? Or is it an honest attempt to reach a conclusion?

- Dr. (b)(6) responded that the base case assumption was no disinhibition. In one of the many other alternates that was investigated included the 25% increase. It is true that there may be additive decrease in risk in the context of a program (not sure this is exactly what he said; could not hear him in the room or on the tape as he was distant from the microphone)

- Risk behavior has been monitored since HIV testing came into being in Seattle. They found substantial increases in the numbers of partners that HIV negative gay men reported following the introduction of antiretroviral therapy. It seemed that that may be one of biggest confounders of looking at data of people participating in vaccine trials. With that in mind, some of the curves that were attenuated, or did not go down as much was hoped, were perhaps more an impact of the availability of antiretroviral therapy which makes HIV less frightening and lethal. Plotting those over the years in the HIV vaccine trial would have been more interesting than to see at various points along the line where people recruited into the study.

- Dr. (b)(6) responded that they adjusted their analysis, recognizing that there could be history effects in behavior over time, and there were actually differences in risks depending upon when a person was enrolled in the trial. This was a significant but minimal influence.

- With regard to cultural and religious aspects, in the early days of HIV prevention planning in the 1990s, when everyone first started using the term MSM; however, beginning with the Vancouver conference last summer, many people began using the term "gay men and other men who have sex with men." The breakouts sessions for this meeting are defined as "MSM" and "MSW," which felt to this participant like they were taking away the cultural aspects. When it comes to sexuality, culturally it is all about heterosexuality with an interesting and long-standing history which informs much of what everyone does. Gay, lesbian, bisexual, transgender (GLBT) culture is relatively new, but there are some aspects specific to that cultural community which must be considered. Even within the GLBT culture, there are racial, ethnic, age, and other differences, all of which are very important in looking at the cultural determinants and the culturally related opportunities for successful interventions to prevent the transmission of HIV.

- At this point in this epidemic, 80% of UK transmissions of HIV are likely to be gay men. The UK has overlaid on top of that an enormous effect of the African epidemic as migrants from Africans move to and are diagnosed in the UK. Predominantly, that is from people who acquired their infection in African context. It is not clear whether the UK can conduct an equivalent study to the three superb RCTs in African context. Clearly, the most at risk people are gay men having anal sex. Circumcision in them is going to be of no benefit to them acquitting HIV as the insertive partner who it might be beneficial to. The 13.5% beneficial effects of circumcision that Dr. (b)(6) introduced are probably too high a level for the UK. Then the only thing they can do is circumcise HIV positive men like the ongoing trial within the Ugandan context to determine whether transmission is lessoned in discordant partnerships. In terms of the discordant partnerships in Dr. Bartholow's data, with the seroincidence being at it lowest level, and therefore the size of any trial in trying to get that, a) they would be circumcising people who are already HIV positive, and b) the lowest seroincidence in discordant partnerships. In casual partnerships it is very difficult to undergo follow-up of the receptive partner in those sorts of situations. This participant expressed profound disappoint in the whole thing from the point of view of where the UK epidemic is. In addition, if they wanted to target a heterosexual group in the UK, that would be recent African migrants who are already powerfully stigmatized. Trying to circumcise men from that community without it totally being a racist intervention, is going to be extremely difficult. They will further stigmatize those groups.

- It was noted that part of the work that needs to be done is more discussion about alternative designs and concepts. In terms of looking at total effects, indirect and direct effects instead of just direct effects, there are other designs besides discordant couples studies, for example cluster randomized controlled trials. It does not appear to be known at this point whether there would be an indirect effect for receptive partners. While the end of the day was not the time to raise that discussion, it should be addressed at some point during this consultation. In addition, the implications of the RCT results for additional prevention trials, including vaccine and other trials, represented a very important set of issues raised by Dr. (b)(This also needs further discussion because it would seem that to take one of the paths proposed by Dr. (b) (e.g., just to look at additional interventions such as HIV vaccines in populations that cannot use condoms or will not be circumcised) pertains to the notion of large multi-component trials that do allow investigators to put together the best science on the behavioral and biomedical intervention sides as the platform upon which new interventions are introduced. That will be both expensive and challenging. With that in mind, an inquiry was posed to Dr. (b) with respect to whether this was what he was suggesting.

- Dr. (b) explained that the premise behind a large, simple trial is that there will be a lot of variation in standard of practice in a country where there is good access and high quality care. The way to take advantage of that is by randomization and by not trying to specify in as much detail as American studies tend to, exactly what intervention everybody in the study gets. It is a way of trying to account for variation in things like condom use and counseling—having a minimum standard, but allowing for variation as determined by the personal physician of each participant. This requires good standard of care and access. It is very different from doing this in a resource-poor country. It is a way to get at the fact that investigators are going to want to look at different combinations of prevention approaches, all of which have only partial efficacy. "Simple" in the technical sense means instead of collecting reams of data about each patient. The point is to have simple endpoints and make the trial feasible by collecting fewer pieces of information on lots of patients.

- Not only do the cultural and religious aspects need to be taken into account, but also it was suggested that the spiritual aspects must be addressed. However, no reference had been made so far during this consultation to the spiritual. It was suggested that in their discussions, they should not make the issue the ways in which functional and dysfunctional belief systems become a part of the way in which buy-in is obtained from communities, especially those being disproportionately impacted by the diseases before them. If they anticipate in any way being able to advance some strategies that would include effectively bringing those communities into the equation in terms of participating, they must deal with all of the issues driven by trust and all of the historical contradictions that stand in the way of involvement in trials on every level. The conspiracy theory is always a part of the conversation in some communities. This participant referred to a photograph shown earlier of a black penis being circumcised by a white hand (it was noted that the physician in the photograph is black, but was wearing white surgical gloves). Nevertheless, the image of black penis with white hands getting ready to cut on it rings bells of the kinds of fears and concerns that have haunted the African American community for a long time. The African American experience is different from the African experience, because the African American experience is laced and riddled with reasons why the trust factor is not there. This participant quoted the Great Prophet, Richard Prior, who when asked why black men always walk around holding their genitals, responded, "Hell they've taken everything else. We're not going to let them take this, too." While that sounded somewhat ridiculous on a certain level, in terms of the thoughts and experiences of the people they want to work with, it illustrated the kinds of issues that must be considered in this process, even if unfounded or based on myth. For that not to be a part of this conversation would be a great mistake.

