

***Male Circumcision and HIV/AIDS:
Opportunities and Challenges***

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Preface

This review was commissioned by the Ford Foundation in order to deepen our understanding of the current research on the interfaces between male circumcision and HIV/AIDS. The experience of our grantees in working in the community development, sexuality, sexual health, and human rights fields tells us that many factors would have to be considered before making a decision to implement male circumcision as an HIV/AIDS prevention mechanism. It would need to take into account questions of personal autonomy, bodily integrity, and human rights; of social and cultural dynamics in specific contexts; and of health system capacity to deliver integrated HIV/AIDS prevention and treatment interventions to the majority of the population.

We wanted to understand what the new research tells us about these broader contextual factors, and what kinds of issues would need further exploration in order to ensure that any new preventive intervention would only be implemented after a thorough consideration of the individual, social, and health system implications, as well as the likelihood of success outside of a research environment.

This review aimed to provide us with such information. Since there are many others in the field who are asking similar questions, we asked the authors to make it available to the public as a contribution towards constructive dialogue on the options.

Barbara Klugman and Jacob Gayle,
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Executive Summary

This report summarizes available information on male circumcision (MC) as an HIV prevention strategy, and the policy and prevention implications of its implementation. To this end, the report examines:

1. Summary of HIV prevention science and practice;
2. A review of the currently available data from observational studies and randomized controlled clinical trials;
3. Adult male circumcision, other health benefits, and the implications for women's health;
4. Biological mechanism responsible for reduced susceptibility to HIV infection and other medical benefits among circumcised males;
5. Medical professional group policy statements pertaining to male circumcision;
6. Challenges related to male circumcision;
7. Research priorities;
8. Ethical concerns; and
9. Potential next steps.

While the results of the recently stopped clinical trials demonstrating the protective effect of male circumcision on HIV infection are extremely promising and can have enormous impact on the HIV epidemic, there are numerous implementation challenges, contextual considerations, and ethical concerns that require rigorous attention.

We identify here 15 such challenges, and the list can probably be expanded. Nonetheless, we present these to encourage discussion, and to ensure that these issues are considered as new medical findings are released and implementation plans are drawn up. Furthermore, we hope that these challenges will enrich and add nuance to the discussions as to how male circumcision should be offered as an HIV prevention intervention, and what steps need to be taken to ensure it is implemented in an ethical and effective manner.

We highlight the following:

1. **Acceptability:** Price, pain, and lack of complications seem to be universal concerns and need to be attended to in rollout of male circumcision. Rollout programs will consider these and other issues as plans for scale-up and implementation are considered.
2. **Level of protection:** The benefit from male circumcision is relative, not absolute, and communications strategies will need to be devised to reinforce this point clearly. Further, any rollout must take into account the fact that male circumcision will be introduced into a relatively complicated prevention environment. Ideally, discussions of these issues will reinforce the benefits of other prevention strategies, and all prevention techniques will receive a needed boost in attention and funding.
3. **Risk** is typically defined in terms of medical risk; how can conceptions of risk be expanded to include social, psychological, cultural, or sexual factors? Acceptability on a population level, societal perception, and implications for gender dynamics, sexual practices and other issues should be factored into these discussions and given appropriate weight.
4. **Interventions** using male circumcision (as with other technologies) absolutely require behavior modification and educational components. It will be essential to place male circumcision within a broad prevention context in order to avoid many of the difficulties that may be associated with it. Ideally, the introduction of male circumcision will be used as impetus to gain support for the

wider use of all prevention technologies and strategies. Male circumcision may help to focus attention on *combination prevention* and the need to use multiple prevention strategies in concert.

5. It will be essential to maintain funding for broader commitments in the fight against HIV, especially with regard to fighting gender inequity, stigma, and other issues related to disease spread. The implications of MC can be helpful if, as a result of the ongoing MC clinical trials, the scientific community and those who support HIV/AIDS prevention were led to increase their commitment to all solutions to the HIV/AIDS epidemic, and the broader fight against social inequalities that fuel the epidemic, such as gender inequality.
6. Benefit to women: How can male circumcision benefit women? How can male circumcision not harm women?
7. Religious and cultural practices need to be taken into account. Actual risk reduction, versus that of reduction rates achieved in controlled trials, is likely to have more regional variance and is dependent on local behaviors surrounding sexual practices, local drivers of the epidemic, and current prevalence rates.
8. The questions of when to circumcise—in infancy or adulthood—are hotly debated and will continue for some time. It may be easiest in infancy, but infants will not benefit immediately and cannot make informed choices.
9. Male circumcision and female genital mutilation (FGM): Opportunity to further distinguish the two? This raises at least two questions: a) whether promoting MC will in any way undermine current efforts to eliminate FGM, and b) how to understand the social and cultural discourses about the penis, about sexuality, and about sexual maturation that may all be affected, and potentially have positive or negative impacts on, an ostensibly neutral public health intervention.
10. Assessment and surveillance of safety and complications is essential to ensure that circumcisions are performed safely, that training is adequate, and that oversight is in place.
11. The challenges to health systems are enormous. The fact that health systems in many countries with high or growing HIV incidence are very poor and can not cope with the systemic or human resource requirements of an MC program without major additional short- and long-term investments. The estimated costs per circumcision could be significant when considering a developing country's per person health budget. The global experience with prevention of mother-to-child transmission of HIV (PMTCT) has already demonstrated the inability of global health systems to deliver on the promise of technical advances.
12. Male circumcision also needs to be considered and evaluated in a broader context of sexual and reproductive health, beyond the constraints of HIV alone.
13. Some have asserted that the trials and the calls for widespread implementation are being fueled by a form of racism. These issues need to be addressed seriously and included in the discussion.
14. It will be essential to determine how to avoid stigma associated with male circumcision or the lack of it.
15. It will also be essential to carry on the discussion around male circumcision to deliberately avoid branding men as perpetrators of infection.

We highlight the following research priorities:

1. What is the effect of male circumcision on female partners—not just related to HIV, but also sexually transmitted infections (STIs), cervical cancer, female pleasure, and female perceptions of sexual viability of the male partner?
2. There are often few ethical guidelines on the social and behavioral effects of biomedical trials—only medical effects and adverse events are examined. Social and behavioral effects need to be defined, and studies need to be carried out on the positive and negative consequences related to study participation.
3. Is penile hygiene as good as MC? Clinical trials that include a penile hygiene study arm should be conducted. These studies should also conduct analyses of feasibility, required resources, and infrastructure requirements.
4. Although much cost analysis, particularly in the United States, has been conducted to project the cost savings from averted HIV infection, STIs, and urinary tract infections (UTIs), there is a lack of data projecting the costs of treating circumcision-related complications. How will complications be addressed in resource-poor settings?
5. The development of models that include cost analysis for training practitioners in resource-poor settings is urgently needed. Modeling should project the cost of equipment and its maintenance, and the treatment of complications. These projections should be comprehensive modeling strategies including PMTCT, condom provision, voluntary counseling and testing (VCT), and treatment.
6. Interventions that combine reproductive health services, HIV VCT, and male circumcision should be explored.
7. Should MC rollout begin, it is essential that surveillance systems be put into place to track who is presenting for services, incidence of adverse events, and disinhibition in circumcised populations.
8. Qualitative studies that shed light on people’s understanding of protection afforded by male circumcision—both for males and females—will be essential. It will be important to repeat these over time as events change. The perspective of parents will also need to be included.
9. Prevention models that include male circumcision, but do not focus on it exclusively, are needed to elucidate how male circumcision can be incorporated into a broader prevention framework.
10. Legal research is needed to understand barriers and facilitators of male circumcision, and the protections necessary to maximize benefits and reduce harms.
11. Stigma remains a central impediment in HIV prevention. Understanding how male circumcision reduces or enhances stigma will be essential.

