

A NEW WAY TO PROTECT AGAINST HIV?

*Understanding the Results of Male Circumcision Studies
for HIV Prevention*

A PUBLICATION FROM THE AIDS VACCINE ADVOCACY COALITION'S
ANTICIPATING AND UNDERSTANDING RESULTS SERIES
SEPTEMBER 2007 UPDATED EDITION





A NEW WAY TO PROTECT AGAINST HIV? UNDERSTANDING THE RESULTS OF MALE CIRCUMCISION STUDIES FOR HIV PREVENTION

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This brochure is designed to help prevention advocates understand the ramifications of findings from studies of male circumcision for HIV prevention, and to explore the opportunities and challenges associated with implementation. 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 avac.org/publications.htm#series.

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A PIVOTAL MOMENT IN THE SEARCH FOR A NEW WAY TO PROTECT AGAINST HIV

In December 2006, new evidence from clinical trials confirmed male circumcision as the first new biomedical HIV-prevention strategy in over a decade.¹

This announcement brought exciting opportunities as well as challenges. Based on data from three trials, it appears that male circumcision reduces men's risk of HIV infection during vaginal sex by roughly 50%. Even though the rates of protection may not be as high outside of the controlled environment of a clinical trial, this is still a striking finding.

Adding the offer of safe, sterile male circumcision to existing HIV-prevention programs could avert many infections and save many lives. These programs could also provide a new way to reach men and adolescent boys who are frequently under-represented in health clinics and HIV-prevention programs.

HIV-prevention advocates have a very important role to play in the rollout of male circumcision at the global, national and local levels. Two specific priorities for this work are:

- 1) To ensure that male circumcision is made available in programs that are staffed by trained personnel with the necessary supplies for performing safe, sterile, and confidential procedures.
- 2) To ensure that these programs offer male circumcision *in addition to*, and not as a substitute for, other tools for risk reduction including counseling, male and female condoms, clean needles, and harm-reduction information.

Adding safe, sterile male circumcision to comprehensive HIV-prevention programs could save many lives.

In March 2007, WHO/UNAIDS issued *New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications*.² This document emphasizes that swift and urgent action is needed to realize the benefits of this newly-identified intervention.

Rollout of male circumcision requires work in many quarters: human resources, commodities procurement, communications, training, and technical assistance for governments and health ministries.

WHO and UNAIDS should be fully funded to provide necessary leadership and technical assistance. It is critical that these and other normative agencies continue the important efforts to provide technical assistance tools for countries considering introduction or expansion of male circumcision programs to reduce the risk of HIV infection.

As important as these steps are, they are not sufficient. Neither WHO nor UNAIDS are implementers and the world has already witnessed the failure of funders and implementing groups to meet the “3 by 5” target that these groups set for treatment access, which aimed for

3 million individuals on antiretroviral treatment worldwide by 2005.

Operational research is needed, as is leadership from developing countries.

Simply put, guidance alone is not enough. Operational research is needed, as is leadership from developing countries and funding

for health programs to ensure that male circumcision is introduced in addition to, and not instead of, other interventions.

Research and dialogue are also needed to explore the feasibility of rolling out infant circumcision. This approach will not show immediate benefits in terms of HIV incidence but could be a highly cost-effective implementation strategy over the long term.

¹ The US Food and Drug Administration approved the female condom for sale in the US in 1993; in 1994 AZT was identified as an effective means of preventing mother-to-child transmission of HIV. Male condoms, clean needles, blood bank screening, post-exposure prophylaxis and universal precautions for health care workers had been previously identified.

² Full text available at <http://aidsvaccineclearinghouse.org/MC>

Box 1: THE KEY POINTS

- Three clinical trials in sub-Saharan Africa have shown that circumcision reduces men’s risk of HIV infection during vaginal sex by approximately 50 percent. Men in these studies received condoms, STD diagnosis and treatment, and HIV counseling.
- Only one trial to date has studied the impact of male-to-female transmission among HIV-positive, circumcised men. The data from this trial are indeterminate. There is a possible finding that circumcision of male partners increases women’s risk of acquiring HIV. This risk may be related to resuming sex before wound healing. However more information is needed, as none of these findings have been confirmed.
- Based on the data from the trials in HIV-negative men, there is a strong rationale for rolling out male circumcision to complement current effective HIV-prevention strategies like condoms, clean needles, and behavior modification. These programs must stress what is known and what is not known about male circumcision with particular emphasis on impact on women in a predominantly heterosexual epidemic.
- Male circumcision must not replace or divert resources from any proven prevention method.
- There are no randomized clinical trial data on the impact of male circumcision among men who have sex with men.
- Urgent, coordinated, well-funded action will be needed to translate these results into the real world, where shortages of human resources and medical commodities present significant challenges.
- Male circumcision represents an exciting opportunity to reach adolescent boys and young men. These benefits will be offset if the intervention is not provided in safe, sterile, and confidential settings as part of a comprehensive package of services and information related to HIV/AIDS and health.

