

The Future Direction of Male Circumcision in HIV Prevention

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Introduction

Background

Male circumcision, one of the oldest surgical procedures in the world, has been the subject of renewed international attention in recent years.

Approximately 30 percent of men worldwide are circumcised, most of them for religious or cultural reasons. The procedure also has health benefits. Uncircumcised men and boys have a much higher risk of contracting urinary tract infections, syphilis, human papilloma virus and invasive penile cancer.¹ Some studies have suggested that their female partners have a higher risk of cervical cancer.

In 2007, it became clear that male circumcision also protects men against HIV infection. During the three decades of the AIDS epidemic, breakthroughs in prevention technologies have been few and far between. The realization in the 1980s that condoms help prevent HIV transmission was followed by the discovery that antiretroviral drugs could prevent transmission from mothers to their babies. Since then, and despite intensive research into vaccines and microbicides, no new biomedical interventions have emerged.

The results of three randomized controlled trials conducted in South Africa, Uganda and Kenya showed that male circumcision reduced the risk of HIV infection in men by 60 percent.² It is believed that because the foreskin's inner mucosa is rich in HIV target cells, removing the foreskin sharply reduces the risk of transmission from women to men. Widespread uptake of circumcision in communities with high HIV prevalence but low rates of circumcision could avert millions of new HIV infections in the coming years.

For this to occur, however, success in the trials needs to be replicated in the field. As continued limited condom use in many parts of the world has shown, just because a technology works does not mean people will use it. Effective implementation of male circumcision faces many challenges, and many questions remain unanswered.

Male circumcision trials in Africa have found that the procedure reduces HIV transmission in men by 60 percent.

The conference

In order to address some of these challenges and tackle some of the questions, UCLA's Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), in partnership with the National Institute of Mental Health, convened "The Future Direction of Male

¹ World Health Organization (2008): Information Package on Male Circumcision and HIV Prevention. WHO, Geneva. Available at: <http://www.who.int/hiv/pub/malecircumcision/infopack/en/index.html>. Accessed on 14 July 2008.

² Auvert B, Taljaard D, Lagarde E, et al. (2005): Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*;2(11):e298; Bailey C, Moses S, Parker CB, et al. (2007): Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomized controlled trial. *Lancet*;369: 643-56; Gray H, Kigozi G, Serwadda D, et al. (2007): Male circumcision for HIV prevention in young men in Rakai, Uganda: a randomized trial. *Lancet*;369:657-66.

Circumcision in HIV Prevention" on 29-30 November 2007, two days before World AIDS Day and several months after publication of the results of the three circumcision trials. The conference was the first in a series of five annual meetings looking at the social and behavioral implications of new and emerging biomedical interventions for HIV prevention.

The goal of the conference was to identify the opportunities and challenges presented by male circumcision, and to examine the behavioral, social and policy implications of rolling out circumcision globally and in the United States.

The conference combined presentations by leaders in the biomedical, social and behavioral fields who are working on male circumcision research and implementation. Each presentation was followed by a facilitated group discussion. Participants were then assigned to working groups to consider the opportunities and challenges in detail.

One: Welcoming Remarks

Andrew D Forsyth, Ph.D.

National Institute of Mental Health, Bethesda, USA

This is the first in a series of five interactive meetings which, from our perspective at NIMH, will focus on the intersection of the behavioral and social sciences issues that are raised by a number of biomedical strategies that are currently under investigation. Our hope is that this conference will lead to new collaborations and perhaps new grants specifically to focus on the behavioral and social science aspects of male circumcision.

Over the course of the next two days we would like to be able to identify a number of new research priority areas in the male circumcision field that are worthy of attention. It doesn't take much of a review of the literature to realize what those are: for example, understanding the barriers and the facilitators of acceptance of male circumcision, particularly given some of the socio-cultural factors, will be key. Understanding how best to counsel after surgery, how best to encourage adherence to abstinence from sex during wound healing, and how to make sure that people understand that male circumcision is only partially efficacious are further vital areas for investigation.

Two: Male Circumcision: Lessons Learned from Africa

In the first session of the conference, scientists involved in the three African male circumcision trials outlined the implications of the trial findings for circumcision rollout strategies.

Maria Wawer, M.D., M.P.H.

*Johns Hopkins Bloomberg School of Public Health
Baltimore, USA*

Dr Wawer summarized findings from the three African trials, with a focus on the trial conducted in Rakai, Uganda, on which she was Co-Investigator. She described how male circumcision protects against HIV infection and discussed the potential benefits and risks for women.

How male circumcision protects against HIV

Dr Wawer outlined the biological reasons why circumcision can protect against HIV infection.

In uncircumcised men, the foreskin of the erect penis retracts, exposing its inner mucosa to vaginal secretions that can transmit HIV and other infections. The inner mucosa is rich in HIV target cells and is much more susceptible than the external surface of the foreskin to tears and ulceration, which facilitate the entry of HIV. In cells grown in petri dishes and exposed to HIV, a large quantity of those from the internal surface of the foreskin become infected, compared with almost none from the outer surface. "Basically," Dr Wawer summarized, "the foreskin is a superhighway for the virus."

The trials

In the years before the three randomized controlled trials (RCTs), a large number of observational studies found that circumcised men have a much lower risk of being infected with HIV than their uncircumcised peers. For example, an observational study in Rakai, Uganda, of couples where the woman was HIV-positive and the man negative found that transmission of the virus to uncircumcised men occurred to the extent expected and depended on the woman's viral load, but that there was no transmission of the virus to circumcised men.

