



Advocacy to accelerate ethical research & global delivery of AIDS vaccines and other new prevention technologies

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AVAC Position on Research Priorities for Male Circumcision

This background paper is designed to help advocates and community educators understand the ramifications of findings from the ongoing studies of male circumcision for HIV prevention and to anticipate and address the opportunities and challenges which emerge for additional research efforts. It is part of AVAC's "Anticipating and Understanding Results" series, which provides timely analysis of trials of AIDS vaccines and other new prevention technologies. For other publications in this series, visit www.avac.org and for more information on male circumcision, visit <http://www.aidsvaccineclearinghouse.org/MC>.

PRIORITY 1) Research on efficacy of circumcision in HIV-positive men as a tool for reducing male-to-female transmission

Research plans to explore risks and benefits for women with circumcised, HIV-positive male partners must be developed, funded and executed concurrently with implementation of male circumcision programs.

Critical questions include:

- *Is there an increased risk of male-to-female transmission following male circumcision?*
- *If yes, is this risk due to the circumcision itself or due to behavioral factors or both?*
- *What is the effect (if any) of the healing period on the risk of HIV transmission?*
- *Does this risk change over time?*
- *What is the relationship between the viral load of circumcised men and likelihood of transmitting?*
- *Is there a protective benefit in terms of reduced risk of HIV acquisition among women? If so, at what point after the surgery is performed does this emerge?*

Rationale:

The data to date on the safety of male circumcision in HIV-positive men, and its efficacy in reducing male-to-female transmission during vaginal sex are incomplete and indeterminate. The Bill & Melinda Gates Foundation-funded trial in Rakai district, Uganda halted enrollment in December 2006. The reason for this development has been inaccurately reported in several media outlets. The critical points regarding this development are:

- Following the finding of significant benefit in the circumcision trials enrolling HIV-negative men, investigators requested an unscheduled Data and Safety Monitoring Board

(DSMB) review of the data from the Rakai trial of HIV-positive men, which had enrolled men who were aware of their status and those who declined to learn their test results. Given that the trial of HIV-negative men was unblinded, continuation of the study of HIV-positive men would, potentially, subject them to stigma and unwanted disclosure in that members of the community who were outside the trial but familiar with it might assume they were HIV positive; in some instances the men themselves were not aware of their serostatus.

- At the time of the review, the trial had not met its enrollment targets. After review of extant data in 12/06, the DSMB recommended that the trial halt enrollment because of concern that the trial would not be able to deliver a statistically significant result based on the numbers currently enrolled; follow up was continued of all men and women enrolled in the study.
- A second recommendation was to continue follow up through December 2008 to assess for the potential of increased risk of infection among women partners of HIV-positive, circumcised men. This recommendation was *not* the basis for halting enrollment. This recommendation was made based on non-statistically significant data and on a very small sample size, which accounted for one half of the Person Years of follow up that the study will be able to collect with the current pool of volunteers.

It is critical to further explore whether HIV-positive, circumcised men are more likely to transmit to their partners than their uncircumcised counterparts, particularly prior to complete wound healing, as well as to continue exploring the trial's original hypothesis that circumcision of HIV-positive men could reduce the risk of transmission to female partners via vaginal sex. It is equally important to convey that the current data are inconclusive in this regard.

Unlike the observational and cross-sectional studies of male circumcision in HIV-negative men which preceded the randomized trials, and which showed a significant association between male circumcision and reduced prevalence, the observational data on male circumcision as a strategy for reducing male-to-female transmission are highly variable.

Earlier, retrospective analysis of the Rakai Cohort that looked at factors associated with male-to-female transmission found the lowest rates of transmission among circumcised men with <50,000 copies/mL viral load. In this cohort, men who were circumcised and had higher viral loads were also less likely to transmit to their partners than their uncircumcised counterparts with comparable viral loads. Viral load data were collected from the male volunteers in the recent, randomized prospective trial to further investigate this effect. More information is needed on the impact of viral load on transmission of circumcised men to their female partners.

PRIORITY 2) Research on safety of male circumcision in HIV-positive men

Operational research is needed on the safety of male circumcision among HIV-positive men who may be immunocompromised or have <350 CD4 T cells and on related issues of relevance to both HIV-positive and HIV-negative men around wound healing – what are the risks at various timepoints after surgery; what determines when the protective benefit of male circumcision is fully realized, etc.