Acronyms

AAP	American Academy of Pediatrics
ABC	Abstinence, be faithful, use condoms
AIDS	Acquired immunodeficiency syndrome
ANRS	Agence Nationale de Recherches sur le Sida (France)
ARV	Antiretroviral
BMA	British Medical Association
DFID	Department for International Development (UK)
DSMB	Data and safety monitoring board
FGM	Female genital mutilation
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HPV	Human papillomavirus
HSPC	Human subjects protections committee
HSV-2	Herpes simplex virus type 2
IDU	Injecting drug user
IRB	Institutional review board
MC	Male circumcision
MSM	Men who have sex with men
NHDS	National Hospital Discharge Survey
NIH	National Institutes of Health (U.S.)
PEPFAR	President's Emergency Plan for AIDS Relief (U.S.)
NGO	Nongovernmental organization
PLWH/A	Person/people living with HIV/AIDS
PMTCT	Prevention of mother-to-child transmission (of HIV)
PrEP	Pre-exposure prophylaxis
SRH	Sexual and reproductive health
STI	Sexually transmitted infection
TDF	Tenofovir disoproxil fumarate
UCLA	University of California, Los Angeles
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
UTI	Urinary tract infection
VCT	Voluntary counseling and testing
WHO	World Health Organization

Introduction

This report summarizes available information on male circumcision (MC) as an HIV prevention strategy and the policy and prevention implications of its implementation. To this end, the report examines:

1. Summary of HIV prevention science and practice;
2. A review of the currently available data from observational studies and randomized controlled clinical trials;
3. Adult male circumcision, other health benefits, and the implications for women's health;
4. Biological mechanism responsible for reduced susceptibility to HIV infection and other medical benefits among circumcised males;
5. Medical professional group policy statements pertaining to male circumcision;
6. Challenges related to male circumcision;
7. Research priorities;
8. Ethical concerns; and
9. Potential next steps.

It is urgent that we immediately address the myriad cultural, economic, social, ethical, moral, and political challenges related to male circumcision (MC) as an HIV prevention strategy. The first randomized controlled clinical trial to report impact of MC on HIV infection, the South African "Orange Farm" trial, released results at the July 2005 International AIDS Society meeting in Rio de Janeiro that demonstrated that MC could provide up to a **60% protective benefit** in 3,274 men aged 18-24 that were enrolled in the study. On December 13, 2006, the National Institutes of Health (NIH) announced the early termination of two additional randomized controlled trials of male circumcision—in Kenya and Uganda—based on interim evidence that MC has a significant protective benefit against HIV infection. The Kenya trial reported a **53% reduction** in HIV incidence among 2,784 enrolled men; the Uganda trial reported a **48% reduction** in HIV incidence among 4,996 enrolled men. The combined results from the three trials provide sufficient evidence that MC does provide protective benefit from HIV acquisition, but many additional questions remain unanswered.

Now that results are available from these three studies, it is urgent that planning for large-scale implementation begins. Plans for implementation of this magnitude need to account not only for the medical risks and benefits, but also social, cultural, economic, sexual, and other risks and benefits. We outline these issues and the associated challenges surrounding them to stimulate discussion about policy and planning.

Background

At the time this report was produced, approximately 39.5 million people globally are infected with HIV, of which, 24.7 million live in sub-Saharan Africa(1). Currently there are no available strategies that provide complete protection from HIV infection (other than complete abstinence, which is difficult to maintain and in the case of couples trying to conceive, unrealistic). Nor is a vaccine providing either full or partial immunity likely to be developed in the short term, and fundamental questions about whether a preventive vaccine is even feasible remain unanswered.

Significant emphasis has been placed on the development of novel prevention technologies and behavioral and social approaches that are intended to work in concert with one another. Currently, there are approximately a dozen such approaches being investigated. Current trials include:

- **Pre-exposure prophylaxis (PrEP)** is chemoprophylaxis using tenofovir disoproxil fumarate (TDF) or a combination of TDF and emtricitabine. Both agents are existing, well-tolerated antiretrovirals licensed in the U.S. and Europe to treat HIV infection.
- **Treatment or suppression of herpes simplex virus 2 (HSV-2).** With chronic or episodic use of acyclovir Infection with HSV-2 has been associated with higher HIV prevalence rates.
- **HIV viral load suppression** uses antiretroviral medications to treat HIV infection. and also has the potential to dramatically lower transmission rates.
- **Diaphragms** might prevent HIV from reaching the cervix and endocervix where most female infections occur, as well as providing women with the potential advantage of being able to protect themselves without the need to negotiate with a partner.
- **Vaginal, rectal, and topical microbicides** are substances that could be placed inside the vagina, inside the rectum, or topically on the penis to prevent infection.
- **New strategies for treating sexually transmitted infections**, a co-factor for HIV acquisition (eg, treatment of bacterial vaginosis); and for improving vaginal health.
- **New behavioral and pharmacologic strategies** for preventing and treating abuse of substances, including opiates, stimulants, and alcohol.
- **New strategies for making voluntary counseling and testing (VCT)** uptake more attractive and available. This has the potential to challenge stigma, reduce risk behavior, and heighten community level discussion about HIV.
- **More effective strategies for reducing mother-to-child transmission**, including reducing transmission of HIV through breast milk, and strategies for women whose HIV is not diagnosed until labor.
- **Treatment of depression**, as this has been related to HIV infection in several different studies.
- **Male circumcision**, the focus of this report, which has a rapidly growing body of literature, and findings from three randomized controlled clinical trials suggest has a substantial protective benefit against HIV-1 acquisition.

Why Do We Need Additional Prevention Strategies?

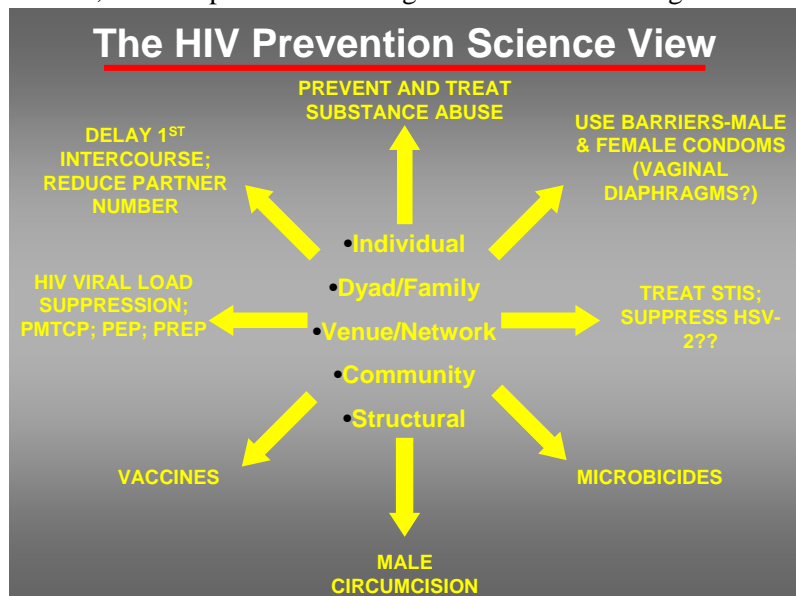
One might wonder why it is necessary to develop new prevention strategies and technologies when current devices such as the male and female condom are highly effective when used correctly and consistently. There are several reasons. The first is that the prevention literature demonstrates that it can be difficult to motivate certain groups of people to use male or female condoms every time that they are in a high-risk situation (eg, when consuming alcohol or using other psychoactive substances). The second is that it requires consistent effort to ensure that individuals continue to use condoms over time. Most studies show that it might be possible to get an immediate or even short-term (eg, 12 months) increase in condom use, but that this effect wanes over a longer period of time. The third is that there is substantial evidence demonstrating that condoms use drops significantly at the initiation of emotional, intimate, or long-term relationships, as use of condoms often signifies lack of trust. Nonetheless, there is also substantial literature demonstrating that women, especially in resource poor countries, are at risk for HIV and other sexually transmitted infections from their regular, not secondary or casual partners.

The search for other prevention strategies is not intended to replace condoms, but rather to add to the armory of available HIV prevention strategies. We know that having multiple prevention strategies allows more dynamic interventions that are able to respond to locally specific resources, culturally specific issues, as well as structural and geographical limitations. It may be possible that people will choose one strategy in preference to another, or choose one strategy at one time and a second at another time.