Three randomized controlled trials were set up to test the observational findings. The sites for the trials – Rakai, Kisumu (Kenya) and Orange Farm (South Africa) – had wide variations in population make-up, HIV incidence and prevalence of male circumcision. Some populations were at high risk, others at lower risk. The sample sizes used and the age ranges examined differed, as did circumcision techniques. In Rakai the sleeve method was used, where the foreskin is dissected off like a sleeve, whereas the trial in Kisumu used the forceps guided method, where the foreskin is pulled up above the penis, clamped and cut off.

Despite these variations, the results of the three trials were almost identical. In each of the studies, circumcision reduced HIV incidence among men by approximately 60 percent. Further analysis in Rakai found that the protective effect increased over time – although there was some protection during the first six months after surgery, the strongest effects were seen later. The largest reductions in incidence, moreover, were among men who had greater exposure to HIV via a larger number of sexual partners; among this group, the protective effect was 70 percent.

The trials also found that circumcision was associated with a 50 percent reduction in genital ulcer disease, but there was no effect on discharge or dysuria. Studies on the impact on HSV-2 (genital herpes) transmission are ongoing.

Acceptability of inclusion in the trials was high. In Rakai, 45 percent of eligible men agreed to participate. Circumcision itself is also widely accepted; 80 percent of men in the Rakai control group who were offered circumcision when the trial stopped have subsequently been circumcised.

That circumcision has a negligible effect on sexual pleasure may contribute to the high acceptability rates. There have been some concerns that the procedure would reduce pleasure, but twenty-four months after surgery there was no difference in reports of sexual satisfaction between the intervention and control groups in the Rakai trial. This finding supports a number of studies in the urologic literature in recent years.

Although the quality of circumcisions performed in the trials was high, Dr Wawer noted the potential risks of surgery carried out by traditional circumcisers; there are post-surgical adverse events in up to 35 percent of traditional circumcisions. If done poorly, men can experience more tears during their sexual life, thus potentially increasing their risk of HIV infection.

Male circumcision was found to have a negligible effect on sexual pleasure.

Traditional puberty ceremonies where newly circumcised boys are expected to have sex soon afterwards, pose similar risks. Despite these concerns, however, Dr Wawer argued that traditional providers should be incorporated into safe circumcision programs in order to increase the acceptability of male circumcision – if not to perform the surgery, then at least to oversee any ceremonial aspects.

Many commentators have raised concerns that male circumcision, by protecting men against HIV, will encourage them to engage in higher risk behavior, such as neglecting to use condoms and increasing their number of sexual partners. Although none of the trials found evidence of such behavior, Dr Wawer warned that the men in the trials, since they were given repeated and intensive counseling which may not be available as circumcision is rolled out more widely, may not be fully representative. She highlighted the need for further research in this area.

Ongoing research

An ongoing trial in Rakai is investigating the effects of circumcision on HIV-positive men. This is an important issue, since if circumcision programs target only HIV-negative men,

those who are left out may be stigmatized as positive. To avoid this “badge of seropositivity,” positive men might seek out circumcision from unsafe sources instead. As Dr Wawer observed, these risks mean that in reality programs will have to include HIV-positive men, so “we will need to know what the implications are for them.”

The trial has already yielded interesting findings. As with the negative men in the main RCT, rates of genital ulcer disease were 50 percent lower among HIV-positive men who were circumcised than among those who remained uncircumcised. Rates of surgery-related adverse events, such as bleeding and infection, were similar to those in the trial of negative men, but the wound took longer to heal among positive men. Thirty percent of the latter were not fully healed after 30 days, compared to 19 percent of negative men.

The study found that positive men resume sex earlier than negative men. Resuming sex before wound healing is complete increases the risk of surgical complications, so it is important that counseling of positive men who present for circumcision incorporates advice about the longer healing period.

A trial of HIV-positive men found that post-circumcision healing took longer than in negative men, and that positive men resumed sex earlier. It is important to encourage positive men to delay resumption of sex until the wound is fully healed.

The trial also assessed the female partners of the positive men. Although statistically insignificant, there was a slightly higher incidence of HIV infection in women married to circumcised HIV-positive men than in those married to uncircumcised men. Further analysis revealed that the higher rates were among couples who resumed sex before healing; incidence among women whose partners waited until they were fully healed before having sex was similar to that among partners of uncircumcised men. In other words, resuming sex too early can pose risks for women whose partners are infected with HIV.³

Key findings

Dr Wawer outlined the key findings from the studies:

- Male circumcision is a highly effective HIV prevention measure in men, supported by overwhelmingly compelling data.
- Circumcision is particularly effective in protecting high risk men; it should therefore be offered to high risk men even in countries with low HIV prevalence.
- Circumcision also promotes reductions in some other sexually transmitted diseases.
- Acceptability of circumcision, at least in the three sites in Africa, was encouragingly high.

³ This trial was halted early because of futility – although findings were suggestive of a negative impact on women, the sample size of discordant couples was too low to continue.

- All couples, irrespective of HIV status, must be instructed to avoid premature resumption of sex.
- Condom use must be promoted, in order to avoid an increase in risky behavior among circumcised men.

Bertran Auvert, M.D., Ph.D.
University of Versailles, France

Dr Auvert designed and led the Orange Farm trial in South Africa. Here, he presented some of the key lessons learned from the research. He covered issues of impact, cost-effectiveness, sustainability and political leadership.

The impact on Africa

Dr Auvert described male circumcision as, "a key factor explaining the heterogeneity of HIV prevalence in Africa." There is a very high correlation, he said, between HIV prevalence across the region and circumcision prevalence. Rolling out the procedure could therefore have very strong impacts on the epidemic.