AVAC is committed to working with partners to advocate for new resources to support programs that follow WHO/UNAIDS recommendations and address local community concerns.

WHAT NEEDS TO BE DONE?

To be effective, rollout of male circumcision programs should achieve the following five overarching goals:

- Male circumcision must be offered in addition to, not instead of, the full array of proven HIV-prevention strategies.
- Male circumcision must be offered in programs that clearly explain the benefits and limitations of the procedure and what is known and unknown about protection for women and men who have sex with men.
- Male circumcision must be offered in appropriately-staffed programs: a well-trained medical aide can perform the procedure as well as a surgeon provided he has adequate supplies of essential commodities.
- Programs offering male circumcision must also contain clear culture- and context-specific messages that counteract changes in risk behavior that might follow the procedure.
- Programs offering male circumcision must be sensitive to the different meanings of the procedure, delineating its use as a strategy for HIV risk reduction separate from its uses as marker of religious or tribal affiliation and from the dangerous and wholly unrelated practice of female circumcision.

There are significant barriers to achieving these goals. To overcome them, funders, health ministers, program managers, advocates and other stakeholders will need to:

Anticipate and address human resources and infrastructure needs

The slow progress of rollout of antiretroviral therapy, lack of services to prevent parent-to-child transmission, and abysmal shortages of male and female condoms worldwide are all stark reminders of how the world has failed to make good on providing access to proven interventions.

As with the services listed above, male circumcision will be affected by gaps in funding and staffing of health care systems in the developing world. Without trained staff and supplies, male circumcision will not be safe and its efficacy will be severely compromised.

Developing countries must take the lead on this issue. Ministries of health should develop rollout plans that allocate new resources to male circumcision and make provisions for cadres of trained service-providers including medical officers and aides, given the extreme shortage of surgeons in virtually all developing countries.

In many instances, these plans will require financial and technical assistance. Donors and normative agencies like WHO and UNAIDS have begun to play this role and should continue with expanded financial support and recognition of this issue as a top priority for 2007 and beyond.

Male circumcision must be offered in programs which clearly explain the benefits and limitations of the procedure.

Create and execute operational research agenda(s)

An efficacy finding from a clinical trial (or even three clinical trials) does not mean that all the questions about a procedure have been answered.

Operational research is needed to learn more about best practices for male circumcision as it is being rolled out. Operational research answers questions about how to design effective programs in different settings. AVAC has created a separate scientific position paper that details some of the critical open questions that must be considered as rollout moves forward. This is available at <http://aidsvaccineclearinghouse.org/MC>.

The following are some of the issues to research:

1. **Effective strategies for conveying complex messages about male circumcision**
 - Male circumcision is partially protective for HIV-negative men having vaginal sex with women. It may increase risk of male-to-female transmission among HIV-positive men—particularly if men resume sex before the wound is completely healed. Programs will not necessarily require HIV testing prior to surgery. It is therefore essential that men and, where possible, their partners receive effective counseling around abstaining from sexual intercourse until the

wound is fully healed. It is essential that programs develop clear and accurate approaches to addressing the current state of knowledge on male circumcision, in order to reduce potential stigmatization of uncircumcised men, while also minimizing risks to sexual partners. More information is also needed on safety of the procedure in HIV-positive men, particularly those who may be immunocompromised.

2. Best practices for integrating male circumcision services with existing HIV-prevention programs and messages

- From the community and individual perspective: How can male circumcision be positioned as an *additional* strategy rather than a replacement for male and female condoms and other risk-reduction techniques?
- From the provider/program perspective: What resources are needed to add male circumcision to clinic services? For HIV-counseling centers and other points of service that may provide information about male circumcision, what are the best approaches to communicating with staff who are performing the procedure and follow-up for adverse events? Who should perform male circumcision and how should they be trained and monitored?
- From the policymaker perspective: How do countries evaluate whether to add male circumcision to their preventive offerings? What are optimal strategies for phased rollout in different settings?

3. Changes in risk perception or behavior in circumcised men and their partners

The benefits of male circumcision could be offset by changes in risk-taking behavior if circumcised men and/or their partners assume that male circumcision provides full protection against HIV. Introduction of male circumcision therefore has to take place in the context of campaigns that reinforce the limitations (as well as the benefits) of male circumcision as an HIV-prevention tool and the need to use other forms of protection.