- Dr. (b)(6) responded that they were very concerned that there would be religious objections in the Rakai Trial because Muslims in this population were circumcised and Christians were the only ones who were not. Therefore, they consulted religious leaders and conducted a lot of qualitative studies with the people. An interesting theme that arose time and again was that people said, "Jesus was circumcised, so it is not going to affect my religious identification." Nevertheless, Dr. (b)(6) agreed that these are extremely sensitive concerns. In terms of disinhibition within a trial, the problem faced is that a trial is such an artificial situation. Investigators intensively educate and reinforce messages throughout the process. The most important question is: What happens after the trial when we take the lid off that health education? That is why it will be so important to see in both Kisumu and Rakai whether they observe disinhibition after the trial has ended. Both groups plan to conduct post trial surveillance. Dr. (b)(6) also addressed another issue raised pertaining to whether it would be ethical to conduct a trial with people for whom the intervention would be of no direct benefit to the individual, but would be for another person. That was a dilemma faced in the trial of circumcision of HIV positive men because the only thing they could argue as a potential benefit to those men was the potential of reducing ulceration and some STIs. The benefit they hoped to observe was in the men's female partners. NIH felt that that this was not ethical and the investigators had to go to Gates to obtain support. There are other trials that face the same dilemma, so there must be a detailed discussion of the ethics of couples studies, because Dr. (b)(6) did not believe these were against federal regulations or ethical principles.

- Dr. (b) responded that he would distinguish between clinical trials testing interventions for which the primary benefit will be for other populations versus public health interventions. In public health it is not uncommon to recommend interventions for which the primary benefit does not affect everybody. There is a major difference in *recommending* versus *mandatory*. Within clinical trials, investigators should start with the idea that in any clinical trial the primary benefit is to scientific knowledge and to future patients. It is not necessarily to the participants in the trial because it is not known whether there is equipoise in the clinical trial, whether there will be harm or benefit to being in either arm. It is so easy to confound proven effective therapies with promising interventions. Promising interventions do not necessarily end up benefiting the people who receive them. How he would argue this to the NIH study section would be that studying promising interventions that may primarily benefit others besides the participants in the study is done all of the time in clinical trials.

- Dr. (b)(6) replied that there is a double standard. Everyone will support trials of prevention of mother to child transmission, giving antriretrovirals to mothers when it does not benefit them and it may actually do them harm by selection of resistant virus. However, nobody questions the ethics of that, although the benefit is only to the baby.

- Regarding the control condition, one alternative Dr. (b) suggested was study a select population to get around the issue of the control condition and whether it involves circumcision or not, such as the population not willing to use condoms or not willing to be circumcised. With that in mind, it seemed they still had to get back to the central research which is: In a population who has access to the intervention, what is the additional benefit of the intervention? In thinking about other intervention trials it seemed to be important not to choose very selected groups of very high seroincidence even. Not even to say it is only going to be studied in individuals who do not use condoms, because data presented earlier in the day suggested that the relative benefit of circumcision might be different in a very high risk group than in a low risk group. It seemed that they should always structure the population to be one that looks like the population for whom they are trying to get the answer. In addition, some prevention trials are struggling with the issue of whether to provide circumcision to the control condition when they are testing a different prevention strategy. In some contexts circumcision is not yet available, so if it is offered in this setting, could that be considered undue incentive.

- Dr. (b) responded that these questions illustrated how complicated and difficult the issues are. He completely agreed that there was something very ethically troubling about conducting a study that is not answering a research question pertinent to the health and public health needs and priorities of the community of the population being studied. Investigators must ask themselves whether it is a trial of the efficacy of circumcision per se independently of everything else, or if the research question really is about what circumcision adds to all of the other interventions available and that people are sometimes getting in real life. What they must be honest about is that if it is the latter question, the real life question, they must accept the implications for funding. They are much bigger, longer, hard to conduct trials. The budget has to be commensurate to the task at hand. In terms of what it is ethically permissible and mandatory to offer people in both arms of a prevention trial, investigators can be criticized either way. If they do not do it, they will be criticized for discriminating against and exploiting people by not giving them something that they would never think of not giving to someone in a developed country that is known to work and which is known to be feasible within a research setting. There needs to be a distinction between undue inducement and a good deal. An undue inducement is morally bad if it makes

someone do something that they would never in the clear light of day do. It makes someone undergo risks that are so horrible they would not have done it but for the influence, or that leads them to make a decision that is totally uniformed and to overlook risks, consequences, et cetera. There are ways to protect against both. Studies must ensure that participants are truly informed. Protection against undue influence leading people to accept inappropriately high levels of risk is really a rigorous design of study. It may well be that just giving good background care to people in a prevention trial in a resource-poor country, plus having study staff who know and bond with the people, will be reasons for people to enroll. In a sense, that is an undue influence because they may not be able to get that anywhere else. If the trial is well-designed, the risks are acceptable, and the consent is informed, it is not said to be morally bad even though they are getting a good deal.