Male circumcision does not explain everything, however. Cameroon and Uganda both have HIV prevalence of around 5 percent, but Uganda has much lower male circumcision prevalence than Cameroon and Cameroon has much higher rates of risky behavior. Altering sexual behavior should therefore remain a primary goal of HIV prevention, and should be included in circumcision programs.

Because of the success of the trials, acceptability of circumcision is very high in the localities studied. There is 70-80 percent acceptability among parents for having their sons circumcised. In Rakai, men are queuing up for surgery. Women, too, are keen for their husbands or partners to become circumcised. As Robert Bailey (University of Illinois) noted, women in studies in Uganda, Malawi, Kenya and Zambia perceive circumcision as hygienic. For many, hygiene and the reduction in sexually transmitted infections are the main reasons they support male circumcision.

"Male circumcision is a key factor explaining the heterogeneity of HIV prevalence in Africa."

Cost-effectiveness

Male circumcision appears to be highly cost-effective. Calculations for Orange Farm in South Africa, where one circumcision costs US\$56, show a cost of US\$181 per HIV infection averted among adult males. In Kisumu, Kenya, the cost is higher, at about US\$2000 per infection averted, but this is still lower than the cost of nevirapine, a widely used method of preventing mother-to-child transmission of HIV (cost-effectiveness studies have not yet covered neonatal circumcision).

There are sixteen settings in Africa where HIV prevalence is above 5 percent and circumcision rates below 80 percent. These areas are home to a total of 30 million

uncircumcised adult men. Circumcising all these men would cost approximately US\$2 billion which, as Dr Auvert argued, is a very low price for a very high benefit.

Sustainability

For circumcision programs to be sustainable, they need to target children as well as adults. Circumcising at an early age, even in Africa where health facilities are often weak, is not associated with significant health problems. In West, North and Central Africa, most men are circumcised as babies or children, usually by traditional circumcisers. Complication rates are extremely low. However, it is important to circumcise as early as possible, since circumcision at the age of six months or more is riskier than during the first two months of life, when babies are more resilient and rarely need stitches.

Sustainability will be increased if there are larger numbers of circumcisers. Given Africa's dearth of GPs, Dr Auvert argued that nurses must be trained to carry out circumcisions and traditional providers given information on how to enhance safety. Simplifying surgical techniques will assist in this process, and trials are ongoing of sutureless circumcision methods.

Political leadership

Circumcision rollout will not be sustainable without strong political backing. Dr Auvert bemoaned the lack of leadership in Africa: "I haven't seen any champions," he said, "I haven't seen any politician really involved in the process saying we have to offer free male circumcision to the population of my country."

Dr Auvert refuted the arguments used by those who are lukewarm about rollout. These include cultural acceptability and the risk of increased risky behavior discussed by Dr Wawer – an argument that is still persuasive despite a number of studies showing only limited impacts. The argument that male circumcision is not acceptable in many cultures is countered by data showing the popularity of circumcision among uncircumcised men at the trial sites. Dr Auvert believes large-scale rollout is therefore possible even in cultures where circumcision is not a tradition.

Debate on the cultural acceptability of male circumcision continued in the discussion following Dr Auvert's presentation. A conference participant from Malawi pointed out that circumcision has different meanings in different settings. In some cases, tribal groups who are traditionally circumcised are dominant, "and therefore circumcision may be a symbol of oppression," he noted. In other cases circumcision is more common among the least dominant tribes, and may be seen by others as a mark of inferiority. Those rolling out circumcision programs will need to be sensitive to such issues and design communication campaigns accordingly.

"Male circumcision is highly cost-effective."

Robert Bailey, Ph.D
University of Illinois
Chicago, USA

Dr Bailey, who led the Kisumu trial, described the preparatory steps taken for the trial and the subsequent rollout of circumcision in Kenya.

Preliminary studies

Preparations for the Kisumu trial involved a number of studies:

- A study comparing existing HIV prevalence among circumcised and uncircumcised men in the province, which found that uncircumcised men were twice as likely to be infected.
- A feasibility study in Kisumu asking 110 men if they would participate in the trial. Ninety-two percent said they would be willing to enroll.
- An acceptability study among uncircumcised Luo men in Nyanza Province in western Kenya. The study found high rates of acceptability of circumcision.
- A needs assessment of health facilities in the province, to establish feasibility in terms of the facilities available and clinicians' experience of circumcision.
- A pilot introduction of circumcision services in one district. At this stage, the potential protective effect against HIV was not mentioned. Cost was found to be the most important determinant of uptake – when it was reduced to 100 shillings (US\$1.6), “people came flocking.”

Dr Bailey also listed a wide range of additional preparatory activities that were carried out to enlist the support of the local community. These included intensive discussions with key stakeholders from national and provincial government, including the national Director of Medical Services, the National AIDS Control Program, the Provincial Medical Officer, and local districts and municipalities. The investigators also consulted local councilors and community elders and leaders, local non-governmental organizations, including the Lions and Rotary Clubs, women's and youth groups, business associations, the local university, and national and local media.

Cost was the most important determinant of male circumcision uptake.

Young men who were to participate in the trial took responsibility for most of the pre-trial outreach and recruitment. The men put on road shows in the community that included entertainment and educational talks about circumcision, as well as details of the study. Outreach also involved sponsored football matches and appearances by the researchers on radio programs.

After the trial was completed and the positive results revealed, the researchers used similar mechanisms for putting across messages about the benefits of circumcision and the fact that it is not 100 percent protective. As in the pre-trial period they used community

meetings, sponsored football matches, flyers and peer outreach to educate local people about the results. Stakeholder meetings were held nationally and internationally to communicate the findings to policy makers.

