Civil Society call to discuss early stoppage of adult male circumcision trials in Uganda (Rakai) and Kenya (Kisumu)

Thursday, December 14, 2006 - 11:00-12:00 EST (USA)

This call was organized by the AIDS Vaccine Advocacy Coalition (AVAC) in collaboration with the Community HIV/AIDS Mobilization Project (CHAMP) and the Global Campaign for Microbicides. Over 40 participants from various organizations internationally joined the call. These organizations included civil society, researchers, funders and implementers.

Maria Wawer from Johns Hopkins University and the PI from the Rakai trial was on the call to provide background on the male circumcision trials:

- When the male circumcision trial in Orange Farm (South Africa) was stopped earlier this year there was talk about stopping the other circumcision trials. Ultimately it was decided that the Ugandan and Kenyan trials should continue (as often other trials are stopped and don't show positive findings). But they did decide to add an additional interim review by the DSMB which took place Tuesday, December 12, 2006.

- After the DSMB reviewed the data they decided to end randomization in both trials and offer circumcision to the control arms. Both trials showed statistically significant results: Kisumu showed 53% efficacy and Rakai showed 48% efficacy. The Orange Farm study showed 60% efficacy. The confidence intervals of these results overlap which suggests that the data is generalizable.

- The three trials were done in different age populations (Rakai 15-49, Orange Farm 18-24, Kisumu 18-24), used different circumcision methods (both the forceps-guided and sleeve method were used and both are internationally recognized surgical methods), studied different geographic populations and recruited trial participants had varying risk profiles. These considerations further increase the strength of the data as efficacy is consistent across the trials.

- The recent data is also consistent with previous observational data (which is quite rare as observational data generally tends to overemphasize results/relationships).

- The data appears to be generalizable across populations and with varying techniques and presumably creates long-term protection. Both trials are looking to continue individual participant follow up as well as review HIV incidence at a community level over the next several years.

Maria then discussed some of the challenges now that we have these positive findings, including the potential for risk compensation/behavioral disinhibition?

In the Rakai trial there was little evidence of risk compensation in those participants who were circumcised. Maria emphasized that we need to be remember that even if there was no disinhibition in the trial setting, it does not necessarily predict actual post-trial experience – we

need to evaluate what happens in the 'real world' where people aren't constantly being bombarded with the same level of motivation for risk reduction as one gets in a trial. And keep in mind that a 25-50% increase in the number of partners could negate the protective effect of circumcision.

Male circumcision is a minor surgery but highly trained and experience personnel are needed to carry it out. It's going to be very important that countries take this seriously and realize that you can't just roll it out. Quality control issues are critical. There's been some discussion of creating centers of excellence where well-trained practitioners could teach others and make subsidiary clinics. Could also train and equip personnel with mobile vans and make sure there is availability of post-op care.

Male circumcision is likely to be a very cost-effective prevention strategy as it is a one-time procedure (assuming biological effect is for life). If we can maintain necessary behavior-related prevention strategies then circumcision could be effective at decreasing incidence.

What about women?

There is a fourth circumcision trial that is currently ongoing in Rakai, Uganda. While the other three studies (that have all been stopped) have looked at the protective effect of circumcision on HIV acquisition by HIV-uninfected men, this fourth trial is looking to see if circumcising HIV-infected men will have any protective effect for their female HIV-uninfected partners.

This Gates-funded trial has enrolled over 800 HIV-infected men. The first question is safety. Are there more post-op wound infections in HIV-infected men? This data is not blinded and so far post-op healing in HIV-infected participants has been the same as HIV-uninfected. Note that the trial screened out sick men - needed CD4 count greater than 350.

Not only should this trial give some indication of potential protective benefit for HIV-uninfected female partners, but if circumcision shows to be safe for HIV-infected men then they can be included in circumcision programs. This would help prevent circumcision (or lack thereof) from becoming a stigma marker and could also help dispel any notions that circumcision indicates negative HIV status.

For the female participants in the study, researchers are looking to see if the HIV-infected male partners are circumcised is there an increased risk of HIV infection due to post-op issues, healing, possible infections, etc? And if circumcising the male partners is safe for women, might it also be protective?