- It was noted that communities should be involved in the decisions about what constitutes standard of prevention, standard of care, et cetera. The issue raised about funding is the same globally, so they must ensure that the countries where the studies are being conducted are in the driver's seat. They must hold their own stakeholder consultations, consider all cultural issues, what else gets displaced in the healthcare systems, the equity issues they must deal with, et cetera.

- It was noted that one issue not discussed much so far related to communications. Consideration must be given to how to help communities understand that circumcision is part of a toolbox. They must also ensure that communications get information across clearly enough so that people can make informed decisions (not sure this is exactly what he said; could not hear him in the room or on the tape as he was distant from me and did not use the microphone).

- When Dr. (b)(6) had an article in the *New York Times* about this new intervention, he was immediately sandbagged by reporters. However, for the next two days, the Spanish press carried story after story of doctors saying this new behavioral intervention is safe, it would protect people against HIV, et cetera. A lot of damage was done by not talking about the context for this intervention. This participant stressed that they must all do their homework to clarify what the good doctors on Univision and Telemundo were trying to say and put it in context. This will take a lot of work, but they must all be mindful of that responsibility.

With no further business posed, the meeting was adjourned for the day.

Friday, April 27th

Charge to the Breakout Groups

(b)(6) **MD, MS, MPH**
(b)(6)
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) issued the charge to the three population-specific breakout groups, which included: 1) Circumcision for men who have sex with women (MSW) in the US; 2) Circumcision for men who have sex with men (MSM) in the US; and 3) Circumcision for newborns in the US. She noted that the division recognized that there are men who have sex with both men and women, and that they wanted the consultants to discuss those issues in the relevant groups. The overarching question is: What do we know about the efficacy of circumcision for protecting men when they are having sex with women and when they are having sex with men?

Dr. (b)(6) reported that they attempted to assign people to the breakout groups in a manner that placed those who were experts in particular populations in the corresponding groups, and in an effort to include a mix of epidemiologists, behavioral scientists, community representatives, et cetera in each group. She requested that individuals remain with the group to which they were assigned, and that each group select a rapporteur to deliver the summary of the group discussion at the end of the day. Dr. (b)(6) requested that everyone take their name tents so that they would know each other; however, she assured the consultants that specific names would not be attributed to comments.

Each group was to discuss the US epidemic and remain focused in the populations to which they were assigned. Dr. (b)(6) stressed that they were not seeking consensus, voting, or hashing out any final decisions. Instead, the goal was to ensure that all issues were delineated and that there was an opportunity for people to state the pros, cons, and complexities of those issues. The groups were asked to focus on the following questions:

Question #1: Considering the information presented earlier, what are key issues for male circumcision in this population? List ideas without a lot of discussion to ensure that all issues are noted.

Question #2: What additional data should CDC obtain? What additional data should be collected by others and by whom?

Question #3: What policy and program guidance should CDC consider developing? What guidance should others provide and by whom?

Question #4: What other activities should CDC undertake? What other activities should be done by others and by whom?

In conclusion, Dr. (b)(6) indicated that the consultants would receive a copy of the summary report from the meeting.

Breakout Group Reports

The tables associated with the breakout group reports are contained in Appendix I, and the full breakout group discussions are contained in Appendix II.

Circumcision for Newborns in the US

(b)(6) **MD, Rapporteur**
(b)(6)
(b)(6)
(b)(6)

Dr. (b)(6) reported the findings of the Newborn Working Group, which included the following points [also see tables in Appendix II]:

Issues Raised

- This group spent a great deal of time on the importance of a thorough review of risks benefits (immediate versus future) designs so that they would be comparing, if not apples to apples, at least fruit. They should not be comparing things that are completely different from each other and should be putting things, to the extent possible, in the same metrics so that it is possible to balance benefits against potential harms using the same metrics.

- Disassociating male circumcision versus other prevention messages (e.g., condoms) is an issue. It is important to be cautious with regard to this.

- Ethical issues were raised, specifically that infants do not have input into this decision. Consideration should be given to whether this is critically important, or that at least this should be thought through with respect to the process of making policy.

- Access to quality circumcision is important, specifically with regard to access in terms of payment (e.g., a payor making it possible for somebody to obtain circumcision if desired), and in terms of a properly done circumcision and knowing who is doing the procedure.

- The issue of potential misinterpretation of the CDC statements came from the representatives of the American Academy of Pediatrics who feel that the Academy's statement has been repeatedly misinterpreted, and that CDC's statements are going to be subject to exactly the same risks.

- Non-directive counseling was brought up.

- Before this group began their discussion of the data that are needed, there was a discussion about at what point it would be decided that the data are sufficient. When would the decision be made to continue to collect data and continue to put off making decisions? When should they move ahead?

- Human rights issues, which link back to the infant choice issue, were raised again.

- Infant circumcision probably has considerable advantages in terms of pain, safety, and ease over adult circumcision.

- Quality of male circumcision was addressed, including provider training. Most of those who trained in pediatrics, family medicine, or obstetrics remember that the person who does the circumcision is the person who gets stuck with it. Quality control and making sure these are done appropriately is critically important. Quality assurance is also critically important and more attention is being paid to where it is done, who does it, and how it is done.

- The issue was raised with regard to whether, if male circumcision is tied to sexual transmitted infections, it will suddenly become a moral issue. It did not use to be a moral issue. It might have been a human rights or choice issue, but not a morality issue. Now that sex is involved, it may become a morality issue in view of the public.

- Recognizing and addressing the full spectrum of opinions in the formation of any policy is imperative.

- It is essential to remember that female genital mutilation is not the same as male circumcision.

- Consideration should be given to the applicability of the African adult studies to neonates in the US.