Box 2: URGENT ACTION REQUIRED

The following action items must be accomplished to support access to male circumcision as a strategy for HIV prevention:

1. Developing countries, particularly those in sub-Saharan Africa, should develop communications campaigns with accurate, context-specific information about male circumcision as an HIV-prevention strategy. They should also develop local plans for assessing need and planning for implementation. NGOs, CBOs, professional associations, and ministries of health will be instrumental in developing and disseminating these messages.
2. These countries should use the best available data to estimate the infrastructure and the financial and human resources required for introduction of male circumcision in varying contexts; these data should be integrated into international efforts to improve developing-world health systems.
3. A stakeholder meeting should be used as the foundation for developing a coordinated, funded operational-research agenda to address additional questions about male circumcision.
4. Treatment and prevention advocates should develop a network for holding key stakeholders accountable for these and other action items, including ensuring that funding for male circumcision rollout does not divert resources from other interventions or from additional research on new prevention tools.

4. Maintaining safety and efficacy in non-clinical settings

In the trials evaluating male circumcision for HIV prevention, the surgical procedure was performed by highly-trained health care workers in controlled, sterile settings. Now that male circumcision has been shown to have a benefit, there may be increased demand and it is highly likely that private sector and informal points of service will emerge, which may compromise the safety and therefore the efficacy of the prevention strategy. Scale-up will therefore have to include sufficient resources to meet demand at safe points of service for the procedure.

5. Relationship of male circumcision for HIV prevention to other contexts in which male circumcision is performed

For many communities around the world, male circumcision is a traditional practice with specific, deeply-rooted cultural significance. These traditional practices may sometimes involve non-medical professionals and non-sterile surgical procedures; they may also remove less of the foreskin than is removed during the procedure when performed for HIV prevention. Rollout of safe, sterile male circumcision for HIV prevention must be context-specific, address these concerns, and consider the roles of traditional male circumcision practitioners as conveying critical messages and potentially adapting the practice to ensure safety and efficacy for HIV prevention.

6. Responses to potential negative reactions to male circumcision

Male circumcision can be a procedure with great meaning and significance. There are constituencies that argue against it for a variety of reasons and will likely continue to do so regardless of the data on HIV-prevention benefits. Evidence-based reporting on the attitudes, impact and community knowledge regarding male circumcision as an HIV-prevention tool will be among the most effective responses to these critics. This research should also explore optimal strategies for distinguishing between male circumcision, with its potential health benefits, and female circumcision, which is a painful and dangerous procedure with no health benefits or preventive effect for HIV, sexually-transmitted infections, or other conditions.

Box 3: HISTORY AND RATIONALE OF MALE CIRCUMCISION FOR HIV PREVENTION

Male circumcision is one of the most common surgical procedures in the world, with 25 to 30 percent of men worldwide undergoing the procedure at some point in their lives. Male circumcision is practiced for many reasons: hygiene, religion, tradition, or a combination.

In the last decade, male circumcision has become a focus of attention in international HIV-prevention research. In the late 1980s, scientists observed that in some developing countries, levels of HIV infection were lower in places with high rates of male circumcision. There are always multiple explanations for observed correlations such as this one. Experimental trials were designed to test the hypothesis that providing circumcision to men would reduce their risk of acquiring or transmitting HIV.

The exact reason why male circumcision provides a protective benefit against HIV infection during vaginal sex is unknown, but biology of local tissue likely plays a role.

The male foreskin contains a concentration of HIV target cells including Langerhans cells, which are immune cells that are targeted by HIV during the earliest stages of infection. In particular, the inner side of the foreskin of the penis is highly susceptible to HIV infection; the skin that remains after circumcision is thought to be less so. It is possible that circumcision helps protect men from HIV infection by removing these targets for HIV.

Data from the recent trial in Uganda (see page 8) show that circumcision is associated with a lower prevalence of genital ulcer disease, which is a risk factor for acquiring HIV. Also, removal of the penile foreskin causes more rapid drying of the penis after sex, bathing, or urination. This may reduce the likelihood of bacterial or other sexual infections that flourish in damp environments.

These open questions should not delay implementation. In fact, introduction of carefully-planned programs is the only way this information can be gathered and shared.

MALE CIRCUMCISION TRIALS TO DATE

As of late 2006, three trials have shown male circumcision to reduce men's risk of HIV infection through vaginal sex. These trials took place in South Africa, Uganda, and Kenya and are summarized in Table 1 (p. 8). This reduction in risk was seen in clinical trial settings where men received treatment for sexually-transmitted infections (STIs), free condoms, and circumcision was performed in sterile conditions by trained personnel.

In all of these trials, male study participants agreed to be circumcised and to be randomized to one of two study arms: a group in which all men were offered male circumcision immediately after randomization and a control group in which they were offered circumcision at the end of the study follow-up period.

All three studies were closely observed by a Data and Safety Monitoring Board (DSMB). The role of a DSMB is to assess progress in clinical trials and make recommendations on whether to continue, change or terminate them. If an interim data review by a DSMB shows that there is a significant benefit for individuals in the intervention arm, the DSMB can find that it is unethical to continue the randomized study. In this case, the board can recommend that all participants be given access to the intervention immediately.³

In all three trials, the DSMB conducted interim reviews and found significant risk reduction in the circumcised men versus the men in the control arm. In each trial, the DSMB recommended that all of the participants be offered circumcision immediately. In other words, the evidence of benefit to men who received circumcision immediately was strong enough that it was considered

unethical to continue the study without offering circumcision to the control group.