The Prevention Science View

The Prevention Science View diagram provides one perspective on HIV prevention and the science behind it. Delaying first intercourse and reducing number of partners can reduce HIV infection. Adults have a more mature reproductive health tract, more capable of resisting infection. Adults might also be

more equipped socially and emotionally to take precautions. A greater number of sexual partners increase the likelihood that one will come into contact with someone who has HIV or another sexually transmitted infection. This is especially true because those with more sexual partners are likely to be interacting across sexual networks where more disease is present, thus increasing the likelihood of infection. Stoneburner et al document the impact of partner reduction as a result of the communication about HIV/AIDS through social networks in Uganda(2). Similar effects were noted in Zimbabwe, Kenya and Haiti(3-6).



Psychoactive drugs (eg, opiates, stimulants, alcohol, etc) increase sexual risk. Barrier methods such as male and female condoms protect against infection, but they must be used consistently and correctly. Proponents of the vaginal diaphragm await the results of the efficacy trial in South Africa and Zimbabwe.

Treating bacterial and probably viral sexually transmitted infections reduces both transmission and acquisition of HIV.

Reduced viral load is associated with reduced probability of transmission. This concept has been demonstrated both for sexual transmission and in mother-to-child transmission. Suppression of viral load with antiretroviral medications reduces mother-to-child transmission and may also reduce sexual transmission. The trial to test the hypothesis that reductions in viral load achieved through medications reduces transmission (HPTN 052) is underway (7).

Several Phase III studies are underway to test various vaginal microbicide preparations; rectal microbicides are gaining traction in concept but are still only in preclinical or early human trials. Effective preventive vaccines may not be available for as many as 15 to 20 years in the future. It is possible that a therapeutic vaccine—one that reduces viral load or boosts immune response and therefore reduces infectiousness—may also prevent transmission(8).

As the “Prevention Science View” schema depicted in the figure demonstrates, social, behavioral, and biomedical interventions require work at multiple levels of society, including the individual, the couple and family, the network, the community, and at the level of policy and legal interventions. This also means that any intervention needs to address social inequities related to gender, race, ethnicity, socioeconomic status, occupation, age, sexual orientation, legal status, immigration status, educational status, or any other variable that drives the epidemic.

Ideally, the use of combination prevention strategies would be encouraged, as none of the available prevention strategies work perfectly all of the time. Alternatively, it might be possible for individuals to choose different prevention strategies in different situations.

The Research Evidence on Male Circumcision

Male circumcision may offer a powerful advantage over other HIV prevention strategies in that it involves a one-time surgery that does not require ongoing behavioral modification in order to work. The protection afforded by MC is temporally separate from the risk behavior. Once it is done safely, it is completed and the person does not need to exert any further actions in order to achieve the protection that circumcision affords. This may have significant implications in resource-poor settings where routine access and distribution of technologies that require ongoing use (condoms, antiretrovirals (ARVs), diaphragms, etc) may present operational hurdles that diminish efficacy.

Nonetheless, MC presents challenges. The cost associated with population-level MC may exceed a country’s financial resources and health care infrastructure capacity. Significant financial commitments would have to come from multilateral and bilateral organizations. Furthermore, people may develop the perception that circumcision provides complete protection, when in fact protection is far less than ideal (based on the recent clinical trials, approximately a 50% protective benefit under ideal circumstances at the time of vaginal intercourse).

Observational Studies

Since the mid 1980s, multiple observational studies have correlated male circumcision with reduced risk for HIV-1 infection. Based on results from these studies, it has been hypothesized that variation in HIV prevalence rates in Africa are associated with differences in circumcision practices. High HIV prevalence rates are associated with low circumcision rates.

In response to the mounting enthusiasm generated from the observational evidence of the potential protective benefits against HIV infection that male circumcision may provide, the Cochrane Collaboration published a comprehensive review of the available studies suggesting that circumcision can be used as an intervention to prevent HIV infection(9). The original findings were reported in July 2003 and were then updated in March 2005(10). The Cochrane review differs from previous reviews in that it attempts to assess the likelihood that circumcision will reduce heterosexual transmission of HIV to men. Previous reviews focused on the correlations between circumcision and HIV prevalence. No studies included in the review reported on medical complications associated with circumcision. It is important to note that the Cochrane Collaboration points out that many of the observational studies were poorly designed.

The updated review included 37 observational studies, 18 conducted among the general population and 19 among high-risk populations. Of the 18 general population studies included, 12 reported circumcision as having a beneficial effect (9 were statistically significant). All of the 19 high-risk population studies demonstrated beneficial effect.

Observational studies, unlike randomized controlled trials, might not have comparable groups of circumcised and non-circumcised participants because people were not assigned at random. Meta-analysis was not conducted because of heterogeneity in the multiple confounding factors present, including viral load, sexual behaviors, penile hygiene, religion, etc. Sigfried et al highlight that circumcision status itself may be a confounder, functioning as a proxy measure of knowledge about sexual practice, monogamy, and penile hygiene(10).

For example, a comparison of sub-Saharan Africans by religious affiliation indicates that circumcised Muslim men have lower HIV incidence than circumcised non-Muslims. Although Muslims almost universally circumcise males, there could be many specific behaviors (eg, washing before and after sex, prohibition against substance use, etc) that might account for the lower HIV acquisition risk in Muslims. It is not possible to exclude the possibility that the apparent protective effects of circumcision may reflect subtle differences in risk behaviors between Muslim and non-Muslim men or their partners. Another example occurs in the Rakai District of Uganda where married Muslim men are predominantly polygamous, and polygamous unions may provide a closed sexual network reducing the risk of HIV infection(11). Lower alcohol consumption among Muslims may also be a factor, as alcohol reduces inhibition and potentially increases high-risk behavior.

Randomized Controlled Trials

Randomized controlled trials are the only way to determine with relative confidence a causal relationship between male circumcision and HIV acquisition. Such studies need to conform to standard ethical practices, especially informed consent, counseling for risk reduction, and the promotion and provision of condoms. Using these standards, three major, African, randomized clinical trials were initiated in South Africa, Uganda, and Kenya. The French and United States governments (through ANRS and NIH, respectively) funded these studies with additional support from The Bill and Melinda Gates Foundation.

Public health officials in the United States, Europe, and Canada have been reluctant to make recommendations based on observational data alone, because one cannot rule out alternative explanations as to why the circumcised men might be less likely to become infected than the uncircumcised men. Although there is abundant, positive observational data supporting circumcision as a preventative HIV infection strategy, observational studies alone are insufficient to recommend circumcision as an intervention because extensive confounding variables exist that can mask the true reason as to why an association is found (9, 10).

The first trial to report outcomes, the South African “Orange Farm” study, showed a substantial protective benefit in the circumcised cohort: a 65% reduction in probability of HIV-1 infection(12). The trial was stopped early after interim review by the data and safety monitoring board (DSMB) determined that continuing the trial in light of such overwhelmingly positive results would be unethical. Due to the early termination of the Orange Farm study, it was not possible to continuously monitor participants and therefore will not be able to provide critical information pertaining to how circumcision may or may not change the men’s sexual practices, possible sexual disinhibition leading to riskier behavior, and the effect MC will have on condom use.

In addition to attempting to replicate the Orange Farm study to determine if male circumcision prevents infection, the Ugandan trial (which was designed to involve approximately 6,800 male and female participants) also investigated whether male circumcision will reduce transmission rates from people with HIV to those without HIV. A third randomized controlled trial, the Kenyan study, involved 2,784 previously uncircumcised HIV-negative men, half of whom were circumcised during the trial.

On December 13, 2006, the DSMB of the U.S. NIH announced the early termination of both the Ugandan and Kenyan trials based on evidence that male circumcision in these trials did provide substantial protective benefit against HIV infection. The Kenya trial reported a **53% reduction** in HIV incidence among 2,784 enrolled men, and the Uganda trial reported a **48% reduction** in HIV incidence among 4,996 enrolled men. The HIV prevention community is eagerly awaiting the detailed discussion of the interim results from the Kenyan and Ugandan trials.

South Africa (“Orange Farm”): “Randomized, Controlled Intervention Trial of Male Circumcision for Reduction of HIV Infection Risk: The ANRS 1265 Trial”

Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A.