- Do pediatricians / obstetricians need to bring up male circumcision? If so, should this be brought up at the time of birth or should it brought up later in life? Is there a cost to doing this? Of course, there is. What are the resource allocation issues? For example, if physicians have 15 minutes to talk to their patients, should they allocate that time breast feeding counseling and car seats, or to infant circumcision?

Data Needed

- Magnitudes of risks and benefits should be expressed in comparable terms (e.g., denominators for risks). This is probably the most important point that came out in this group's deliberations. For example, the absolute risk reduction in a particular population. This comes out of the US Preventive Services Task Force. When balancing risks against benefits, they have an outcomes table that uses a hypothetical population and looks at the specific outcomes of interest (both benefits and harms) and enumerates how many of each of those would occur in a hypothetical population if this intervention were done. So, there is an opportunity to look at something using the exact same metric. It does not put values on things. For example, there is clearly a different value that would be placed on minor bleeding versus prevention of HIV, but it allows people to see what the numbers are and place their own values on them. Additional data should be collected by / from: CDC, AHRQ, AAP, AAFP, and NICHD.

- Is there a male circumcision prevalence threshold at which HIV / SDT transmission decreases? The question was raised regarding whether there is a modeling exercise that might be used to determine whether there is a prevalence threshold. Whether this can be done is not crystal clear, but a desire for that information was expressed. Additional data should be collected by / from: CDC.

- What value do parents attribute to outcomes? There was a consensus that they would like to know this, and at the same time a recognition that just because 75% of parents think one thing does not mean that what the other 25% of parents think is not important. The individual valuation of outcomes needs to be recognized. Additional data should be collected by / from: CDC, and Dr. (b)(6) survey data.

- Are there enough data on reduced risks to female partners, and is that data obtainable at relatively reasonable costs? Additional data should be collected by / from: Rakai study.

- Data are needed on complication rates. Existing studies only include in-patient complications. Smaller studies have other data. However, trying to get more information will be difficult because many of these complications are not coded. At (b)(6) when coding what a baby is in for, they can only code the top 70 most common reasons for which babies present. After that, it is all in text, so it is not retrievable data. Therefore, obtaining that data from a database even as revered as (b)(6) would involve manual review of countless charts. Additional data should be collected by / from: AHRQ, NCHS, CMS, and HMOs.

- Data are needed pertaining to who, what, and where, male circumcisions are being conducted. Additional data should be collected by / from: AHRQ, NCHS, CMS, and HMOs.

- More information is needed with respect to community perception (e.g., conspiracy theories, discrimination, et cetera). The group thought that one possible place to obtain this information would be from the AME church if they have a large health outreach program through which data have been collected. Studies coming out of IRB groups might also be a resource. Additional data should be collected by / from: AME Church, IRBs.

- Studies comparing techniques for male circumcision are needed. There have been several studies, but they were not very large. It is important to note that any study of surgical approaches is operator dependent. In terms of different approaches to infant circumcision, there are basically three common procedures. One of them is "idiot proof," but it probably is not as good a procedure as another one done in skilled hands. Additional data should be collected by / from: Available sources.

- The proportion of providers using anesthesia and the best methods should be known. In the briefing materials for this meeting, there was at least one study suggesting that about a third of infant circumcisions are done by obstetricians and they are not using anesthesia very much. Circumcisions used to be done in the delivery room immediately after delivery without anesthesia because during that time, babies apparently felt no pain. They do now, so they must start thinking about this. The best methods for anesthesia are also important to understand. Anesthesia is time-consuming. Topical anesthesia takes 60 to 90 minutes. A dorsal penile nerve block works very well in experienced hands. Additional data should be collected by / from: ?

- Information is needed about who is covering male circumcision (e.g., insurance companies, HMOs, et cetera). It is known that 16 states do not cover male circumcision under Medicaid; however, there is not a thorough understanding of what other insurance policies are doing. This is information that is obtainable through various entities. Additional data should be collected by / from: AHRQ, NCHS, CMS (although CMS does not seem willing to part with information), and HMOs.

- Information is needed pertaining to US versus European rates of infant risks and benefits. In Northern Europe, few babies are circumcised. Northern European pediatricians tend to have thought processes similar to US pediatricians, so it is not clear why they have not gotten as excited about this as the US has in terms of infant benefits. Are things different in Europe? Are they collecting different data there? Additional data should be collected by / from: ?

Policy and Program Guidelines

- There are practical advantages of doing the procedure during the newborn period if the consensus is clear that it is a good idea when a male becomes sexually active that he is already circumcised. Complication rates are lower, the ease of the procedure is higher, it is easier to deal with anesthesia, et cetera. Guidance should be provided by: AAP, AAFP, American Neurological Association, et cetera.

- Does benefit of infant male circumcision merit funding? Does lack of coverage result in discrimination against specific subgroups? If so, how do we address it? If specific subgroups are unfunded systematically, that may represent discrimination. Guidance should be provided by: ?

- Is it worth displacing funding from other programs for infant male circumcision? For example, should it displace the discussion of car seats, breastfeeding, or something else? It would be great if doctors could just add it, but they do not have time to do all of their rounds already, so there is going to have to be some discussion of where this fits in priorities. There are also funding implications. For example, Texas has terrible Medicaid funding, so the hospital is primarily funded by local dollars and decisions are made about what they do: Do they buy car seats, which they do now? Or, do they do circumcisions, which they do not do now? Though they do not like to pit one thing that is good for babies against other things that are good for babies, the fact is it is going to come out of the Women, Infant, Children budget. Guidance should be provided by: ?

- There should be a focus on shared decision making. Guidance should be provided by: ?