The first trial to show efficacy was conducted in South Africa. These data were presented at a conference in July 2005 and were published in November 2005.⁴ The trials in Kenya⁵ and Uganda⁶ confirmed this finding.

The data are comparable across the three trials; in each case, there was a protective benefit of roughly 50% among the men in the intervention arm.

There are some key differences among the trials, particularly the age range, which is wider in the Ugandan trial. Other differences are the technique used for circumcision (both the sleeve method and the forceps-guided method are widely used worldwide) and the frequency of study visits.

A fourth trial in Uganda enrolled HIV-positive men and men who did not know their status. This trial looked at safety and impact on rates of STIs in the male participants and was also designed to test the impact of circumcision on HIV transmission to female partners of HIV-positive circumcised men. Enrollment and surgical procedures in this study were halted in December 2006 following a DSMB review that determined that the study lacked statistical power to answer its study question. The same review identified a non-statistically significant trend towards greater rates of transmission among men in the circumcision arm, particularly those who resumed sex prior to wound healing.

Ongoing follow-up of men who had been enrolled in the study and circumcised before the DSMB recommendation will provide additional information on the important question of impact on women. However, additional studies may be needed to fully understand the implications for women.

The two Ugandan trials have been conducted through the Rakai Health Sciences Project in southern Uganda and are closely coordinated with each other.

Three trials have shown a benefit of male circumcision in reducing men's risk of HIV infection through vaginal sex.

³ AVAC has developed a fact sheet for advocates to learn more about Data and Safety Monitoring Boards and their function. This is available online at <http://avac.org/pdf/AVAC-DSMB-fact-sheet-apr-2007.pdf>

⁴ Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial. *PLoS Medicine* 2005;2:11e298. DOI: [10.1371/journal.pmed.0020298](https://doi.org/10.1371/journal.pmed.0020298)

⁵ Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007;396:643-656.

⁶ Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007;369:657-666.

TABLE 1: COMPLETED AND ONGOING PROSPECTIVE, RANDOMIZED TRIALS OF MALE CIRCUMCISION FOR HIV PREVENTION

Funded by / Conducted by	Study Population	Study Question / Design / Method ⁷	Status / Key Findings / Timeline for Results
SOUTH AFRICA			
Agence Nationale de Recherches sur le Sida (ANRS) / ANRS, National Institute for Communicable Diseases (South Africa)	3,274 18- to 24-year-old men in a semi-urban, informal settlement	Does circumcision reduce male risk of HIV infection by female partners? Study visits at months 3, 12, 21 post-randomization; circumcision performed using the sleeve method.	Trial completed: Male circumcision reduced the risk of HIV infection by 60-61%.
UGANDA			
National Institutes of Health / Johns Hopkins University, Rakai Health Sciences Project	Approximately 5,000 15- to 49-year-old men in rural Uganda (Rakai District)	Does circumcision reduce male risk of HIV infection by female partners? Four visits over two years of follow-up; circumcision performed using the sleeve method.	Trial completed: Male circumcision reduced the risk of HIV infection by 48%
Bill & Melinda Gates Foundation / Johns Hopkins University, Rakai Health Sciences Project	At the time that the trial was halted, more than 200 men had been enrolled concurrently with female partners. In some instances these couples underwent voluntary counseling and testing; in other instances the women were enrolled separately. (Female participants were not informed of their partner's status by the trial staff.)	Is circumcision safe for HIV-positive men; how does it affect rates of acquisition of sexually transmitted infections? Does circumcision reduce female risk of infection by HIV-positive, circumcised male partners? Four visits over two years of follow up; circumcision performed using the sleeve method.	Trial enrollment and surgeries suspended: Enrollment and surgical procedures in this study were halted in December 2006 following a DSMB review that determined that the study lacked statistical power to answer its study question. The same review identified a non-statistically significant trend towards greater rates of transmission among men in the circumcision arm, particularly those who resumed sex prior to wound healing. Based on the data collected, there are no statistically significant differences in rates of wound healing or post-operative complications between HIV-positive and HIV-negative circumcised men. Note: data analyses are ongoing; please consult http://aidsvaccineclearinghouse.org/MC for latest updates.
KENYA			
National Institutes of Health & Canadian Institute of Health Research / University of Nairobi, University of Manitoba	2,784 18- to 24-year-old HIV-negative men	Does circumcision reduce male risk of HIV infection by female partners? Six study visits (months 1, 3, 6, 12, 18, 24) over two years; circumcision performed by forceps-guided method; patients encouraged to receive all outpatient health care at study clinic.	Trial completed: Male circumcision reduced the risk of HIV infection by 53%.