In November 2005, Bertran Auvert et al, reported results from the South African “Orange Farm” trial after the DSMB stopped the trial based on an interim analysis of data collected after all subjects had completed the 12-month clinic visit(12). The results that lead to the early ending of the Orange Farm trial suggested that the risk of HIV infection was reduced by 60% in circumcised men. Important findings that may have implications on future studies and interventions include:

1. The participants were all drawn from the general population with a low lost-to-follow-up rate, suggesting that large circumcision trials can be effectively conducted in resource-limited settings;
2. The study noted that subjects in the male circumcision group had significantly more sexual contacts--an important factor for policy makers to consider as there is growing concern that MC may lead to sexual disinhibition and riskier behavior;
3. Auvert et al concluded that male circumcision provides a degree of protection comparable to what a vaccine with high efficacy would achieve.

With regard to a protective benefit for women, the authors assert; “...MC will indirectly protect women and, therefore, children from HIV infection because if the men are less susceptible to HIV acquisition, women will be less exposed.” This statement needs more rigorous scrutiny, insofar as it assumes that the benefits of MC to female sexual partners will not be counteracted by increased risk behaviors. Among societies where agency over one’s body and imbalances in sexual decision making are heavily weighted towards men, decreasing the susceptibility of men to HIV acquisition without cautious consideration of existing social norms may have a significantly less beneficial impact on HIV acquisition among women.

Uganda: “Trial of Male Circumcision: HIV, STD and Behavioral Effects in Men, Women and the Community”

Serwadda D, Wawer M, Gray R.

The study is being carried out by the Rakai Health Sciences Program, a research collaboration between the Uganda Virus Research Institute/Uganda Ministry of Health, Columbia University Mailman School of Public Health, Johns Hopkins Bloomberg School of Public Health, and researchers from Makerere University, Kampala, Uganda.

The study was conducted in Rakai District, Uganda, and was designed to enroll ~800 HIV-positive men. Following a detailed informed consent process, the men were randomized to receive either immediate (within several days or weeks) or delayed (two years) circumcision. The goals were to assess the safety and acceptability of male circumcision among HIV-positive men, and to assess potential effects of male circumcision on the acquisition of STIs such as HSV-2. The investigators hypothesize that male circumcision will be acceptable to and safe in HIV-positive men, will reduce the rate of acquisition of STIs, and will reduce the frequency of STI symptoms, such as genital ulceration.

The study design also included the enrollment of ~1,000 men who, regardless of their HIV status, decline to receive their HIV results, despite encouragement to do so. Hypotheses are that circumcision will be acceptable and safe in men who decline their HIV results, and will reduce the rate of acquisition of HIV and STIs, and the frequency of STI symptoms such as genital ulcers.

The study also planned to enroll up to ~5,000 female partners of the men in groups above, as well as 5,000 HIV-negative men enrolled in a complementary NIH-funded study of male circumcision for HIV prevention (which is being separately registered). Female partners were to be followed annually to assess the acceptability and safety of male circumcision, and potential effects of male circumcision on HIV and STI acquisition. The hypothesis is that male circumcision will be acceptable to and safe in female partners, and will reduce the acquisition of HIV and STIs such as HSV-2 and human papillomavirus (HPV), which causes cervical cancer.

Finally, the study was also designed to follow ~3,000 men and women in the ~50 communities where the circumcision trials are taking place, in order to assess community attitudes towards and knowledge of male circumcision, and to assess whether other preventive behaviors (abstinence, monogamy, numbers of partners, condom use, etc) change in the community once circumcision becomes available. The investigators hypothesize that male circumcision will be acceptable in the community and will not result in behavioral disinhibition (increased rates of high-risk behaviors).

The Gates-funded study is complementary to a separate NIH-funded trial of male circumcision in HIV-negative men who accept their HIV results and is being carried out by the Rakai Health Sciences Program study team. It is expected to report data in 2008. The latter study, which is enrolling 5,000 HIV-negative men, is designed to answer question about whether male circumcision is acceptable and safe in HIV-negative men, and whether the procedure reduces the acquisition of HIV and STIs.

The complementary Gates-funded trial is designed to answer the following question:

- Is male circumcision acceptable to and safe in HIV-infected men, and will it reduce the rates of acquisition of STDs in these men?

This question is of great importance for future circumcision programs:

- Is male circumcision acceptable and safe in men who decline their HIV results, and will it reduce rates of acquisition of HIV and STIS in these men?

Determining potential circumcision risks in these men (such as potentially delayed healing because of their higher risk behaviors) or benefits (such as potentially reduced rates of HIV and STI acquisition) is thus very important for the design of any future large-scale circumcision programs. From the public health viewpoint, it will be important to know whether such programs should include or exclude men who decline HIV results. The Rakai Program strongly recommends and encourages the receipt of HIV test results, and provides the results confidentially and free of charge. The great majority of Rakai Program research participants (85-90%) accept their HIV results, but a minority continues to decline, although the latter group is getting smaller every year. If participants decline their HIV results, the Rakai Program still provides them with detailed HIV prevention education and counseling. Enrollment of men who decline their HIV results is also congruent with Ugandan Ministry of Health Policy, which encourages but does not force individuals and study participants to receive their HIV results.

Enrollment of female partners is designed to answer important questions regarding potential effects of male circumcision on women. Should male circumcision reduce HIV and STI acquisition in women, this

would represent an additional important public health benefit and would increase the cost effectiveness of male circumcision programs. However, if the procedure is associated with increased HIV transmission (for example, due to increased transmission before a circumcision surgical wound is fully healed), it is crucial that such a potential risk be identified rapidly within a trial, in order to prevent the risk within trials and in any potential future circumcision programs.

Following enrollment, men in the circumcision arm are followed post-operatively, at 4-6 weeks, and at 6, 12, and 24 months. Men in the control arm are also followed at 4-6 weeks and at 6, 12 and 24 months. At baseline and follow up, men respond to a detailed sociodemographic, behavioral, and health questionnaire, and provide biological samples (venous blood, urine, sub-preputial swabs [prior to circumcision] and for circumcised men, foreskins are collected at time of surgery.) Samples will allow assessment of multiple infections, including HIV, HSV-2, gonorrhea, *Chlamydia*, and syphilis.

Female partners are followed annually, through the Rakai Community Cohort Study. Following written informed consent, women are administered a detailed sociodemographic, behavioral and health status questionnaire, and provide venous blood and self-administered vaginal swabs at baseline and study follow-up visits. The samples will allow assessment of multiple infections and conditions, including HIV, syphilis, gonorrhea, *Chlamydia*, *Trichomonas*, bacterial vaginosis, HSV-2, and HPV. Female partners of HIV-positive men receive an additional visit at 6 months post enrollment, in order to ensure expeditious assessment of potential risks.

Kenya: “Trial of Male Circumcision to Reduce HIV Incidence”

Bailey R, Moses S, Maclean I, Parker C, Ndinya-Achola JO, Agot K, Krieger J.

Uncircumcised men aged 18 to 24 were offered voluntary HIV counseling and testing. HIV-negative men were asked to enroll in the study. All study participants were interviewed to obtain sociodemographic information and assess behavioral risk factors. Participants were examined for significant medical conditions. All men were counseled in strategies to reduce their risk for HIV infection. Consenting men was randomly assigned to either the treatment (circumcised) arm or the control (uncircumcised) arm of the study. After circumcision, men were monitored for complications. They were counseled to abstain from sex until healing is complete. Follow-up visits occurred every 6 months for 2 years. Uncircumcised men were offered circumcision at the end of the follow-up period. The primary study endpoints will be HIV incidence and surgical complications. Additional outcomes will be the incidence of other sexually transmitted diseases and behavioral risks. Additional laboratory studies of foreskin tissue will evaluate the number and density of specialized cells rich in HIV receptors in order to illuminate the biological mechanisms by which presence of foreskin may increase HIV susceptibility.