During the post-trial communication campaign, community members raised a number of questions about the trial and about circumcision. The issue of the advantages of clinical over traditional circumcision was among these, and Dr Bailey reported on research showing that in non-circumcising communities people want clinical circumcision that is safe and affordable and do not see traditional providers as likely to provide such a service. Other concerns raised were whether circumcision affects sexual pleasure, how it works, and what is done with the foreskins afterwards. Preparing answers to such questions is likely to smooth the roll out process.

Future projects at Kisumu include a pilot project for infant circumcision, which will find out whether pregnant women are interested in having their infant sons circumcised. The project will offer circumcision when babies are brought for their first immunization visit, four to six weeks after birth.

Implementation

Dr Bailey described the key steps that have been taken to implement male circumcision in Kenya.

The Ministry of Health has formed a Kenya National Task Force, which includes members of the research team and which has signed off a policy to roll out circumcision across the country. A provincial task force is also in the pipeline, in which the research team will work with the provincial Medical Office on roll out strategy, including identifying suitable locations for circumcision, training circumcision providers and building capacity at health facilities. The researchers have also partnered with the International Medical Corps to prepare mobile circumcision teams to take circumcision procedures out into communities, and they are working with district health management teams to consider how to access and train private practitioners.

Dr Bailey reported that people in communities do not want circumcision imposed on them by national governments. Although they want services to be available, they are keen to have input into how those services are designed and delivered and choice over whether to use them.

Lessons learned

According to Dr Bailey, the most important lesson learned as a result of the Kisumu trial process was the need for consultation at all levels, from international to village level. It is essential to garner buy-in to the research from different layers of authority, as well as from those on the ground in communities.

Feedback is a vital indicator of a project's success. At Kisumu, peer outreach workers gathered feedback from the community, and this was supplemented by an anthropological study of the beliefs the community held about the project. Feedback can help in identifying

problems quickly and in nurturing a sense of pride among the staff, clients and community involved. As Dr Bailey related, "Because they were constantly getting positive feedback about their work from the community, the staff took tremendous pride in what they were doing."

Fostering a sense of belonging in the trial was another key lesson. Clients had a sense of pride that they were part of the trial and that they were having an impact. According to Dr Bailey, "clients go around town talking about how they are members, and would actually greet each other on the streets of Kisumu by ID number!"

The final key lesson was the importance of monitoring and evaluation. This should cover adverse events from surgery as well as the quality of services, so that any problems can be quickly corrected. Monitoring uptake of circumcision and the barriers to it will also be important as the procedure is rolled out more widely.

"Because they were constantly getting positive feedback about their work from the community, the staff took tremendous pride in what they were doing."

Three: Male Circumcision: Implementation and Scale Up

The second session addressed the challenges facing rollout of male circumcision.

Jorge Sanchez, M.D., M.P.H.

Asociacion Civil Impacta Salud y Educacion, Peru

Dr Sanchez discussed studies in the US, UK and South America that are relevant for circumcision rollout outside Africa. The HIV epidemic in these regions is driven primarily by men who have sex with men, among whom cases continue to increase.

The HIVNET Vaccine Preparedness Study was a longitudinal study of risk factors for HIV among men who have sex with men (MSM). It enrolled over 3000 HIV-negative MSM in six US cities, with reassessments every 6 months for 18 months.

The study used self-reported circumcision at baseline to assess incidence among circumcised and uncircumcised men. 84 percent of the men, who were mostly white, were circumcised, and the study found that being uncircumcised was associated with a twofold increase of HIV acquisition.

On the other hand, a review of the medical records of over 58,000 men who had attended a San Francisco sexually transmitted disease (STD) clinic between 1996 and 2005 found no association between circumcision and HIV status, although there was a trend towards a protective effect of circumcision against syphilis among heterosexual individuals who were not infected with HIV. A further three-city study found much higher circumcision rates among black MSM (74%) than Latino MSM (33%).

A sentinel surveillance study conducted by Dr Sanchez and his colleagues in the Andean region of Peru and Ecuador enrolled MSM who had not been diagnosed with HIV and were at high risk of infection in three cities in Peru and one in Ecuador. Over 95 percent of the men were uncircumcised. They were asked whether their sexual role in the last five years had been exclusively or predominantly insertive or receptive, or whether they were versatile. Thirty-eight percent reported being exclusively insertive and 19 percent exclusively receptive, with the remainder performing both roles. This information will help researchers determine whether circumcision has a greater protective effect for insertive or receptive partners, and whether the protective effect is eradicated if men perform both roles.

Research on the effect of circumcision on HIV transmission among men who have sex with men is thin on the ground and inconclusive. Evidence so far indicates that there may be a protective effect for men whose sexual role is mainly insertive.

The study found no association between circumcision status and HIV infection among MSM overall, but among those who were mainly insertive, circumcised men had a reduced risk of HIV infection compared to men who were mainly receptive.

The researchers also asked men who were not circumcised whether they would be willing to participate in a randomized controlled circumcision trial. Seventy percent said they would enroll. Dr Sanchez and his team are planning further research to identify the concerns about and barriers to participation in HIV prevention studies, and establish information needs and the optimum recruitment strategies. Since it is possible that a circumcision trial among MSM will take place in South America, Dr Sanchez explained, it is important to prepare the ground.

Dr Sanchez also summarized a proposed RCT among MSM in the UK. Circumcision in the UK is uncommon, and there is little knowledge of attitudes towards the practice. A proposal has been submitted to measure the acceptability, feasibility and costs of such a trial.

Kate Hankins, M.D., MSc.