⁷ Both the forceps-guided (or foreskin clamp) and sleeve method are performed under local anaesthesia. The forceps-guided technique uses a surgical instrument called a forceps to pull the foreskin forward prior to removal; the sleeve method uses surgical incisions to remove the foreskin. In the Ugandan trial of the sleeve method, cauterization and stitches were used to minimize bleeding and close wounds; the Kenyan trial used the forceps-guided method with stitches to close the wound.

WHAT THE CURRENT RESEARCH DOES (AND DOES NOT) TELL US

The most important questions that the research to date has answered are:

- When performed in sterile, clinical settings, is male circumcision safe and does it help reduce the risk of HIV acquisition via vaginal sex in circumcised, HIV-negative men?
- What are the rate and scope of side effects of male circumcision when performed aseptically by trained providers in clinical settings?

In addition, these studies have gathered information about whether male circumcision affects the rates at which men and their partners get other sexually transmitted infections. They have also looked at how sexual behavior is affected by male circumcision, if at all (e.g., after male circumcision, what are the changes in frequency of condom use or number of partners). Finally, the Ugandan site is also gathering information on community attitudes from 3,000 individuals from Rakai District who are not participating in the study.

Here are some areas that are not fully addressed by current research:

These trials do not provide clear answers about the safety and potential risks and benefits of male circumcision to the female partners of circumcised, HIV-positive men.

As described, the single trial to date exploring this question halted its enrollment early. The non-statistically significant findings of potential increased risk to women partners of circumcised HIV-positive men raise questions that must be answered in follow-up analyses of this study and, potentially, in other research. Determining

These trials do not provide any data about whether male circumcision provides protection during anal sex.

the safety of this procedure for women and men partners of circumcised men and further understanding both the risks and potential long-term benefits (for which there is still biological plausibility) is of the utmost importance.

There is still a need to gather and analyze data on rates of risk behavior among circumcised and uncircumcised men in these trials.

Such data are important, since the benefits of male circumcision could be offset by an increase in high-risk acts like unprotected sex or an increase in the number of partners.

In the South African trial, men in the circumcision arm reported slightly higher rates of high-risk acts than did men in the control arm. Nonetheless, the procedure still reduced HIV risk in the intervention arm. The data for the Ugandan and Kenyan trials have not been fully analyzed to learn about patterns of behavior. Early data suggest that there were no major differences between the control and intervention arms. But we must wait for the full analysis and remember that these data have

Box 4:

CIRCUMCISION, CULTURE AND TRADITION

- Male circumcision is a marker for tribal and religious identity in many parts of the world. It is often a rite performed at a specific point in the male life cycle.
- In the studies that have taken place, education about the possibility that male circumcision could reduce the risk of HIV infection appears to have been well-received at the community level, regardless of cultural or traditional attitudes in the surrounding area. The trials enrolled rapidly in both Kenya and Uganda.
- Cultural and religious beliefs, and rituals and attitudes towards circumcision will play a critical role in acceptability of male circumcision when introduced in the context of HIV prevention. This is true for communities that practice circumcision traditionally and for those that do not.
- Internationally, there are groups that are opposed to male circumcision altogether and may mount vocal opposition to the introduction of male circumcision as an HIV-prevention strategy.
- Introducing male circumcision will therefore require as much attention to local context, attitudes, and potential sources of opposition as it will to infrastructure and technical resources.

Box 5: Selected Critical Points for Male Circumcision Public Health Messages

There are multiple messages related to male circumcision that will need to be communicated consistently, clearly, and in context-specific formats to men considering the procedure and to their sexual partners. Rollout of male circumcision as an HIV-prevention strategy should include funding for documentation and dissemination of effective messaging strategies in multiple contexts.

Some of the core messages are:

- **Partial efficacy:** Male circumcision is neither 100 percent protective nor a substitute for other methods of HIV-risk reduction. Its efficacy in protecting against HIV transmission during anal sex has not been studied in clinical trials or proven.
- **A procedure with multiple “meanings”:** Male circumcision is a strategy for HIV prevention and is also part of deeply-rooted cultural or religious traditions in many parts of the world. Introducing it as an HIV-prevention strategy will mean educating medical providers about the relevance of the surgery and reaching out to communities about the potential benefits of male circumcision for HIV prevention, regardless of whether it is a cultural norm.
- **Context-specific programming and positioning:** There are opportunities for programs in which traditional and HIV-prevention functions are complementary; there is also a need for male circumcision programs that stress that the procedure does not denote a specific identity or population as being at higher-risk for HIV exposure.
- **Male versus female circumcision:** Male circumcision, which has a positive health benefit, is in no way equivalent to female circumcision, which is dangerous to the health of girls and women and does not reduce the risk of HIV or other diseases.
- **Male circumcision has only shown efficacy in reducing HIV infection among circumcised, HIV-negative men having vaginal intercourse.** The data on safety, risks and benefits for women partners of circumcised, HIV-positive men are indeterminate. There are no clinical trial data on protection during anal intercourse.

limited relevance to “real world” conditions, since participants received periodic risk-reduction counseling as part of the study.