Rationale:

Additional research is needed to determine the safety of male circumcision among the general population of HIV-positive men. The data to date are indeterminate: Rakai trial enrolled men with >350 CD4 T cells who were clinically well. The men in the intervention arm (n = approximately 500) had comparable rates of adverse events to the HIV-negative men in the intervention arm (n=2472) of the companion study. Median time to wound healing was also the same in both HIV-positive and HIV-negative men. However there were a proportion of HIV-positive men who took a longer time to heal compared to the HIV-negative men. More data may come from the study if circumcision is resumed following a protocol revision which calls for more intensive counseling and post-operative follow up.

These data provide initial information but do not address the full range of safety issues which may arise in programmatic implementation. . In programmatic settings, HIV status or disease stage will not be known *a priori*. It is critical to understand whether male circumcision is safe for all HIV-positive men, and, if not, what determines when risks emerge. CD4 count is not always indicative of clinical health; nor is clinical health an indicator of a high CD4 cell count. Issues around safety of male circumcision for immunocompromised men must be more fully explored through operational research.

PRIORITY 3) Research on behavior pre- and post-circumcision

The study sites in Kenya and Uganda have sought and are likely to receive funding which will support follow up studies to gather additional behavioral data from volunteers in the study over time; this must be complemented by intensive research on behavior change (including condom use, rates of unprotected sex, sexual violence and coercion, numbers of partners and other measures) related to male circumcision carried out in the context of implementation.

Rationale:

The randomized controlled trials of male circumcision have gathered some information on risk behaviors pre- and post-circumcision, but this information does not provide an adequate understanding of the implications for programmatic rollout of MC.

Each trial had a different follow up schedule and a slightly different way of gathering behavioral data (e.g. asking about condom use at last sex, versus in last six months). In addition, each trial ended randomization prior to projected study closure, so there are at most two years of follow up data at this point on any of the men in these studies.

With that caveat, there were few significant differences in numbers of partners, condom use, unprotected sex acts, between male circumcision and control arm volunteers in any of the studies.

However, there are data which support close and careful follow up of possible behavior change in the implementation phase:

- In the Kenya trial, rates of condom use increased and numbers of partners and unprotected sex acts decreased from baseline in both control and intervention arm. The

decrease was *greater* in the control arm; there was less of a shift from baseline over all in the intervention arm.

- In the South African trial, all of the five reported sexual behavioral factors were higher in the intervention group than the control group at M4-M12, and four out of five were higher during the overall period of M3-M21. The only statistically significant difference was in mean number of sexual contacts which was higher among men in the intervention arm at M4-M12 and M13-M21.

These trials did not gather information on what motivated men to volunteer for the trial; what they believed about the protection conferred by the procedure (NOTE: while all men were counseled about the need for continuing to use other means of protection, the potential for volunteers developing a false sense of protection has been well-documented in other prevention research.)

PRIORITY 4) Additional research on the feasibility, acceptability and impact of performing male circumcision on different age groups

The most immediate impact of male circumcision will come from performing surgery on men who are sexually active or becoming sexually active; however there is a strong rationale for introducing neonatal circumcision, which does not require sutures, and involves a population (neonates and their mothers) which has more contact with health services than adult men. However there are few case studies or modeling efforts to date which explore the feasibility, acceptability (to parents, communities, traditional practitioners, etc) of targeting infants versus adolescents or adults. *Effort to address these questions should be systematically pursued and rapidly disseminated.*

PRIORITY 5) Research on the impact of male circumcision on risks of HIV transmission and acquisition in anal sex

Anal sex occurs in the context of both homosexual and heterosexual relationships. The absence of randomized controlled trial data on male circumcision and anal sex has caused confusion in communities of gay men; the absence of data on male circumcision and anal sex in the heterosexual context means that we may not be able to anticipate the true protective effect of male circumcision in many populations where anal sex is practiced as a form of birth control, maintaining virginity, etc. Questions of wound healing, timing of any beneficial effect, and possibility for increased transmission during healing should all be addressed in this context as well.