- Should recommendations from CDC be made in conjunction with other national stakeholders? This was a question about whether CDC should make a recommendation on its own, or whether they should make an effort to pull in others in order to make a joint statement. Objections were raised because it will probably be five years before they get anything out if they do this. However, on the other hand, all stakeholders putting forth a unified voice might have greater impact. Guidance should be provided by: ?

- Should any statement about male circumcision be made in a broader context or only in the context of either HIV or perhaps slightly more broadly to include STIs? Or, should it be made in a broader context of other health benefits of infant circumcision? That is a tough

question. If they are going to do that, there must be an adequate evidence review. What was done for this conference did not cover that, except relatively lightly. Guidance should be provided by: ?

- ❑ Given that, this group agreed that the benefits outweigh the risks for male circumcision in general. The risks and benefits should be explained to parents before they decide to do this in the newborn period. There are many practical advantages of doing the circumcision during the newborn period. This was really getting at the issue of shared decision-making, which is an approach that has been taken for many issues wherein the balance of benefits and risks may not be particularly overwhelming and, as a result, shared decision-making is used. There is a spectrum: You should consider doing this, but you will have to pay for it yourself, to you should consider this and insurance or Medicaid will pay for it, to it is a good idea and we're doing it unless you stop us and you have to pay for it, to it is a good idea and if you stop us, we are calling child protective services (CPS). That is a spectrum and they need to figure out where they are on the spectrum. Is it such a good idea that it is medical neglect not to do it? Or, is it a good idea, but if you decide not to do it you are not doing major harm? We do not call CPS when people choose not to breastfeed, which is known to be extremely beneficial. On the other hand, we do call CPS when people are in car wrecks and their children are not in car seats. Guidance should be provided by: ?

- ❑ They need to provide educational resources for the public and practitioners. If the term "circumcision" is Googled, this results in many hits that are anti-circumcision. It would be nice if what people retrieved from Google at least was balanced. It people know how to make topics show up under the first page of Google instead of page 300. Guidance should be provided by: CDC.

- ❑ They need to figure out how to do quality assurance for hospitals. Guidance should be provided by: AHRQ, NCHS, CMS, and HMOs.

- ❑ If they are going to implement programs, data monitoring will be extremely important. If a program is implemented, no matter how relatively narrow or broad the program is, how it is going should be monitored. Programs need to decide up front what data should be collected and should ensure that it is being collected in a uniform manner across all sites. Guidance should be provided by: CDC and CMS.

- ❑ CDC should talk with more stakeholders. Guidance should be provided by: CDC, CABS, and national organizations.

This group reached consensus on many of the issues upon which they deliberated.

Discussion:

- In reference to human rights, an inquiry was posed regarding whether they were referring to consent by the parents rather than waiting until the child was older.

- Dr. (b)(6) responded that they did not spend much time at all talking about the specifics. It was human rights consent of the child, consent of the parents. One of the issues to weigh in newborn circumcision is whether there is a human rights issue, and that the child should be allowed to make himself at the age of majority.

Circumcision in Men Who have Sex with Men (MSM) in the US

(b)(6) **Rapporteur**
(b)(6)
(b)(6)

Dr. (b)(6) reported the findings of the MSM Working Group, which included the following points [also see tables in Appendix II]:

Issues Raised

- Can data pertaining to male circumcision be extrapolated from the heterosexual transmission model to the MSM population?
- What can we infer from the heterosexual models? The African trials provide data, including enough data to infer a possible protective effect, but the degree is not known. This protective effective may be for the insertive partner only.
- Male circumcision is not 100% effective. This is a risk reduction approach, so it needs to be included in other messages, especially in the US.
- The question was raised: Would a male circumcision message undermine other prevention messages?
- If there are MSM messages, they should be wrapped in penile hygiene messages. Consideration must be given to what can be discussed in general in terms of penile health.
- Message should be developed for specific populations, including urologists and other health care workers.
- There was a lot of acknowledgement that in the US, the epidemic currently affects primarily Black and Latino MSM. Attention must be paid to that as messages, guidance, et cetera are developed given that these two groups are less likely to be circumcised, they may be less likely to have access to circumcision as they make decisions. Much of that has to do with socioeconomic status, cultural issues, et cetera.
- GUD evidence is important and may be applicable to MSM. While caution should be taken when developing messages, GUD should be included.
- Messages are needed for men who are HIV positive and for men who are circumcised and not circumcised. As these messages are developed, attention must be paid to issues of disinhibition. While it is not clear whether there will be any issues around disinhibition, data need to be collected around this.
- Consideration should be given to whether there need to be messages for military and incarcerated MSM. For many people, there are issues of funding.
- Sexual development is a critical component, yet there is a lack of information. It is important to understand whether / how adolescent to adult behavior changes over time.

- What has been learned in the trials about the healing period after circumcision must be addressed. There is not complete agreement about how long healing takes, what constitutes being "healed," the risks during the healing period, if risks vary, and if there are different messages depending upon whether someone is HIV positive, HIV negative, and / or for discordant couples.

- Clearly, as messages are developed for MSM, attention must be paid to cultural distinctions, top / bottom behaviors (e.g., insertive / receptive), whether those behaviors change over time, and whether people are acculturated or not. These may seem simple, but there are challenges as messages are developed or research is pursued.

- With respect to bisexual men, it is clear that vaginal and anal sex must be addressed separately. There was a suggestion that assumptions should not be made for any group regarding who is having what kind of sex. As materials are developed, keep in mind that people may think of themselves as being in one group when they have occasions when they are in other groups. It is not clear whether bisexual men would benefit more from the data, but this needs to be pursued.

- Specific issues should be addressed with respect to whether circumcision would benefit younger gay men *before* they become sexually active. Issues should be considered regarding emancipation and parental consent for younger gay men.