These trials do not provide any data about whether male circumcision provides protection during anal sex.

This is relevant to men who have sex with men and to heterosexual couples. A vaccine preparedness cohort of men who have sex with men was tracked for three years and produced the finding that circumcision was associated with a decreased risk of HIV infection.⁸ Other cross-sectional studies have also suggested possible protective benefits. But there are no randomized controlled trial data. It is not possible to fully extrapolate from the findings related to vaginal intercourse because of a lack of information about HIV shedding in rectal versus vaginal mucosa as well as other biological factors.

Advocacy groups in the United States and Europe have begun to consider the implications of these trial findings for communities of men who have sex with men. The US Centers for Disease Control and Prevention held a consultation in April 2007 to explore these issues. AVAC prepared an advocacy fact sheet on the issue (available at <http://aidsvaccineclearinghouse.org/MC>) and will continue to provide updates on this topic as they become available.

This lack of information has the potential to lead to confusion and conflicting messages, particularly in communities of men who have sex with men. Organizations working with and representing these communities must provide clear information about the strengths and limitations of the data that do exist and must support informed dialogue.

Male circumcision performed by trained personnel in aseptic conditions has health benefits including reducing risk of HIV acquisition during vaginal sex; the data cannot be extrapolated to anal sex, but the procedure will not cause physical harm—and could potentially have a benefit—if performed under these conditions.

⁸ Buchbinder SP, Vittinghoff E, Heagerty PJ, Celum CL, Seage GR, Judson FN, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2005;39: 82-89.

WHAT NEEDS TO HAPPEN NOW?

When a new biomedical intervention for HIV/AIDS is identified, countries, donors and other stakeholders look to agencies like the World Health Organization and UNAIDS to provide guidance on introduction and messaging.

WHO/UNAIDS has prepared a policy document that will be a critical tool for developing countries considering male circumcision. These entities are also expanding activities that will provide technical support to countries that decide to launch male circumcision programs.

These moves at the international level are essential but they are not sufficient to ensure successful rollout of male circumcision to protect against HIV infection.

Development of international guidance must be complemented by funding and technical assistance to help national governments and health ministries develop and implement policy around male circumcision for national AIDS programs.

Some of the focus countries for the US President's Emergency Plan for AIDS Relief (PEPFAR) have also committed resources to expanding access to male circumcision. Male circumcision should be considered for introduction in all PEPFAR-funded prevention programs as part of a comprehensive prevention program that includes male and female condoms and risk-reduction counseling.

PEPFAR and other international initiatives cannot substitute for the work of national health ministries and AIDS-control programs. Male circumcision may be perceived as costly relative to other prevention initiatives (see Box 6, p. 12) and must be funded appropriately, with new resources. Every effort should be made to minimize the diversion of resources from other sectors of the AIDS response and/or sexual and reproductive health programs, to male circumcision.

If safe, effective programs are not put into place quickly, there is a risk of private-sector and informal practitioners filling the void and offering substandard services that carry the risk of wound infection, HIV and hepatitis B transmission (via nonsterile instruments),

other serious and potentially fatal complications, and a missed opportunity for the counseling that needs to be provided as part of the service.

However, while there is a need for swift implementation, introducing and scaling up a new intervention *takes time*. This is true whether it is a commodity such as a condom, or a surgical procedure such as male circumcision. The best-prepared countries will likely adopt a phased-in approach that allows for operational research and the development of best practices that can be applied as the program expands.

Introducing and scaling up a new intervention takes time.

Under these circumstances, timely communication to multiple audiences and through multiple channels is essential. Some of the critical messages to be considered are summarized in Box 5 (p. 10).

In the short-term, AVAC recommends that

- *Countries undertake immediate outreach to medical professionals, community groups, opinion leaders, and AIDS advocates and activists who will play a critical role in disseminating correct information about male circumcision. This step should happen even as the process of developing formal national policies are being developed.*
- *Community groups initiate needs assessments and outreach campaigns to identify effective messages and communication channels for conveying these messages to multiple stakeholders.*

Looking ahead, AVAC anticipates the need to mobilize additional resources to ensure the sustainability of safe, effective male circumcision programs that place the procedure in the context of other HIV-prevention interventions. Advocacy will be needed to meet these goals.