Male Circumcision, HIV Viral Load, and Male-to-Female Transmission

In addition to reducing the risk of exposure to HPV, recent studies in Uganda suggest that in HIV-infected men, circumcision combined with lower viral loads reduces the risk of male-to-female transmission. The Rakai, Uganda study group recently reported that when HIV viral loads are not controlled, the overall effects of circumcision on HIV transmission from HIV-infected men to their HIV-negative partners was modest(8). However, when circumcised HIV-positive men had viral loads less than 50,000 copies/mL, no transmission occurred whereas in uncircumcised HIV-positive men with viral loads of less than 50,000 copies/mL, the transmission rate was 9.6 per 100 person years. For the Rakai group, circumcision afforded no protection from HIV transmission at viral loads greater than 50,000 copies/mL, suggesting that male circumcision may protect women from HIV transmission at lower, but not at higher, viral loads. This finding could have significant implications in Africa, as the majority of transmissions fueling the epidemic are male-to-female. Furthermore, it suggests that controlling the viral loads of HIV-positive individuals could have significant impact on lowering new infections and that this effect is amplified by

male circumcision. It is important to note that the Rakai group looked at individuals with naturally suppressed viral load; they did not look at individuals with suppressed viral loads due to antiretroviral therapy. Studies monitoring male circumcision combined with antiretroviral-suppressed viral loads in HIV-positive individuals should be conducted.

Other Health Benefits

Since the initial paper suggesting protective effectiveness of MC against HIV infection was published in 1986 and Wiswell et al first reported reduced UTIs in circumcised males over two decades ago, there have been extensive and impassioned debates as to the impact that male circumcision used as a public health measure would have on the reduction of STIs in the adult population(13-15). Many of these arguments have highlighted that insufficient and even contradictory evidence existed. Others have cited that although many prospective cohort studies exist, a lack of longitudinal studies limited the conclusions that could be drawn(16).

Indeed, the American Academy of Pediatrics' (AAP) 1999 decision not to recommend routine neonatal circumcisions partially rested upon this assumption(17). Since the Academy's decision, there has been mounting consistent evidence suggesting reduction of STIs in circumcised males. Fergusson et al recently reported results from a 25-year longitudinal study of a cohort of more than 500 New Zealand males that confirm the considerable reduction of STIs in circumcised males(18). Uncircumcised males were 3.19 times more likely to have STIs than circumcised males. The added power of longitudinal data makes it possible to examine circumcision status and infection risk over an extended period of time rather than at a point in time. The investigators report that if the entire cohort had been circumcised, STIs would have been reduced by approximately 50%.

In addition to the potential protective benefits from HIV-1 infection and UTIs, evidence exists that suggests male circumcision is associated with a number of other health benefits, including the reduced risk of genital ulcer disease and HSV-2. Minimizing HSV-2 infection and genital ulcer disease has the dual benefit of reducing HIV-1 transmission rates, as both significantly increase the probability HIV-1 transmission. Additionally, cervical cancer occurs at a higher rate in the female partners of uncircumcised males. The mechanism thought to be responsible for the increased cervical cancer is a higher transmission rate of HPV, which is associated to a greater extent with uncircumcised males.

Biological Plausibility

The mechanism thought to be responsible for reduced risk of incident HIV-1 infection in circumcised males is the presence of a significantly higher concentration of Langerhans cells, which are target cells for HIV-1 in the mucosal layer of the foreskin(19). Additionally, keratin is believed to provide a protective barrier against HIV-1 infection(20). The penile shaft and outer foreskin surface are well keratinized, while the inner mucosal layer of the foreskin is not(21). It is also argued that the sensitive foreskin may be more susceptible to micro-abrasion during sexual intercourse, which could provide an entry for STIs and HIV(22). Initial HIV target cell concentration studies were conducted among samples from Australian, English, and North American men. Recent results from Donoval et al confirmed that samples from African males (Kisumu, Kenya) were consistent with the previous finding(23). Donoval et al report higher concentrations of Langerhans cells in the foreskin mucosal layer and little or no protective keratin layer on the inner foreskin of the Kenyan study participants.

Potential Benefits to Populations

Herd immunity is defined as the resistance of a group to attack by a disease due to the immunity achieved in a large proportion of the members. The consequences of this process lessen the likelihood that an affected individual will come into contact with a susceptible individual.

The concept of herd immunity depends on achieving a critical breaking point in the spread of disease. For each disease, there exists a percentage of the population (the critical immune threshold) that when achieved will effectively stop or slow further transmission. As with smallpox and tuberculosis, the typical threshold for stopping disease spread is high. In the context of HIV infection, it is unlikely that full herd immunity will be achieved in the short term as no single strategy or combination of strategies are currently available to achieve a high enough protection at the population level. Nevertheless, technologies like male circumcision can significantly retard incidence rates and reduce overall prevalence insofar as the protective benefit for any single circumcised individual translates to decreased risk among sexual partners. It is important to note that epidemiologists and virologists point out that when there is insufficient coverage to thwart disease spread, while overall disease spread may be slowed, unforeseen problems can occur (eg, while overall population incidence may decline, incidence in a particular subgroup may rise).

Williams et al used modeling to project that large-scale implementation of male circumcision has the potential to avert approximately 2 million new HIV infections and 0.3 million deaths over the next ten years(24). Over the subsequent 10 years an additional 3.7 million HIV infections and 2.7 million deaths could be averted, totaling almost 6 million averted infections over 20 years. The greatest impact would be in southern Africa where circumcision rates are low and HIV prevalence is high. Additionally, Williams et al report that combining male circumcision with prevention strategies known to reduce transmission rates, such as the use of antiretrovirals, would further reduce new infections.

Table from Williams, 2006(24)

Table 2. Impact of MC on HIV Incidence, Prevalence, and Related Deaths in Africa

Region	Time Period	Incident Cases Averted (Millions)	Reduction in Incident Cases (Percent)	Prevalent Cases Averted (Millions)	Reduction in Prevalent Cases (Percent)	Deaths Averted (Millions)	Reduction in Mortality (Percent)
Sub-Saharan	2005–2015	2.0 (1.1–3.8)	8 (4–17)	2.2 (1.2–4.3)	8 (4–17)	0.3 (0.1–0.5)	1 (1–2)
	2015–2025	3.7 (1.9–7.5)	14 (6–32)	4.1 (2.0–8.3)	13 (6–31)	2.7 (1.5–5.3)	9 (5–19)
	2025–2035	4.4 (2.2–9.0)	13 (6–32)	4.7 (2.4–9.7)	13 (6–30)	4.9 (2.5–9.9)	14 (7–34)
Central	2005–2015	0.2 (0.1–0.3)	8 (4–17)	0.2 (0.1–0.4)	8 (4–17)	0.0 (0.0–0.0)	1 (0–2)
	2015–2025	0.4 (0.2–0.8)	15 (7–36)	0.4 (0.2–0.9)	15 (7–37)	0.2 (0.1–0.5)	9 (4–20)
	2025–2035	0.5 (0.3–1.1)	16 (7–39)	0.6 (0.3–1.2)	15 (7–39)	0.5 (0.3–1.1)	16 (7–39)
East	2005–2015	0.5 (0.3–1.0)	9 (4–18)	0.6 (0.3–1.2)	9 (4–18)	0.1 (0.0–0.1)	1 (1–2)
	2015–2025	1.0 (0.5–2.0)	14 (7–33)	1.1 (0.6–2.3)	14 (7–34)	0.8 (0.4–1.5)	10 (5–20)
	2025–2035	1.3 (0.6–2.6)	14 (7–35)	1.4 (0.7–2.9)	14 (6–34)	1.4 (0.7–2.8)	15 (7–36)
Southern	2005–2015	1.0 (0.6–1.9)	11 (6–22)	1.2 (0.7–2.1)	11 (6–23)	0.1 (0.1–0.3)	1 (1–2)
	2015–2025	1.9 (1.0–3.6)	18 (9–43)	1.9 (1.0–3.8)	18 (8–42)	1.4 (0.8–2.6)	12 (7–26)
	2025–2035	2.0 (1.1–4.0)	18 (9–43)	2.0 (1.1–4.1)	16 (8–39)	2.4 (1.3–4.6)	20 (10–48)
West	2005–2015	0.2 (0.1–0.5)	4 (2–9)	0.3 (0.1–0.6)	4 (2–9)	0.0 (0.0–0.1)	0 (0–1)
	2015–2025	0.5 (0.2–1.1)	6 (3–15)	0.5 (0.2–1.2)	6 (3–16)	0.3 (0.2–0.7)	4 (2–10)
	2025–2035	0.6 (0.3–1.3)	6 (3–15)	0.6 (0.3–1.5)	6 (3–15)	0.6 (0.3–1.4)	7 (3–16)
South Africa	2005–2015	0.5 (0.3–1.0)	11 (6–22)	0.6 (0.3–1.0)	11 (6–23)	0.1 (0.0–0.1)	1 (1–2)
	2015–2025	0.9 (0.5–1.8)	20 (1–48)	1.0 (0.5–1.9)	19 (9–46)	0.7 (0.4–1.3)	13 (7–27)
	2025–2035	1.0 (0.5–2.0)	19 (9–48)	1.0 (0.5–2.0)	17 (8–43)	1.2 (0.6–2.3)	22 (1–53)