- Attention should be paid to loss of sexual pleasure, cultural, identity, and other reasons men believe they must keep their foreskin.

- Regional issues regarding male circumcision should be addressed. There are some data that suggest there are regional differences in circumcision. This should be considered in US and non-US cultures (e.g., Latin American and the Caribbean).

Data Needed

- The need to do formative work is an overarching issue. Additional data should be collected by / from: CDC and NIH?

- Acceptability in high incidence populations should be considered. Additional data should be collected by / from: CDC? and NIH.

- There was a lot of discussion about whether efficacy trials should be conducted in the US and what would happen in terms of equipoise. A large portion of the group agreed that if a trial is conducted outside the US, there should be a US cohort included as well. The group discussed some ways that this might occur, both with Latin America and Europe. Additional data should be collected by / from: CDC and NIH.

- Surveillance of adult male circumcision uptake is needed. Additional data should be collected by / from: CDC.

- Information is needed about specific sexual practices of MSM (e.g., sexual positioning). Additional data should be collected by / from: CDC and NIH.

- The feasibility of enrolling disenfranchised populations who are not usually in cohorts should be addressed. It is not clear whether existing datasets say enough about these populations. Additional data should be collected by / from: CDC and NIH.

- Studies are needed about wound healing, the impact of herpes suppression, and other biomedical interventions that might impact this. Additional data should be collected by / from: CDC and NIH.

- Urologists' attitudes and where people are getting information about circumcision are important to understand. Additional data should be collected by / from: ?

- Condom use and failure in circumcised and non-circumcised males is important to understand. There was acknowledgement that there is a greater incidence of condom failures in MSM. Additional data should be collected by / from: CDC and NIH.

- Review is needed of existing datasets (e.g., case-control, other). Groups should be convened to review these in order to identify additional questions that might be asked about those datasets. In this group, there really was not concurrence on what type of trials are needed (e.g., case-control, other). Additional data should be collected by / from: CDC and NIH.

Policy and Program Guidance

- Most in this group agreed that there is not enough evidence at this time to put out formal guidance / recommendations for MSM and / or MSW. Guidance should be provided by: ?

- The CDC male circumcision fact sheets should include what is known and not known. Guidance should be provided by: CDC.

- This group had a somewhat heated discussion on whether there should be a separate fact sheet for MSM. If so, information should be included about what is known and not known. A separate fact sheet should include information for MSM and MSW. Consideration must be given to the fact that there are people who may identify as MSM, but still have sex with women. There are people who will not read this fact sheet because they will exclude themselves when they see it is for MSM. All of the information should really be in all of the fact sheets even though there are different headers for them. Guidance should be provided by: CDC.

- Information is needed on the fact sheet regarding the healing period. Guidance should be provided by: CDC.

- Community partners are well-equipped to effectively provide information to MSM. CDC should not be the only messenger—they should turn to other partners to disseminate information. Guidance should be provided by: CDC and Partners.

- What has been learned from MSW should not be generalized to MSM. Guidance should be provided by: CDC and NIH.

- ❑ Information should be included on ulcerative disease, paying attention to the fact that in the US, the syphilis rates that exist are higher among MSM than among other populations. Guidance should be provided by: CDC and NIH.

While most members of this group agreed upon these issues, consensus was not sought or reached.

Discussion:

- It was noted that there was a great deal of discussion about the phrasing of the utility of circumcision in CDC's current document. The group thought that with existing evidence, it could be domestically phrased more positively, then followed by all of the qualifications. There was sentiment that the phraseology was too "boogy man" and was not helpful.

- Dr. (b)(6) responded that he thought many people were actually comfortable with what was already said, but thought there needed to be additional information. Although, there were some people who did not think this. However, he stressed that this group did not really attempt to reach consensus.

- It was noted that there was also another section in the fact sheet about subtypes, which said it was unknown. Given the three trials and three different subtypes, that paragraph could be eliminated. One point that maybe did not come out clearly, but which will be important in future decisions, is that if more observational studies are conducted in MSM from available data, if those studies replicate what is seen in the heterosexual trials, and the heterosexual observational data from Africa, it could affect the equipoise needed for a clinical trial in MSM. It seemed to this participant that from a research or information perspective, a high priority should be given to improving the quality and quantity of observational studies in order to understand the ranges of protection if any, as well as to make decisions about trials.

- Dr. (b)(6) concurred, adding that an important piece of that is that observational data should not merely be seen as leading toward an RCT. It really needs to be thought of in terms of helping to decide what information and policies to put in place.

- An inquiry was posed regarding whether, if men are tops only, there was sentiment that current data from the trials would be applicable to those men.

- Dr. (b)(6) responded that most of the discussion around that issue was that there are men who are tops only, or believe that they are tops only, but there are people who have a change of what they are as time goes on, and that there really is not enough data about the natural course of human sexuality to make a strong recommendation to people because that may lead to disinhibition or they may find themselves in this situation.

- A group member indicated that another point made was that the physiologic conditions in the rectum differ from those in the vagina. Different pH and rectal secretions could contain different amounts of HIV presented in different ways. Therefore, automatic assumptions cannot be made that these environments would be the same. There could be an overwhelming threshold effect that in people with higher levels of rectal secretions, that might obviate the benefit. Trauma is also an issue.

- Dr. (b)(6) responded that he thought there was agreement that male circumcision should be part of an overall risk reduction strategy as opposed to any recommendation being individual.

Circumcision in Men Who have Sex with Women (MSW) in the US

(b)(6) **MD, MPH, Rapporteur**

(b)(6)

(b)(6)

Issues Raised

- A universal strategy is preferable to a targeted strategy in the US for MSW. This is in contrast to some of what was discussed by representatives who were from other countries who said that a more targeted strategy, based around race / ethnicity or other characteristics might work better in those contexts.