Box 6: PROGRAM COSTS AND REQUIREMENTS

Cost for implementation of male circumcision will vary. One estimate, based on experience in Kenya, puts the cost at approximately US\$25 per procedure (using the forceps-guided method).⁹ This includes US\$8 for medical commodities (sutures and needle, gauze, bandaging, and analgesic), US\$7 for surgical preparation (preparing the room, cleaning linens, and sterilizing instruments), and US\$10 in overhead (physician's fee, maintaining the room and equipment, and utilities). The investigators in the Ugandan studies estimate the cost per procedure at US\$69 including post-operative care.¹⁰

There is a growing body of work on cost-effectiveness of male-circumcision procedures.¹¹ Current analyses vary considerably depending on coverage rates and assumptions about prevalence and incidence. Implementation of male circumcision will offer critical data that can pinpoint cost-effectiveness ratios for different settings. Collecting and analyzing these data should be an immediate priority.

Operational research will help refine estimates of program costs, identify strategies for lowering them, and further improve cost-effectiveness through

techniques such as “task-shifting” of surgical procedures to nurses and medical officers and negotiation for affordable supplies.

In every setting, advocates should emphasize that successful implementation of male circumcision programs includes

- Spaces for confidential counseling, surgery, and, if necessary, post-operative recovery
- Sterile surgical equipment and supplies including gauze, gloves, steam for sterilizing instruments, bandages, and other commodities
- Trained staff including counselors, medical personnel to perform surgeries, and community educators to conduct outreach and follow-up and who are compensated for taking on these responsibilities

Funding for these elements must be sustainable.

In Zambia, a USAID-funded project conducted prior to trial completion helped strengthen male circumcision services in three public health facilities. When barriers such as cost to the patient and lack of trained staff were removed, the project saw a three- to four-fold increase in the number of surgical procedures performed. However, this work was done before the results of the three clinical trials were known, when male circumcision was still viewed largely as a low-priority, elective procedure that had to compete with other priority health services in a highly resource-constrained setting. As a result, these services were not fully sustained when donated consumable supplies ran out.¹²

⁹ Wilson D, de Beyer, J. Male Circumcision: Evidence and Implications. World Bank Global HIV/AIDS Program 2006.

¹⁰ Gray RH, Li X, Kigozi G, Serwadda D, Nalugoda F, Watya S, et al. The impact of male circumcision on HIV incidence and cost per infection prevented: a stochastic simulation model from Rakai, Uganda. *AIDS* 2007;21(7):845-50.

¹¹ Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision in sub-Saharan Africa. XVI International AIDS Conference. Abstract. Toronto, 13-18 August 2006.

¹² Otolorin E, Hughes R, Like K, Bowa K. Strengthening male circumcision in Zambia: End of project report. JHPIEGO/AIDSMARK. February 2005.

In the mid-term, AVAC recommends that:

- *The Global Fund to Fight AIDS, Tuberculosis and Malaria allow countries to shift prevention funds to male circumcision where needed, and consider proposals for male circumcision in the next funding cycle.*
- *PEPFAR and other funding streams provide new resources for scale-up of male circumcision programs, including funds for training, monitoring and evaluation, and staffing.*
- *Funders, advocates, and other stakeholders working on human resource challenges related to health systems in the developing world incorporate staffing needs for male-circumcision programs into their plans and advocacy agendas.*
- *An operational research agenda is developed and funded to ensure that answers to important questions are gleaned as rollout unfolds.*

Finally, the next several years will bring data from studies of other new HIV-prevention approaches including cervical barriers, microbicides, vaccines, pre-exposure prophylaxis, and treatment of HSV-2 infection. An efficacy finding from any of these studies will raise many of the same challenges around messaging, funding, and implementation. Many of the solutions will also be the same. Steps should be taken to maximize the impact of male circumcision today and of additional interventions in the future.

Starting now, and continuing over the long term, AVAC recommends that

- *Researchers, implementers, and community groups working on HIV prevention develop and share consistent messages and best practices concerning the introduction of new interventions into existing programs.*
- *Country-level programming take a comprehensive and forward-looking approach to HIV prevention, with new interventions added to existing offerings in the context of clear messages about partial efficacy, the research pipeline, adolescent vulnerability and other related issues.*
- *Clinical trial sponsors and sites develop scenarios for the cost and size requirements of future prevention trials of new partially-effective interventions (see Box 7, p. 14), and use these estimates to secure adequate funding for the next generation of trials.*

Box 7: Implications for Future Trials of AIDS Vaccines and Other New Prevention Technologies

The positive finding for male circumcision is terrific news for the field of HIV prevention. It also brings new challenges for trial sponsors and sites that plan additional trials of AIDS vaccines and other new prevention approaches.

These trials are still important and relevant. One reason is that the impact of male circumcision as an HIV-prevention strategy will be greater in men. There is still a critical and unmet need for HIV-prevention methods that women can initiate and control. Another reason is that a wide array of options, ideally including a safe and effective vaccine, is the best strategy for slowing the rate of new infections worldwide. Choice is essential, as is accessibility to men, women, and children in different countries, communities, and contexts.