The study is also looking at female partners of both positive and negative men to see if there is an effect on acquisition of other STIs, including HPV.

Researchers are blinded to women's data but presumably incidence hasn't risen as trials are still ongoing (and have not been stopped due to safety issues).

Data from this trial should be available sometime before the end of 2008. Trial enrollment was slower than initially projected as it has proved challenging to find couples with an HIV-infected male and HIV-uninfected female.

The caveat for the results of all these studies is that results come out of a clinical trial context with trained staff, sterile surgical instruments, rigorous counseling and messaging.

Question from Judy Auerbach, San Francisco AIDS Foundation:
- What do we know about the type of intercourse involved? Anal/vaginal? How do we talk about male circumcision related to particular sex acts?
- Male circumcision is a religious marker in at least two major religions, how transferable is it where religious divides are very well pronounced?

Maria comment:
In the Rakai population, intercourse is largely penile-vaginal. Anal intercourse is very rare (as reported by participants). Reports from the local STD clinic confirm this as there are not many cases of anal/rectal trauma or STDs seen, which would be an indicator of more prevalent anal intercourse. Believe it's the same for Kisumu but can't speak for them.

There will be additional trials needed to determine if male circumcision has a protective effect for MSM.

As for the cultural/religious significance, it really depends on the population and is hard to generalize. Pre-trial focus groups showed a rather pragmatic response for those who were not circumcised, and for whom there was no religious or cultural significance. Response was largely that if there's a health benefit - why not?

Surveys across ten African countries show rates of acceptance between 30-80%. As circumcision is rolled out, if the experience is good then presumably it will continue to be more acceptable.

Carly Williams, NIAID comment:
A prospective study among MSM in California showed a 30% reduction in HIV acquisition in circumcised men. From what we know right now circumcision is relevant for HIV acquisition through the penis. Related to acceptability, if there is no cultural significance of circumcision then most men surveyed said that cost and pain were their top considerations. Thus far acceptability studies have been conducted in Africa but little data exists from Asia.

Question from Chris Collins:
What do we have to do now with this news to make sure that the service is delivered as part of a package? How do we message that for male circumcision to be an effective prevention strategy that it must come with a high-quality and comprehensive prevention package?

Maria comment:
We must pound the message that male circumcision can be 50% effective at preventing HIV infection ***if*** it's combined with a comprehensive prevention package. We need to be persistent in communicating this in the discussions about male circumcision and do what we can to help

governments and health ministries to implement circumcision programs with other HIV prevention. This can't be a simple message.

Melanie from NIAID comment:
WHO has been conducting meetings and discussions with lots of people involved in funding HIV prevention programs, and they're going to be reviewing the trial results and coming out with guidance. It's important to consider how circumcision might be included in prevention packages and what the messaging is going to be. Need to plan what the response will be and how the messaging will go from country to country. Male circumcision rollout needs to be integrated into existing HIV prevention programs.

WHO is meeting in January to discuss male circumcision implementation and guidelines will be released shortly thereafter.

Maria comment:
We also need to be sure to address the issue of unqualified practitioners who will try to drum up business. This a double threat as not only could they potentially do it incorrectly but it will also be performed as a standalone procedure and not as part of a comprehensive prevention package.

Part of the messaging strategy needs to include a word of caution about unqualified practitioners and also to give advice about how someone can find the appropriate practitioner. We need to promote intelligent consumers. And we must also educate men and their families about what a good circumcision is - what it should look like, what you should expect and what a provider should have as qualifications.

As advocates we need to work with governments and NGOs and have the courage to say what is and isn't acceptable. In some places there is a lack of political will to tangle with traditional practitioners but we must work carefully with them. Traditional practitioners can do damage if we don't work with them in our programs as they carry a lot of weight in many of the communities we'll be looking to reach.

Question from Judy Auerbach:
What does anyone think of the implications these data have for other prevention studies?

Carly comment:
NIAID will be assessing that and it is clear that we need to work with other US government partners in the field to make sure we're making services available. At this time NIAID is not going to require that their trials pay for the circumcision of all the men in trials.