Chief Scientific Advisor, UNAIDS

Dr Hankins' presentation focused on how the knowledge acquired in the circumcision trials can be translated into policy and programming on the ground. She discussed the role of UNAIDS and donors, reviewed UNAIDS recommendations, and outlined progress at country level.

UNAIDS' role

UNAIDS' role in circumcision rollout spans the global to the local. Globally, it includes advocacy about the benefits of the procedure, coordinating research priorities, supporting monitoring and evaluation, and assessing the legal, ethical and human rights implications of rollout. It is at country level that policies must be formulated and implemented, however, and UNAIDS is supporting countries in holding national stakeholder meetings, sharing experiences, creating national task forces and drafting national policies based on situational analyses. Much of this work is being carried out in conjunction with other UN agencies and partners such as PEPFAR, the Gates Foundation and the US National Institutes of Health.

Recommendations for rollout

Dr Hankins presented eleven key UNAIDS recommendations for consideration as male circumcision is implemented across the world:

1. The evidence for the impact of male circumcision is compelling, and promoting it should be an additional strategy for the prevention of heterosexually acquired HIV infection in men.
2. It should not replace other known methods of HIV prevention, but be considered as part of a comprehensive prevention package.
3. It is essential to emphasize that circumcision only provides partial protection against HIV. Moreover, it should be made clear that men should abstain from sex for six weeks after surgery, and should not resume sex without a medical inspection to check that the wound has healed. All communication messages

should be carefully tailored to local contexts and addressed to both men and women.

4. Given the potential for circumcised or uncircumcised men to become stigmatized, depending on local cultures and beliefs, it is important to include a wide range of stakeholders in consultations over rollout. These should include local communities and traditional practitioners. There may be tensions between traditional and modern health systems that are heightened by male circumcision, so engaging both sets of stakeholders is critical if rollout is to proceed smoothly.
5. Those implementing male circumcision programs should take human rights principles into account. Laws and regulations should ensure accessibility, quality and safety, and circumcision should be carried out with full adherence to medical ethics, including principles of informed consent, confidentiality and absence of coercion. Minors should be given an opportunity to consent if they have the capacity to do so, and parents should be given clear information on the risks and benefits before they assent to their sons being circumcised. Non-discrimination is also important, and this should include reaching out to isolated and poor communities who might otherwise be unable to access health services.
6. Efforts to improve gender equity should be incorporated into the circumcision process. This is a rare opportunity to access young men, who seldom use health services, with health and gender messages; promoting shared sexual decision-making and more equal gender roles should be combined with efforts to reduce violence against women.
7. Programs should aim for maximum public health benefit. As Dr Hankins argued, "the biggest bang for the buck is going to be in high priority geographic settings with hyper endemic HIV epidemics and low male circumcision prevalence." All countries with high HIV prevalence have set universal access targets for HIV prevention and treatment, and UNAIDS is encouraging countries to include male circumcision in these targets. Adolescents, young men and older men who are at particularly high risk of infection (such as men in STI clinics and men whose wives are HIV-positive) should be the focus of these targets.
8. Health services must be strengthened in order to roll out circumcision effectively. Needs assessments should be conducted, and providers trained and certified to deliver safe and high quality services. Supervision systems should be put in place to monitor quality and ensure rapid referral of adverse events and complications.
9. Mobilizing additional resources is also important. UNAIDS has encouraged countries to develop national cost plans and seek new funding from donors so that existing health services are not weakened. Male circumcision has such a large public health benefit, and demand for the procedure is so closely linked to cost, that free provision should be the goal. Rapid scale-up, moreover, is essential. Faster rollout means far fewer HIV infections and a lower cost per infection averted. "We

need to be telling policy makers to move quickly on this if they are going to move," argued Dr Hankins.

10. UNAIDS advocates providing circumcision to all men, including HIV-positive men, if it is medically indicated and if positive men request it following counseling on its risks and benefits. HIV testing should be recommended, but not mandatory, for all men seeking male circumcision.
11. Key areas for further research include investigating the best models and packages for circumcision rollout, assessing how to achieve optimum quality surgery, and analysis of resource needs. More work is needed to determine the benefits and risks of circumcision for other sexually transmitted infections, while the Bill & Melinda Gates Foundation and Clinton Foundation are currently attempting to develop safer methods for resource-limited settings, such as sutureless techniques.

Country progress

Dr Hankins provided a whistle stop tour of the state of male circumcision rollout in southern Africa. The picture is a varied one, with some countries making more concerted efforts than others. While political leaders in Botswana, Kenya, Zambia and Swaziland have taken active steps to develop national plans, governments in South Africa and Zimbabwe have been slow to respond, and leadership there is lacking. Lesotho, Malawi, Mozambique, Rwanda, Tanzania and Uganda are planning situational analyses, with a view to implementation of programs once these are completed.

James Khan, M.D.

University of California, San Francisco

Dr Kahn briefly discussed data and modeling issues in assessing the impact and economics of scaling up adult male circumcision.

Male circumcision, Dr Kahn recapped, is likely to prevent between 2 million and 7 million HIV infections, depending on the time frame considered and the countries included. The cost effectiveness ranges from \$100 to \$1000 per infection averted, varying by epidemic and cost.

Dr Kahn discussed specifically the cost-effectiveness study he conducted with Dr Auvert at Orange Farm in South Africa. The study calculated the number of HIV infections averted per 1,000 male circumcisions of HIV-negative and positive men. The cost of one circumcision was US\$56, which included paying a surgeon, dealing with side effects and publicizing the availability of circumcision. This was compared to a lifetime cost of US\$1800 to treat someone with HIV/AIDS; with three circumcisions required to avert one infection over 20 years, the cost-effectiveness estimate was US\$181 per infection averted.