Now that male circumcision has proven effective, future trials of other HIV-prevention strategies will have to address key questions:

- Should male circumcision be offered by the trial site to all male participants as well as to the male partners of women enrolled in a trial?
- How will trials control for the effects of circumcision in data analysis of outcomes?
- Would referral to an offsite facility be sufficient or should sites provide the procedure themselves?
- How should sites support access to male circumcision for the broader community?

AVAC recommends that the offer of male circumcision become part of the standard prevention package provided to trial participants, with immediate steps taken to explore how to implement this offer (see box, right). Where male circumcision is introduced, it is likely that overall incidence (rates of new HIV infections) in trial communities will drop. While desirable, this also means that trials may have to be bigger and/or longer in order to generate statistically significant findings.

Increasing the size or length of a trial increases its costs. Some trial networks have already begun to develop estimates of how the introduction of a new, partially-effective intervention might affect future trials. This work is essential and should continue, with the end result that scenarios and budgets are available as advocacy tools to ensure appropriate funding for HIV-prevention research in the future.

Why is a Vaccine Organization Writing About Male Circumcision?

AVAC was founded in 1995 to advocate for the ethical development and global delivery of vaccines against AIDS. Over a decade later, we are still committed to that cause. We are also well aware that other new prevention tools are likely to arrive sooner than a vaccine. And we think many of the issues we work on—accelerated research, community involvement and education, research ethics, global access, and policy analysis—are highly relevant to male circumcision. In the coming years, AVAC will continue to work in partnership with other advocates to advance ethical prevention research and ensure that the benefits are shared globally.

AVAC believes that the field of HIV-prevention research should be in the vanguard of implementing new, proven prevention strategies. Where epidemiology and rates of circumcision suggest that the procedure could reduce individual and community incidence, there is an ethical obligation on clinical trial sites to work with local and national partners to make the procedure available to participants and the broader community. This offering should follow recommendations from WHO/UNAIDS guidance documents on the subject, placing emphasis on abstinence until wound healing, couples counseling where feasible, and counseling about the need to continue using condoms and other risk-reduction strategies. Where government policies are still in formation or do not exist, trial administrators should partner with health ministries to ensure that trial-initiated services inform and are in line with the national approach as it is developed.

To Learn More

“Male Circumcision for HIV Prevention” (<http://aidsvaccineclearinghouse.org/MC>) is an online clearinghouse of regularly-updated information on male circumcision including published data, UNAIDS/WHO statements, media releases, and other resources.

ABOUT AVAC

Founded in 1995, the non-profit AIDS Vaccine Advocacy Coalition (AVAC) seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of AIDS vaccines and other prevention options as part of a comprehensive response to the pandemic. This work is guided by the following principles:

- Translate complex scientific ideas to communities AND translate community needs and perceptions to the scientific community.
- Manage expectations.
- Hold agencies accountable for accelerating ethical research and development.
- Expand international partnerships to ensure local relevance and a global movement.
- Ensure that policy and advocacy are based on thorough research and evidence.
- Build coalitions, working groups and think tanks for specific issues.
- Develop and widely disseminate high-quality, user-friendly materials.

AVAC focuses in four priority areas:

1. Develop and advocate for policy options to facilitate the expeditious and ethical development, introduction, and use of AIDS vaccines and other new prevention technologies.
2. Ensure that rights and interests of trial participants, eventual users and communities are fully represented and respected in the scientific, product development, clinical trial, and access processes.
3. Monitor the AIDS vaccine field and mobilize political, financial and community support for AIDS vaccine research as part of a comprehensive response.
4. Build an informed, action-oriented global coalition of civil society and community-based organizations exchanging information and experiences.

A major part of AVAC's work is to translate complex scientific ideas to communities through the development and wide dissemination of high-quality, user-friendly materials. In addition to our annual report, which analyzes progress toward the development of an HIV/AIDS vaccine and makes recommendations for actions in the coming year, AVAC publishes the *AIDS Vaccine Handbook* and operates the AIDS Vaccine Clearinghouse (www.aidsvaccineclearinghouse.org), a comprehensive and interactive source of AIDS-vaccine information on the internet.

This special report and AVAC's continuous policy, advocacy, education, and outreach work are made possible by the dedicated labor of AVAC advocates and support from the Blum-Kovler Foundation, Broadway Cares/Equity Fights AIDS, the Ford Foundation, the Bill & Melinda Gates Foundation, the International AIDS Vaccine Initiative, the Overbrook Foundation, the Until There's a Cure Foundation, UNAIDS, the WHO-UNAIDS HIV Vaccine Initiative, and many generous individuals who have become AVAC Members. AVAC is an IRS-certified 501(c)3 tax-exempt organization, and donations are tax-deductible. AVAC does not accept funding from government or the pharmaceutical industry.

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