We will look to facilitate access or give referral to services where they exist but will not require that sites provide or pay for male circumcision for trial participants.

PEPFAR will make efforts to improve services and work with country teams and programs to increase the availability of services.

Mitchell Warren, AVAC comment:

It's interesting how all this fits together as positive results for male circumcision presents a challenge for other prevention research beyond the issue of access. As circumcision is rolled out incidence should go down which makes prevention research trials longer and more expensive. While it's a welcomed challenge, it's nonetheless a challenge we need to understand and plan for.

Lori Heise, Global Campaign for Microbicides comment:
One of the things that GCM is doing is convening a working group to discuss the issue of ethics related to multiple prevention efforts and what it means for other trials. The issue of what should be provided for prevention research trial participants as various prevention technologies show efficacy down the line needs to be more thoroughly examined. The working group will address these issues that are important for all prevention technologies.

Mitchell question:
Is there a specific plan for the publication of the data from the trials?

Maria comment:
Right now there are plans for simultaneous publication (of the data from both trials) as soon as possible, possibly in the Lancet. We're looking to potentially submit something in January. The issue of open access was discussed and it was decided that Lancet was better than NEJM. While PLoS would be the best for open access, it's still a young journal and thus doesn't carry the same global credibility that the Lancet does.

Question from Anne-Marie Duliege:
Do we think that the result might be different in areas with lower prevalence of HIV and what will the implications be for these areas with lower prevalence?

Maria comment:
The individual protective effect should be the same but the cost effectiveness of circumcision will vary.

In Rakai it was calculated that it would take approximately 40 male circumcisions for each HIV infection averted. In areas with lower prevalence it will 'cost' more circumcisions to avert each HIV infection and will thereby be less cost effective. The opposite is true for areas with higher prevalence.

Cost effectiveness will vary and this will likely have an effect on government resource allocations. And if the current trial shows male circumcision to be protective for women then the cost effectiveness will go up.

David Stanton, USAID comment:
This is the first in a series of technologies that we'll have to deal with and we'll have to watch how people react. Last summer, Bob Bailey looked at behavior changes and that an increase in risk-taking behaviors in those who were circumcised was a worry but not inevitable.

Worthwhile to point out that men have never known its protective effect before now and we could see a resulting risk effect. The situation needs to be monitored closely and we need to keep pounding the message that circumcision is effective as part of a package.

Also, health education must be provided community-wide, not just for the men who are getting the procedure. Women in the community need to know that circumcision is not 100% protective and these additional messages will be mutually reinforcing.

Judy Auerbach question:
To what extent has there been discussion about circumcising young boys?

Melanie comment:
WHO is going to address first adult males and the fact that benefit occurs when men become sexually active. However, the training manual that's been put together does include infant and pediatric guidelines for circumcision although it remains the parents' decision.

The health benefit is seen more rapidly when circumcision happens in adulthood or just before sexual debut. Article by Williams et. al. (in PLoS Medicine) examines the potential impact of male circumcision (if performed in adults) and that the health benefit is seen within the first decade (as opposed to a program in infants where health benefit not shown until sexual debut, well over a decade away).

The age at which males are circumcised varies widely throughout Africa.

Mitchell closing comment:
You can find the Williams article and other related information on a special webpage devoted to male circumcision for HIV prevention. It is linked from the AVAC website as well as AVAC's AIDS Vaccine Clearinghouse at http://aidsvaccineclearinghouse.org/MC/index.html.

At the end of the day it's about expanding all prevention options.

Also note that AVAC has released a pre-publication draft of a document that describes many of these issues related to the male circumcision studies, rollout and related advocacy. Please review and comment on it as we work towards a final draft for publication in the beginning of 2007.

AVAC and its partners are very grateful to Maria for taking the time to discuss this issue with civil society, and we look forward to future discussions and collaboration to ensure that we can translate research results into policy recommendations and ultimately into public health impact. And many thanks to Deirdre Grant, AVAC's Project Assistant for preparing these notes.