Dr Kahn outlined some challenges for modeling studies. Existing models do not take account of the risk level of those being circumcised, for example. Circumcising men aged 21 to 28 years provides the quickest benefit, but circumcising 15-21 year olds might pay a

larger dividend in the long-term; without information on the risk levels of men of different ages, understanding what different scale-up strategies will achieve is difficult.

Models also need to be able to look at heterogeneous costing. Incorporating the different unit costs of facility-based and mobile strategies will strengthen cost-effectiveness models. The number of infections averted will also vary; changes in HIV incidence and risk compensation and differences in program characteristics increase the uncertainty. Modelers need to respond to these challenges via sensitivity analysis, which provides cost-effectiveness results for different incidence and averted infection scenarios.

Four: Ongoing Research on Male Circumcision

In the third session of the meeting, Dr Helen Weiss provided an overview of continuing and planned research on male circumcision in the wake of the successful trials.

Helen Weiss, D.Phil.

London School of Hygiene and Tropical Medicine

Dr Weiss outlined ongoing research and research needs in six key areas:

1. *The impact of male circumcision on population-level HIV incidence:* Empirical longitudinal studies are under way in Rakai, Kisumu and Orange Farm to determine whether the strong community effect of male circumcision extends to reduced HIV incidence in the population as a whole. Modeling studies have shown reductions in HIV incidence of 15-30% over ten years, depending on the level of coverage. The impact is stronger with longer follow-up periods, when the effect of circumcision can spread to the female partners of circumcised men and even to uncircumcised men who benefit from the lower HIV incidence in a population. The models suggest that the strongest long-term impact of male circumcision will occur if programs target younger boys, although the most appropriate target group in the short-term is high risk young men.
2. *The impact of male circumcision on other STIs:* Preliminary data from the three trial sites have shown mixed results in terms of the effect of circumcision on STIs other than HIV/AIDS. In Rakai and Kisumu, circumcised HIV-negative men had a reduced risk of contracting genital ulcer disease, but there was no impact at Orange Farm. Ongoing research is investigating these differences. There is some evidence that circumcision reduces human papilloma virus (HPV) and penile cancer is also much reduced among circumcised men. Research is continuing on the impact on HSV-2.
3. *Risk compensation:* Ongoing five-year follow-up of the Kisumu and Rakai trial cohorts is gathering information on the longer-term behavioral patterns of the men who were circumcised as well as those who decided against circumcision. A separate study in Kisumu is looking at risk compensation among 1600 circumcised and 1600 uncircumcised men. Modeling studies are also addressing risk compensation. Most models run so far indicate that circumcision will be protective even if risky behavior doubles (such as a halving in condom use or a doubling of sexual partners).
4. *Neonatal circumcision:* Circumcision of babies is safer and cheaper than adult circumcision. It is already widely practiced in America, the Middle East and parts of West and North Africa. Globally the majority of male circumcision procedures are carried out at the post-neonatal stage. There is therefore strong interest in expanding neonatal circumcision, which could have a large long-term impact on HIV incidence. The Gates Foundation is supporting a review of circumcision practices

with a view to developing models for neonatal circumcision rollout in southern and eastern Africa.

5. *Using self-reported circumcision status:* Planning expanded services relies on accurate estimates of current circumcision prevalence, but self-reported status is not always reliable. Studies in the US and Africa have found that significant minorities of boys and men who say they are circumcised prove to be uncircumcised on medical inspection. Even clinicians are not always correct in their assessments; research in South Africa found that a number of boys who were seen more than once by clinicians were deemed to be circumcised at one visit and uncircumcised the next. Clinicians should be trained to ascertain circumcision status and studies should, where possible, assess status through clinical examination rather than self-reports. Foreskin length naturally varies, and some circumcisions are only partial, so more research is needed on differing circumcision techniques and the amount of foreskin each technique leaves. One conference participant reported that the RCTs used four-stage objective criteria for judging circumcision status and the degree of foreskin presence, which should be promoted to agencies implementing circumcision rollout.
6. *Circumcision outside sub-Saharan Africa:* The vast majority of research on male circumcision for HIV prevention has taken place in Africa. There are few studies elsewhere. The Latin American work described in the second session by Dr Sanchez is an exception, as is a study in India by the University of California, San Francisco. There is a perception that introducing circumcision in India would be extremely difficult, since being uncircumcised is closely tied to the Hindu religion (most Muslims there are already circumcised). However, the study has found high levels of acceptability. In the Caribbean, which has quite high HIV prevalence, there have been no studies of circumcision.

Five: Workgroup Discussions

Workgroup discussions were the focus of the second day of the conference. Participants covered a wide range of circumcision-related issues, including social and policy research needs, funding strategies, the communications needed for rollout and the effect of circumcision for men who have sex with men.

Workgroup 1

The first group discussed male circumcision in the context of vaginal transmission of HIV, and in particular the social and policy research needed to support rollout globally and in the US.

Social research needs

The influences on men's decisions to circumcise are poorly understood. Some delegates argued that women might have a vital influence in encouraging their partners to circumcise, and that they might be useful allies in efforts to expand the procedure. More knowledge is needed of how broader social networks determine decision-making. Experience of voluntary counselling and testing in Uganda, reported one participant, suggests that a "family-oriented approach", where prevention methods are delivered at home and in the presence of relatives, "makes it more of a social event rather than an event that an individual has to grapple with and figure out how to tell family members about." We do not yet know, observed another participant, how people choose a "personal risk reduction strategy that would fit the context of their lives". Finding out whether and why people choose circumcision or condoms, for example, would help in the development of educational programs on HIV prevention."