- It is important to clarify that the issue pertains to MSW currently or in the future. The age range should include adolescents *before* they initiate intercourse.

- In the US, given the incidence and prevalence of HIV and other STDs, it is critical to focus not only on HIV, but also on the broader range of outcomes, including STDs and potentially UTI with regard to male circumcision.

- There was sentiment that there is lack of equipoise for a US trial of male circumcision among HIV negative MSW for HIV prevention in light of the data from the three trials.

- Tailored messaging is absolutely critical in the context even of a universal strategy (e.g., MSW, MSM, MSM and MSW, already circumcised MSW, race / ethnicity, HIV positive versus HIV negative). There should be companion messages for HIV positive MSW.

- As this goes forward, do not lose the other HIV prevention messages. This is part of a package of messages. Particularly in the US setting, in which the majority of men are already circumcised, this is an important addition, but it should not overwhelm the other messages.

- There is a need to understand the benefit of male circumcision to women, and to be able to message that as well.

- Discussions should include a broad range of stakeholders, as was mentioned by the other two groups (e.g., lay / professional communities, urologists, other providers, women's groups, et cetera).

- There are messaging challenges, particularly around partial protection of male circumcision, attempting to message in the context of pre-existing distrust in many communities, and the importance of not stigmatizing men who choose to remain uncircumcised.

- There is a potential to use male genital hygiene as an entry point for this conversation, and to frame it more broadly, particularly in certain communities. The point was made that while for most adolescent girls, as they go through menarche, there is a discussion of hygiene. However, there is not necessarily a discussion entry point for boys and for many boys the hygiene conversation never occurs.

- The issue was raised of the effect of male circumcision interventions on the design and cost of future intervention trials.

Data Needs

- A key data need is the impact of male circumcision on HIV incidence in female partners of HIV positive MSW. There was a general sense that there is not a need for additional trials in the US concerning the impact of male circumcision in HIV negative men. While they initially discussed potential design options, they came around to the notion that perhaps the next step for this is for NIH, in collaboration with CDC and others, including Gates, should convene a group to consult on trial design options, particularly in light of the data from the Gates trial that was terminated. Their feeling was that this would not be a trial or study that would be limited to the US. On the contrary, this would be a multi-center, international trial. Additional data should be collected by / from: CDC, NIH lead, and Gates.

- Data are also needed on the impact of male circumcision on a range of issues, particularly disinhibition and the impact on the discharge syndromes (e.g., CT / GC), given that the international data of the impact of male circumcision on GUD are pretty substantial. Although there was some disagreement on this, in general the sense was that it would not be a great use of resources to focus on male circumcision and GUD one more time. The sense was that there should be a consultation to develop studies in the context of relevant existing data. Rather than trying to design these studies in a two-hour session, there should be a separate discussion about how these trials should be designed in the context of doing that broader review of the existing literature. This was also mentioned by the other groups. Additional data should be collected by / from: CDC jointly with NIH.

- There was a strong sense of need for data on a range of implementation issues and impact (e.g., messaging, acceptability, uptake, safety, quality assurance, disinhibition, cost). There was a great deal of discussion around the issue of communication and social and behavioral issues, particularly with respect to: who trusted messengers might be, what message content should include, framing, preferred provider, provider attitudes, et cetera. Here the group discussed the potential for multi-center demonstration projects tied to well-designed evaluation and data collection instruments. Additional data should be collected by / from: CDC lead, State and Local Health Departments, and Community and Professional Stakeholders.

- This group believed that it would also be useful to examine the potential to obtain additional data on male circumcision through existing databases or large on-going trials, either through databases that already have variables on male circumcise in them or through the addition of male circumcision variables to existing databases or to large on-going trials. With respect to on-going trials, the point was made that in large intervention trials into the future, it will be very important to be able to analyze the data without the potential for confounding or to address the potential for confounding if raised by circumcision status. Additional data should be collected by / from: CDC jointly with NIH, and HRSA.

- ❑ Tied to those data needs was the notion that limited existing data suggest that self-reports of circumcision status are not necessarily reliable and probably partner reports of circumcision status are even worse. If all of these data are going to be collected, it probably would make sense to examine the validity of self-report and partner reported in order to better understand how useful the data are. If necessary, methodologic work should also be done in order to get a better handle on what it is that is being recording. Additional data should be collected by / from: CDC and NIAID.

- ❑ More data are needed on cost and who will pay. Additional data should be collected by / from: CDC and Insurers.

Policy

- ❑ This group believed strongly that there are enough data pertaining to male circumcision as an additional HIV / SDT prevention tool for HIV negative MSW. The guidance around this needs to be developed. This group also believed strongly that this guidance must be crafted in the context of other key prevention strategies (e.g., risk reduction counseling, condoms, HIV testing, et cetera). Guidance should be provided by: CDC, Community and Professional Stakeholders, and HRSA.

- ❑ Clear messaging is important for a range of issues, particularly with respect to partial protection, use in the context of non-vaginal sex (e.g., oral and anal), and being very clear about what this means for HIV infected MSW. Guidance should be provided by: CDC, Community and Professional Stakeholders, and HRSA.

- ❑ Guidance is needed concerning reimbursement and should be focused to ensure equal access across states to male circumcision and other prevention methods. Guidance should be provided by: CDC, Community and Professional Stakeholders, and HRSA.

- ❑ Guidance is needed on how to monitor the impact of these programs and policies as this effort moves forward. This should be considered up front. Guidance should be provided by: CDC, Community and Professional Stakeholders, and HRSA.