Data are as defined for the countries and regions given in Table 1. Data are given separately for each region and for South Africa over the next ten, twenty, and thirty years. Full coverage of MC is reached in 2015. The table gives the reduction in incidence and deaths, over each ten-year period, and in prevalent cases at the end of each ten-year period. Reductions are relative to the baseline which assumes no change in MC prevalence. The calculations are done using the expected reduction in female-to-male transmission from the RCT and using the lower and upper 95% confidence limits of the reduction observed in the RCT [9].
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Although these projections are promising, there are several important caveats. First, the modeling analysis was based on the results from a single clinical trial (Orange Farm) and thus additional modeling based on

data from ongoing trials, once it is available, should be conducted. Second, the impact of a circumcision intervention depends on the current prevalence of male circumcision and HIV. Comparing the Williams modeling to the current epidemic in South Africa, a recent article in the *Mail & Guardian Online* reported that fifteen-year-olds in South Africa now have a 56% chance of dying before turning 60, versus ten years ago when they had a 29% chance of not making their 60th birthday(25). The article continues, “A third of women between the ages of 25 and 29 years are infected, while 19% of the country's working-age (age 20 to 64) population is HIV positive.”

Men Who Have Sex with Men and Penile-Anal Transmission

There is currently limited data available on the rate of HIV transmission for the receptive partner of a circumcised man in penile-anal intercourse. In a study evaluating sexual risk factors conducted among 3,257 MSM in six U.S. cities, Buchbinder et al reported that uncircumcised men were almost twice as likely to seroconvert than circumcised men (26). The effect of male circumcision on reducing the risk of HIV transmission among men who have sex with men has not been studied in a randomized controlled trial. It is also unclear what proportion of men involved in the South African, Ugandan, and Kenyan circumcision trials engaged in MSM or penile-anal intercourse. The protective benefits afforded by MC accrue primarily to the circumcised man. The rectal and vaginal epithelium do not contain traditional receptors for HIV-1 and provide a protective barrier to the underlying target cells. Because the rectal epithelium is a single layer, and mucosal trauma is often associated with anal sex, receptive anal intercourse is significantly higher risk than receptive vaginal intercourse(27, 28). The MSM population will likely not achieve the same prevalence reduction as the heterosexual population. Within the heterosexual population, it is also unclear what percent of men engage in penile-vaginal and penile-anal intercourse. The combination of penile-vaginal and penile-anal intercourse will also likely be a confounding factor in measuring prevalence reduction.

Male Circumcision, Sexual Functioning, and Post-Procedural Satisfaction

There is no current consensus on the role of foreskin on penile sensitivity(29). Limited comprehensive data on sensation loss after male circumcision currently exists. Many early studies conducted to evaluate the effect of MC on sexual function enrolled subjects with preexisting morbidities, which may be confounding factors of the results(30). Fink et al conducted a retrospective chart review of 123 men circumcised after the age of 18, of which 43 responded to a mailed survey. Although the study concluded overall satisfaction¹ rates, it also reported slightly reduced erectile function and decreased penile sensitivity (which bordered on statistical significance, $p = .08$). Senkul et al, responding to the power limitations and pre-existing morbidities of the Fink study, looked at 42 males who were circumcised between ages 19-28, none of whom had pre-existing pathologies(31). Of the participants, 39 were circumcised for religious reasons and 3 were circumcised for cosmetic reasons. Subjects were evaluated before and after using the Brief Male Sexual Function Inventory(32). The study concluded an increase in ejaculatory latency time (which the authors note could be interpreted as a benefit) and that the subjects' sexual function was not adversely affected.

The fields of reproductive health and sexually transmitted diseases have a long history of balancing prevention technologies as public health measures with diminished sexual sensation. Consistent and correct use of condoms has proven protective benefits against unwanted pregnancies and STIs; yet even in areas where access to condoms is not a barrier and >90% coverage is feasible, condom use is not consistent. One of the major cited barriers has been the diminished sexual sensation for both men and women. Nevertheless, the global campaign for 100% condom coverage is viewed as one of the most

¹ Satisfaction was defined as a more pleasing appearance of the penis to the men and their partners, and less pain experienced with erection.

effective strategies to thwart unplanned pregnancies and STIs. Several of the emerging prevention technologies (eg, topical microbicides, diaphragms) will likely encounter similar concerns regarding diminished sensation. While condoms, microbicides, and diaphragms are not permanent physiological alterations as is MC, there are several advantages to MC: 1) the protective benefits are separate from risk behavior; 2) unlike condoms and diaphragms, the protective benefits of MC do not require behavioral adherence; 3) MC has proven reduction of UTIs, STIs, and HPV transmission; 3) MC will easily work in concert with other prevention strategies.

Official Medical Professional Statements Regarding Male Circumcision

Medical professional groups have addressed male circumcision, especially of infants, and these official positions have changed over time. It is interesting to note that the U.S., European, and Australia/New Zealand groups have interpreted recent evidence in quite different ways. Further, it is important to note the change that has taken place in Botswana.

American Academy of Pediatrics (AAP) Circumcision Policy Statement

It is useful to consider U.S. circumcision policy and understand its origins, because many governmental agencies and nongovernmental organizations in the U.S. significantly influence global HIV prevention policy. This is particularly true in regards to ethical considerations of U.S.-funded international research, and interventions targeted primarily at high-prevalence areas in Africa, Latin America, and Southeast Asia that may result in international policy that is not consistent with that of the United States.

On March 1, 1999, the AAP issued recommendations stating that although evidence demonstrating medical benefits exists, the benefits associated with neonatal circumcision are not sufficient to warrant the recommendation of circumcision as a routine procedure(17). The policy statement, which was reaffirmed in 2005, indicates that in circumstances where a procedure has potential risks and benefits, yet is not essential to well-being of the neonate, the decision as to what is in the best interest of the child should be left to the parents. The statement continues, “To make an informed choice, parents of all male infants should be given accurate and unbiased information and be provided the opportunity to discuss this decision.”

The AAP’s focus on the immediate well being of the neonate, rather than the individual’s well being through their adult life and any public health benefits, is inconsistent with the Academy’s other recommendations. Specifically, the Academy recommends newborn immunization against hepatitis B. Unless in circumstances where a mother is hepatitis B positive, hepatitis B presents primary risk to the adult, sexually active population, not the neonate. This recommendation is clearly based on consideration of the well-being of the adolescent or adult population. It is important to note that the hepatitis B vaccine is relatively safe. This type of inconsistency may suggest that factors other than object assessment of neonatal well being are influencing policy.