There is an urgent need for research which explores the plausibility of a protective effect of male circumcision in the context of anal sex, including, potentially, trials in MSM communities. These studies are needed to help refine public health messages overall.

PRIORITY 6) Research on intersections between culture, traditional practice, individual identity, and male circumcision

The WHO/UNAIDS recommendations are likely to provide some recommendation regarding the need to engage with traditional practitioners. However additional advocacy for resources and careful program design will be needed to ensure that rollout proceeds in a way that provides

information on how medicalization of a traditional rite will impact cultural practices, assumptions and identities and, by the same token, how male circumcision programs can have a positive impact on gender roles and norms. At present, little is known about how male circumcision affects or changes men's sexual identities and sexual experience at the individual level and/or how these factors play into individual decisions to seek circumcision. Gathering this information is critical as it will help inform communications campaigns that address assumptions, beliefs and desires underlying uptake of male circumcision. These issues will differ by community, sexual orientation, economic status and many other factors, and therefore must be addressed in multiple, localized projects. It will also be important to collect information on strategies for collaborating with traditional practitioners who might be trained to perform the surgery in a way that meets the criteria for reduction of HIV acquisition—i.e. removing an adequate amount of foreskin with safe, sterile instruments and careful counseling on post-operative abstinence and/or condom use until wound healing.

PRIORITY 6) Operational research to gather information on human rights, HIV status and gender in the context of male circumcision programs

The WHO/UNAIDS recommendations state that:

- Male circumcision has a protective benefit for HIV-negative men
- Countries consider targeting men at high risk for HIV as priority audiences for circumcision messages and programs
- There are no data supporting a recommendation for HIV-positive men
- HIV testing should be recommended as part of the male circumcision process but that knowledge of serostatus should not be a pre-requisite for receiving circumcision.

These recommendations raise a variety of questions for program designers.

Experience with rollout of other interventions such as hepatitis B vaccine and PMTCT has shown that explicit targeting of high-risk populations is a relatively ineffective way to deliver services, as people may avoid them in order to avoid being labeled as “high-risk”. Targeting male circumcision towards high-risk individuals could have similar consequences and is likely to be less effective than generalized programs with clear messages about the benefits and limitations of male circumcision in reducing risk of HIV acquisition.

In addition to exercising caution in targeting specific high-risk groups, program designers should also exercise caution in messaging regarding male circumcision and knowledge of HIV serostatus. The recommendations state that knowledge of serostatus should not be a prerequisite for services; they also state that services should be targeted at HIV-negative men. Explicit targeting of this kind could lead to a false assumption that circumcision is a marker of HIV-negative status, undermining women's efforts to negotiate condom use as well as general public health campaigns around HIV prevention. It could also lead HIV-positive men to seek male circumcision from unlicensed practitioners, placing them—and, potentially, their sexual partners and perhaps the unlicensed practitioners—at greater risk of HIV infection.

By the same token, testing without knowledge of serostatus in settings which may have limited capacity for follow up around wound healing and adverse events could lead to circumcision of

HIV-positive men who are at an increased risk of infecting their partners. Granted, these data are inconclusive and, at best, suggestive. But can the potential for increasing women's risk be set aside? Or the unknowns around safety for immunocompromised HIV-positive men?

Finally, in the context of increasingly widespread "routine counseling and testing" there is a potential that the likely WHO recommendation against requiring knowledge of HIV status will give way to a de facto policy of routine testing prior to surgery.

Each of these scenarios has the potential to compromise human rights and the overall efficacy of the intervention.

It is therefore critical that community participation in program design, careful monitoring of roll out, and widespread dissemination of best practices are essential and be built into every male circumcision program.

About AVAC: Founded in 1995, the AIDS Vaccine Advocacy Coalition (AVAC) is a non-profit, community- and consumer-based organization that uses public education, policy analysis, advocacy and community mobilization to accelerate the ethical development and global delivery of AIDS vaccines and other prevention options. AVAC's report on understanding the results of the male circumcision trials as well as a more detailed statement on research priorities for male circumcision and advocacy fact sheets for civil society in the US and in sub-Saharan Africa are available at <http://www.aidsvaccineclearinghouse.org/MC>. For more information, please contact us at avac@avac.org, www.avac.org and +1-212-367-1279.