Discussion:

- It was suggested that if observational studies were going to be conducted on MSW, it would be interesting to collect more information on anal sex to determine if there is protection in the women with male circumcision. It is assumed that a rectum is the same in both genders, so it could be informative for MSM.

- It was noted that this thought process was raised in other groups.

Summary Comments / Adjournment

(b)(6) **MD**
(b)(6)
Division of HIV / AIDS Prevention
Centers for Disease Control and Prevention

Dr. (b)(6) thanked everyone for their attendance and input. Clearly, the issues are not at all clear. He pointed out that a little over 20 years ago, the first truly effective intervention for preventing HIV transmission was developed, which was HIV antibody tests. The blood supply is now clean. Currently, there is a 1 in 2 million risk for HIV transmission through the blood supply in the US. Perinatal transmission is down over 95%, with only 140 cases last year. These are incredible success stories; however, neither was a major component of the HIV epidemic. Now they are talking about an intervention, male circumcision, with a 50% to 60% or more efficacy in reducing HIV transmission. They should be thrilled, but that was not the sense he got in the room. He thought the reason was because they were still nibbling at the edges. Heterosexual transmission in men in the US is about 3,000 to 5,000 cases. In the context of the total epidemic, that is not a lot. That can be reduced, so he was interested to hear the recommendation coming out of the MSW group. However, the problem is that the heart of the epidemic is MSM and it is not clear at all at this point whether male circumcision will help. Even for heterosexuals, the benefits of male circumcision are not as cut and dried as screening the blood supply or perinatal transmission prevention. He reiterated that CDC was grateful for their hard thinking, input, and willingness to help shape policy about male circumcision and HIV transmission for the US, stressing that those in attendance were the world's experts on this topic. This is about issues that are broader than HIV. One pearl Dr. (b)(6) said he was taking away from this gathering was that, because perinatal transmission has become such a small component of the epidemic, they no longer have the opportunity to interact with pediatricians. He found their perspective on the matter during this meeting to be enjoyable and refreshing.

In terms of how they would organize within the Division of HIV / AIDS around the outcome of this meeting, a summary report of the meeting will be disseminated to the consultants. There likely will be an *MMWR* pertaining to male circumcision, but it will probably go beyond the issue of HIV. In addition, the division will work to revise the fact sheets. They will convene communications and data needs workgroups as well. Communications clearly came across as a critical piece, as did additional data needs. Many questions remain, for example: Are men who are infected heterosexually disportionately uncircumcised? There are some questions CDC can ask pretty quickly in some on-going studies to obtain some additional observational data that will be valuable. They can also help work to coordinate publication of the observational data. In terms of the perinatal transmission, they certainly can work with AHRQ and AAP. With respect to making recommendations, CDC heard clearly from the MSW breakout group that their answer was that recommendations should be made. However, given that this meeting was not a FACA approved consultation, they were merely seeking individual input and could not come to consensus or make recommendations. However, there are other powers at CDC beyond the division. CDC is going to have to make a statement about male circumcision at some level. They cannot ignore the African trials, given that they do have relevance. The STD Division is interested in this issue as well. With respect to the African

trials, there are probably some obvious statements CDC can make at this point about the relevance to heterosexual transmission; however, other statements beyond that are much more difficult and require a lot more thought.

In conclusion, Dr. (b)(6) thanked all of those who orchestrated the meeting, noting that because consultations such as this one were not a major piece of what the HIV / AIDS Division has been doing and staffing is limited, this was a major feat.

Discussion:

- A participant reiterated that in the MSM group, there was sentiment that self-report is not necessarily accurate and that it could be important to validate self-report with physical examination.

- It was noted that surgical procedures have never been used for prevention of infectious disease, HIV or otherwise. Given that this is a novel innovation for public health, they must recognize that there is bound to be a steep learning curve.

- Reflecting on major interventions in public health, a participant noted that it had been a long time if ever that three RCTs were stopped early because of efficacy. In terms of population attributable risk, this may be around the edges, but they should be very clear as these messages go out that this is a major breakthrough both in terms of the consistency of the results in outstandingly conducted trials and the estimated impact of this intervention. Therefore, moving to the next step in terms of additional research and policy guidance is absolutely essential.

- In pediatrics, in terms of counseling patients, the use of the word "recommendations" is not necessary. The patients merely need to be presented with the benefits and risks and then allowed to make up their own minds.

- From a global perspective, a participant stressed that this consultation was significant because, since WHO put out their recommendations on March 28, the US was the first country to hold this kind of consultation to consider what it means for this country in this context. In terms of what CDC should do as a next step, it is important to present and acknowledge the evidence, as well as state what it means in this context. If it means nothing in this context, then CDC must say that as well. That does not take away from what the evidence actually says.

- To the extent that a recommendation is made and however it is framed, funding implications and wherewithal must be taken into account or a recommendation carries very little weight. That is, recommendations must be issued and contextualized in terms of their implications for funding and other actions that would need to be taken for them to have meaning in terms of equitable access.

- Dr. (b)(6) replied that recommendations could drive funding. Having been a co-author on the most widely ignored CDC recommendations ever made, he pointed out that currently when CDC makes recommendations, they aggressively implement them. If they do not believe an issue is something CDC needs to push, then it is not something they need to be doing because they have many other pressing issues to address.

- A participant reported that when she told her 86 year old mother she was attending this conference, her mother said that as a practicing Christian, she wanted to point out that there is discussion in the Bible about circumcision, which states that it cannot be the only thing—there must be more. It cannot stand alone.

- Dr. (b)(6) encouraged consultants to submit additional thoughts, ideas, suggestions, et cetera to circumcision@cdc.gov.

With no further business or comments posed, the meeting was officially adjourned.