Beginning in the Academy’s 1971 manual, *Standards and Recommendations of Hospital Care of Newborn Infants*, and reiterated in the 1975 and 1985 revisions, the AAP concluded that there was no absolute medical indication for routine circumcision. In 1989, in response to research exploring the links between circumcision status and both UTIs and STIs, particularly HIV, the Academy concluded that newborn male circumcision did have potential medical benefits and advantages, as well as risks. In 1997, the AAP redefined nontherapeutic circumcision of the newborn as an elective procedure. Although the current recommendations (1999; reaffirmed in 2005) acknowledge the potential medical benefits and risks, the statement asserts circumcision is an elective procedure that is not necessary for the immediate health of the neonate and as such, defers to the parents’ judgment. The National Hospital Discharge

Survey (NHDS) provides the most comprehensive data set of incidence rates of circumcision over time. The data offers limited sensitivity insofar as only 5% of U.S. hospitals participate. The NHDS divides the country into four census regions and also produces a combined average circumcision rate of all regions. For circumcision, from 1994-2001, rates fluctuate by region, but the combined national average was approximately 60% of male neonates being circumcised. Since 2002, there has been a decline in all four regions.

The British Medical Association (BMA) Position

As of June 2006, the BMA's position was:

Circumcision for medical purposes: Unnecessarily invasive procedures should not be used where alternative, less invasive techniques, are equally efficient and available. It is important that doctors keep up to date and ensure that any decisions to undertake an invasive procedure are based on the best available evidence. Therefore, to circumcise for therapeutic reasons where medical research has shown other techniques to be at least as effective and less invasive would be unethical and inappropriate. Male circumcision in cases where there is a clear clinical need is not normally controversial. Nevertheless, normal anatomical and physiological characteristics of the infant foreskin have in the past been misinterpreted as being abnormal. The British Association of Paediatric Surgeons advises that there is rarely a clinical indication for circumcision. Doctors should be aware of this and reassure parents accordingly.”

Non-therapeutic circumcision: Male circumcision that is performed for any reason other than physical clinical need is termed non-therapeutic (or sometimes “ritual”) circumcision. Some people ask for non-therapeutic circumcision for religious reasons, some to incorporate a child into a community, and some want their sons to be like their fathers. Circumcision is a defining feature of some faiths.

There is a spectrum of views within the BMA’s membership about whether non-therapeutic male circumcision is a beneficial, neutral or harmful procedure or whether it is superfluous, and whether it should ever be done on a child who is not capable of deciding for himself. The medical harms or benefits have not been unequivocally proven except to the extent that there are clear risks of harm if the procedure is done inexpertly. The Association has no policy on these issues. Indeed, it would be difficult to formulate a policy in the absence of unambiguously clear and consistent medical data on the implications of the intervention. As a general rule, however, the BMA believes that parents should be entitled to make choices about how best to promote their children’s interests, and it is for society to decide what limits should be imposed on parental choices.

Australia and New Zealand

Routine Circumcision of Male Infants and Boys - Summary Statement:

The Pediatrics and Child Health Division. The Royal Australian College of Physicians (RACP) has prepared this statement on routine circumcision of infants and boys to assist parents who are considering having this procedure undertaken on their male children and for doctors who are asked to advise on or undertake it. After extensive review of the literature the RACP reaffirms that there is no medical indication for routine neonatal circumcision.

Circumcision of males has been undertaken for religious and cultural reasons for many thousands of years. It remains an important ritual in some religious and cultural groups. In Australia and

New Zealand, the circumcision rate has fallen considerably in recent years and it is estimated that currently only 10%-20% of male infants are routinely circumcised. Circumcision is now generally performed with local or general anesthesia, and when the procedure is carried out for a medical indication this is usually outside the neonatal period. The best recognized medical indication for circumcision is phimosis.

In recent years there has been evidence of possible health benefits from routine male circumcision. The most important conditions where some benefit may result from circumcision are urinary tract infections, HIV and later cancer of the penis.

Urinary tract infections affect 1%-2% of boys, and may be about 5 times less frequent in circumcised boys, whilst circumcision has a complication rate of 1% to 5%. On current evidence routine neonatal circumcision cannot be supported as a public health measure on this basis.

Whilst there is some evidence, particularly from sub-Saharan Africa, that male circumcision reduces the risk of acquisition of HIV, evidence is conflicting and would not justify an argument in favour of universal neonatal circumcision in countries with a low prevalence of HIV.

Penile cancer is a rare disease with an incidence of around 1 per 100,000 in developed countries. Even though the evidence suggests neonatal circumcision may reduce the risk 10-fold, the rarity of the condition and its other recognized predispositions are such that universal circumcision is not justified on these grounds alone. The complication rate of neonatal circumcision is reported to be around 1% to 5% and includes local infection, bleeding and damage to the penis. Serious complications such as bleeding, septicaemia and meningitis may occasionally cause death. The possibility that routine circumcision may contravene human rights has been raised because circumcision is performed on a minor and is without proven medical benefit. Whether these legal concerns are valid will be known only if the matter is determined in a court of law.

If the operation is to be performed, the medical attendant should ensure this is done by a competent operator, using appropriate anesthesia and in a safe child-friendly environment.

In all cases where parents request a circumcision for their child the medical attendant is obliged to provide accurate information on the risks and benefits of the procedure. Up-to-date, unbiased written material summarizing the evidence should be widely available to parents.

Review of the literature in relation to risks and benefits shows there is no evidence of benefit outweighing harm for circumcision as a routine procedure in the neonate.

South Africa and Botswana

In July 2006, President Thabo Mbeki of South Africa signed into law the Children's Act which contains a clause that no male under the age of 16 may be circumcised except when, "performed for religious purposes in accordance with the practices of the religion concerned", or "for medical reasons on the recommendation of a medical practitioner".

The Government of Botswana also recently mandated that all mothers of newborn boys should be counseled on the potential health benefits of circumcision. The Eastern Cape Province of South Africa recently legislated against traditional circumcision. The law raises concerns regarding parents' ability to choose to circumcise their male infants for future health benefits. The law was passed in attempt to curtail the rising number of circumcisions performed as part of traditional initiation school ceremonies resulting in serious medical complications or death. The provincial department of health says that 243 deaths and

216 genital amputations from circumcisions were recorded between 1995 and 2004. Last year there were more than 20 deaths. Furthermore, traditional surgeons must now be officially registered with the department of health. Many health care practitioners and human rights advocates point out that “medical grounds” allowing circumcision should be clarified.

Challenges

While the results of the clinical trials are extremely promising and can have enormous impact on the HIV epidemic, there are numerous implementation challenges, contextual considerations, and ethical concerns that require rigorous attention. We identify here 15 such challenges, and the list could probably be expanded. Nonetheless, we present these to encourage discussion, and to ensure that these issues are considered as new medical findings get released and implementation plans are drawn up. Furthermore, we hope that these challenges will enrich and add nuance to the discussions as to how MC should be offered as an HIV prevention intervention, and what steps need to be taken to ensure it is implemented in an ethical and effective manner.

We highlight the following:

1. **Acceptability:** Price, pain, and lack of complications seem to be universal concerns and need to be attended to in rollout of male circumcision. Rollout programs will consider these and other issues as plans for scale-up and implementation are considered.
2. **Level of protection:** The benefit from male circumcision is relative, not absolute, and communications strategies will need to be devised to reinforce this point clearly. Further, any rollout must take into account the fact that male circumcision will be introduced into a relatively complicated prevention environment. Ideally, discussions of these issues will reinforce the benefits of other prevention strategies, and all prevention techniques will receive a needed boost in attention and funding.
3. **Risk** is typically defined in terms of medical risk; how can conceptions of risk be expanded to include social, psychological, cultural, or sexual factors? Acceptability on a population level, societal perception, and implications for gender dynamics, sexual practices and other issues should be factored into these discussions and given appropriate weight.
4. Interventions using male circumcision (as with other technologies) absolutely require behavior modification and educational components. It will be essential to place male circumcision within a broad prevention context in order to avoid many of the difficulties that may be associated with it. Ideally, the introduction of male circumcision will be used as impetus to gain support for the wider use of all prevention technologies and strategies. Male circumcision may help to focus attention on *combination prevention* and the need to use multiple prevention strategies in concert.
5. It will be essential to maintain funding for broader commitments in the fight against HIV, especially with regard to fighting gender inequity, stigma, and other issues related to disease spread. The implications of MC can be helpful if, as a result of the ongoing MC clinical trials, the scientific community and those who support HIV/AIDS prevention were led to increase their commitment to all solutions to the HIV/AIDS epidemic, and the broader fight against social inequalities that fuel the epidemic, such as gender inequality.
6. **Benefit to women:** How can male circumcision benefit women? How can male circumcision not harm women?