There was much discussion of circumcision outside Africa. As the example of India outlined by Dr Weiss showed, our assumptions about circumcision are sometimes misguided.

Knowledge of circumcision perceptions outside Africa is slim. In the US, for example, male circumcision rates are extremely low among Latinos, and little is known of the reasons for this. The beliefs of both women and men are important in this regard, as are the attitudes of those Latinos working in the health professions. A conference delegate reported that she is beginning to research acceptability among black and Hispanic men who have sex with men in the US, but there is little research among the heterosexual population. Workgroup 1 emphasized that gathering information on the acceptability of the procedure in Asia, South America and Europe should be a high priority research area.

Little is known of the reasons for low male circumcision rates among Latinos in the United States. Outside Africa, perceptions of circumcision have not been extensively studied.

One group member identified a potential barrier to circumcision rollout in the lack of benefits to women. Research is ongoing into whether male circumcision reduces transmission of STIs to their female partners, and the procedure has not been found to reduce HIV infections in women. However, she argued, this should not prevent investment

in such an effective intervention. Researchers should not be defensive about circumcision, but promote it with enthusiasm. In the long-term, reduced HIV among men should lead to reduced infections among women. "If we were talking about microbicides," the speaker added, "nobody would be asking 'what's the benefit to men?' It would be 'hallelujah there's something that at least helps one gender.'"

Policy research needs

Now that the randomized trials have proven the efficacy of male circumcision in reducing HIV transmission, the next challenge is to implement the procedure in high HIV-prevalence settings. Effective implementation will require a strong research base, but conference participants lamented the lack of funds available for operational research. Key funders, it was argued, such as the US National Institutes of Health (NIH) and CDC, are not oriented towards operational research. Their focus on randomized controlled trials means that they do not have a mandate for the more observational and descriptive research required to support policy. Several participants agreed that a "different mindset" is needed, where research moves from an exclusive interest in discovering new interventions towards ensuring that existing interventions are successfully implemented. In order to bring about this shift, researchers and advocates for circumcision need to push agencies such as NIH and international donors such as the Gates Foundation and PEPFAR to develop operational research programs.

The key operational research question identified by Workgroup 1 was, "What makes a male circumcision program successful?" Finding out what helps and impedes implementation in different communities and countries is essential. There are many gaps in current knowledge. For example, we do not yet know if uptake in communities will be high without the intensive counseling provided at the trial sites. In tobacco research, as one participant observed, if nicotine patches are placed in groceries without any support from counseling, they have no effect on continuation of smoking. Will we see the same occurring with male circumcision?

Moreover, although we know that antiretroviral treatment, voluntary counseling and testing, condoms, AIDS education, prevention of mother-to-child transmission, and male circumcision work in isolation to prevent HIV, policy-makers faced with decisions over resource allocation need to know the most effective combination of these methods for their locality. As several group members pointed out, modeling can play a role here, in examining the combinations that provide the maximum reduction in transmission.

Research needs to move from discovering new interventions to working out how best to use existing ones. This requires a new mindset among funders.

A further gap in knowledge is the potential effectiveness of incorporating male circumcision into other prevention services, such as home-based voluntary counseling and testing. One workgroup member recounted an example from the Dominican Republic, where a clinic in a poor urban area provided tuberculosis services, family planning, infant immunization and HIV testing under one roof. Such clinics could also offer circumcision, which could reduce

any potential AIDS-related stigma around the procedure. As the delegate explained, "these programs reinforce each other, the community supports them, and it's not stigmatizing to go to a place because they are providing a variety of services – it's not all HIV-related."

Leadership was identified by many as a key barrier to rollout. Without support at high levels, research proving the effectiveness of circumcision will fall on deaf ears. As Robert Bailey reported in his presentation, researchers at Kisumu made great efforts to involve policy-makers at all levels, but the Ministry of Health has still to incorporate circumcision fully into its strategies. Another conference participant highlighted the opposition by HIV prevention service providers, who are not always medically oriented, steeped as they are in community behavior work, and who are therefore sometimes resistant to medical technologies such as circumcision. "There are groups within the social and behavioral science research community that take a really negative attitude towards male circumcision," he said, "and there is a rift between the more medical orientation of the prevention services that are coming to light and the agencies that have been set up to provide services to communities." He argued that work is needed to garner all providers' support for circumcision: "You've got to stop coming up with a list of problems and come up with lists of solutions."

Other participants agreed, suggesting that research be carried out on how to influence stakeholders and how to advocate effectively for circumcision rollout. In the US, sixteen state Medicaid programs do not currently pay for male circumcision, and advocates need a better understanding of the factors that influence such programs. Further research should ask how governments, religious organizations and community groups work together to change or preserve elements of culture. Some suggested that major funders should be enlisted to help target leaders with positive messages on circumcision.

Workgroup 2

The second workgroup also discussed circumcision in the context of vaginal transmission of HIV. They focused on implementation challenges and on the communications needed to encourage high uptake of circumcision.

Implementation challenges

It is not yet clear which is the most effective male circumcision technique. As discussed above, different methods at the trial sites produced similar results, but questions remain as to the most cost-effective and safest methods in different settings. The optimum setting for circumcision also remains to be established; mobile circumcision teams, sexually transmitted disease clinics or holistic provision in mainstream clinics are among the possible options. Who should deliver circumcision is a further open question; resource-strapped countries will have to decide whether to allow nurses or trained traditional healers to carry out surgery, and cultural issues of whether women or men should provide services will need to be considered.

There is a need to develop medical guidelines for circumcision, and some conference participants believe that the scientific community is reaching the point at which formalizing

such guidelines will become possible. However, standards require quality assurance and monitoring procedures, and several members of the working group noted that this creates a tension between rapid rollout and service quality. It is important to expand services as quickly as possible, with some participants arguing that programs should first attempt to reach the low hanging fruit – that is, people who are keen to be circumcised in countries that are culturally and politically more favorable towards circumcision. As Maria Wawer summarized, “if we don’t get good programs up in an appropriate way quickly enough, people are going to start going to bad programs, and there could be a backlash against circumcision if it is not available quickly.”

On the other hand, argued one delegate, “if you roll this out quickly and make a mess of it by having poor quality circumcisions being done, then the community will turn against it and you will not only have jeopardized the opportunities for circumcision within that country but also within related countries around that region.” Finding a balance between speed and quality will be a key implementation challenge as circumcision rollout proceeds.

Messages

Understanding attitudes to circumcision will help advocates communicate its benefits. All three workgroups deliberated on the messages needed to promote the procedure. Who to target with messages was the first question discussed. The importance of consulting national and community decision makers is evident from the Kisumu trial. Further potentially important stakeholders identified by the workgroups include private health care organizations and insurers, who “will quickly see it’s in their best interest to promote circumcision.” Research has yet to establish whether targeting women, in their role as partners and mothers, is effective as a way to reach men.

Private health care companies could be key allies in spreading messages about the benefits of circumcision. As conference participants noted, these organizations have expertise in marketing. Specialists from the marketing and advertizing industries could also play a part in convincing publics about male circumcision’s benefits. Marketing campaigns, argued one delegate, should adopt a variety of formats depending on who they are targeting – it is likely, for example, that different messages will be needed in brothels, college campuses, internet campaigns and national advertising efforts.

All communications should be clear about the science behind circumcision. In particular, they should not over-promise and should drill home the message that the procedure is not fully protective against HIV and that other prevention methods are therefore still needed. As one group member said, “circumcision is not a magic bullet.” On the other hand, advocates should not be defensive; many men are worried that circumcision reduces sexual pleasure, so the research that shows this is not the case should be clearly communicated. Circumcision also has health and hygiene benefits beyond HIV, and these too should be promoted. Those targeted by communication efforts, in short, should be given sufficient and unbiased information to enable them to make an informed choice over whether to be circumcised.

Communication campaigns promoting circumcision should present the benefits and risks clearly and objectively.

A further communications challenge is to counter the potential for male circumcision to become stigmatized because of its links to HIV. Throughout its history, the stigma surrounding AIDS has deterred millions from testing for the virus, accessing treatment or making use of prevention tools. With circumcision, as Maria Wawer noted in her presentation, there is a danger that presenting it solely as an HIV prevention strategy may, because of stigma, be less attractive to men than including it as part of a male health package. There was some agreement that the latter approach offers more promise, but research is needed to back up this as yet unproven hypothesis. Indeed, one participant raised the prospect that, if it was packaged as part of an overall men's health or child health program, it might be seen as covert and secretive; he referred to concerns in Africa that the polio vaccine was a Western attempt to sterilize Africans, and suggested that being less than explicit about the reasons for circumcision might cause similar suspicions.

Opposition to circumcision is unlikely to be limited to Africa. There is a strong anti-circumcision lobby in the US, and advocates will need to prepare to deal with its arguments. One American participant reported having been a target of this lobby for decades. "You can't underestimate your opposition," he said, "they are very powerful and they dominate the media, they dominate the internet, they are very active politically and they are responsible for sixteen State legislatures failing to fund circumcision because they have lobbied them." In order to counter the anti-circumcision arguments, he argued, "you're going to have to learn how to work with the media." Developing websites with accurate information will be crucial, since many internet sites with information on circumcision are populated by opponents of the procedure. Respected organizations such as CDC and NIH should also have web pages on the subject. As another participant argued, moreover, there is a role for research in dealing with the doubters: "There's so much information being put out against circumcision that I think that needs to be part of the research and communications agenda, to recognize it and figure out how to work effectively in that environment."

Workgroup 3

The third workgroup focused on anal transmission of HIV. It covered many of the same issues as the other workgroups, but also raised a few new points.

There has not yet been a clinical trial to determine whether male circumcision protects men who have sex with men (MSM) against HIV infection via anal sex. Research so far suggests that there may be some protective effect for the insertive partner, but this may be wiped out by role variability, since in many couples men vary in their sexual roles. More information is needed on role variability in different cultures and communities. Knowledge of circumcision's protective effect for heterosexual anal intercourse is also weak, while the effect on STI transmission via anal sex is unclear.

Much more research is therefore needed on the effect of circumcision on both HIV and other STIs that are transmitted anally. However, there was disagreement over whether observational studies would be sufficient or whether a clinical trial, which would take much longer, would be required. One participant suggested including questions on anal sex in

existing circumcision and sexual behavior surveys as a quick way of gathering more knowledge.

Workgroup 3 also discussed the messages around circumcision for men who have sex with men. In the US, as one group member reported, some MSM choose partners based on circumcision status – he described this as “circumsorting.” In personal advertisements, there are requests for “cut” or “uncut” partners. This may influence the acceptability of circumcision in one’s partner, and messages promoting the procedure should be aware of these preferences. There are questions, moreover, as to whether framing circumcision in terms of HIV prevention or STI prevention or as part of an overall men’s health service will be more effective in encouraging men who have sex with men to access the procedure. Many of the policy questions for circumcision rollout among heterosexual men, it was argued, also apply to rollout among men who have sex with men.