7. Religious and cultural practices need to be taken into account. Actual risk reduction, versus that of reduction rates achieved in controlled trials, is likely to have more regional variance and is dependent on local behaviors surrounding sexual practices, local drivers of the epidemic, and current prevalence rates.
8. The questions of when to circumcise—in infancy or adulthood—are hotly debated and will continue for some time. It may be easiest in infancy, but infants will not benefit immediately and cannot make informed choices.
9. Male circumcision and female genital mutilation (FGM): Opportunity to further distinguish the two? This raises at least two questions: a) whether promoting MC will in any way undermine current efforts to eliminate FGM, and b) how to understand the social and cultural discourses about the penis, about sexuality, and about sexual maturation that may all be affected, and potentially have positive or negative impacts on, an ostensibly neutral public health intervention.
10. Assessment and surveillance of safety and complications is essential to ensure that circumcisions are performed safely, that training is adequate, and that oversight is in place.
11. The challenges to health systems are enormous. The fact that health systems in many countries with high or growing HIV incidence are very poor and can not cope with the systemic or human resource requirements of an MC program without major additional short- and long-term investments. The estimated costs per circumcision could be significant when considering a developing country's per person health budget. The global experience with prevention of mother-to-child transmission of HIV (PMTCT) has already demonstrated the inability of global health systems to deliver on the promise of technical advances.
12. Male circumcision also needs to be considered and evaluated in a broader context of sexual and reproductive health, beyond the constraints of HIV alone.
13. Some have asserted that the trials and the calls for widespread implementation are being fueled by a form of racism. These issues need to be addressed seriously and included in the discussion.
14. It will be essential to determine how to avoid stigma associated with male circumcision or the lack of it.
15. It will also be essential to carry on the discussion around male circumcision to deliberately avoid branding men as perpetrators of infection.

Numerous ethical challenges will emerge as researchers define and apply the ethical principles of justice, beneficence, and respect for persons to current and future MC trials and research projects.

Challenge #1: Acceptability

The effectiveness of any circumcision intervention will be dependent on male uptake and community acceptance. In a review conducted by Westercamp et al, 13 acceptability studies conducted in sub-Saharan Africa among non-circumcising communities were evaluated(33). Of these studies, 8 were designed to specifically investigate acceptability of MC, of which 4 included women. The median acceptability was 65% among men; 69% of women favored their partners being circumcised, and 81% of both men and women were willing to circumcise their male children. Variance in acceptability ranged from 29% in Uganda to 87% in Swaziland, and is at least partially attributed to how the questions were

posed and in what context. Higher acceptance rates were achieved when participants received information regarding the potential health risks and benefits. One of the highest acceptance rates was achieved by Halperin et al (2006), who asked participants if they would prefer circumcision if it was proven to have protective benefits against HIV(34). While the majority of studies on acceptability of male circumcision demonstrate general favorability, meaningful evaluation of available data requires understanding of diverse ethnic and regional specificities.

The three most common barriers to circumcision are costs associated with the procedure, fear of pain, and safety concerns. This suggests that public health and other bodies responsible for considering implementation of MC will need to ensure that the procedure is affordable, especially to the most vulnerable populations. Further, great care will need to be taken to ensure that the procedure is done as painlessly as possible and that adverse events occur as infrequently as possible.

Concerns related to costs vary from study to study; with some studies reporting that subjects feel that circumcision should be free and offered by government health clinics, other studies showing that participants perceive free or inexpensive circumcisions as being of lower quality. Notably, the cost of traditional circumcisions in some areas was viewed as prohibitive due to the costs associated with ceremony or initiation schools. In one study, 34% of participants initially opting to remain uncircumcised changed their minds when the proposed cost was set at US\$3.00. Similarly, a pilot intervention in Siaya, Kenya reported that men came in large numbers when the cost was set at US\$1.45. Concern for lost salary from missed work due to the healing period was also widely expressed these costs are difficult to quantify in economic projections.

Concerns regarding safety and pain are common. Many non-circumcising groups are familiar with circumcising practices of other groups, and cite the endurance of pain as a key component in the rite of passage. Furthermore, circumcision is widely understood as a surgical procedure with inherent risks. This concern is partially shaped by either personal knowledge or periodic media reports of complications or death. In general, most studies reviewed suggest a preference for circumcision to be provided by trained medical professionals in public health clinics. Given these results, it is likely that if male circumcision proves to have a protective benefit consistent with available results from ongoing clinical trials, acceptability is high enough to have a potentially significant impact on the reduction of HIV incidence. The greatest impact will be dependent on the age of intervention and among mixed- or non-circumcising areas that have high HIV prevalence rates(24).

Westercamp et al note that local regions of ethnically homogeneous non-circumcising groups may present greater resistance to circumcision interventions than ethnically diverse populations, insofar as circumcision may be identified as a break from identifying custom(33), although this may not be a universal trend. For example, Swaziland is a predominately non-circumcising country with high acceptability of circumcision as a protective technology.

The generalizability of any acceptability result may be limited by the context in which the study took place. One of the most important contextual factors is whether the epidemic is generalized or concentrated, and whether or not there is adequate availability of ARVs. In the United States, for example, male circumcision might not be viewed as necessary for the majority of the population because they are not at high risk for HIV, and ARVs are widely available and seemingly effective. African American, Caribbean, and large immigrant populations of males might be more interested, especially if they know that they are at extremely high risk for becoming infected with HIV. The procedure might have more attraction in sub-Saharan Africa, unless ARVs become widespread, inexpensive, and easy to access. Under those conditions, HIV might start to be seen as a more manageable, less lethal disease.

If male circumcision is a common practice, or is practiced by some groups and not others in a heterogeneous society, then individuals may feel more kindly disposed to it. If it is a foreign practice, or seen as something that some other religious or cultural group practices, then it may be less acceptable. The answers people give also depend on how the questions are asked and how well people can understand the concepts. If circumcision is proposed to prevent HIV, it may have greater acceptability than if it is proposed to prevent some other sexually transmitted infection, especially if that infection is quite treatable. If circumcision is proposed to prevent HIV, have people been told that the protection is not perfect, but is perhaps only 50% effective or maybe even less? What is the breaking point? Would it be 50% or 75% or 90%? When that concept is presented, do people understand that the probabilities refer to populations and not to individuals, and that the probability for a given individual in a given act of intercourse is either 0 or 1?

We do not understand enough about what determines acceptability for men and for women. Are men interested in male circumcision because it will render them more attractive to women (who might think that they are not susceptible to HIV)? Are they interested because they think it removes the need to use condoms? Are women interested in men being circumcised because they think it is less likely that the man will have HIV? Is it ethical to promote the intervention on an individual basis when we know the greatest public health impact would require wide scale rollout?

How price sensitive will circumcision be? Would incentives work to increase acceptance in specific situations? If a popular or important leader got circumcised or endorsed it for the population, would the procedure become more acceptable?

All of these questions are raised to reinforce the point that facile interpretations of acceptability studies are hazardous. Acceptability studies may need to use more sophisticated marketing strategies, and probably need to rely heavily on qualitative methods so that we can understand and "unpack" what people might mean when they say that male circumcision might be acceptable. And, acceptability will wax and wane over time. If people are getting circumcised, and the procedure goes well, many more may want it. If it is inexpensive, or even incentivized, many more may want it. If there are reports of serious adverse events, such as occurred in the Eastern Cape of South Africa(35-37), or if there are relevant sociocultural or ethical issues that are not adequately being tended to, then people may mistrust the medical establishment or not be so eager to expose themselves to the risk.

Challenge #2: The Benefit from MC is RELATIVE Not Absolute: How Can This Be Communicated?

Ideally, what might happen is that discussion of these issues reinforces the benefits of other prevention strategies, and all prevention techniques are given a needed boost in attention and funding.

Maintaining clear and nuanced communications about male circumcision will be difficult, when passions for and against the practice are so pronounced. We know from other circumstances, such as for the rollout of ARVs, that such passions cause people either to emphasize the problems or the benefits in ways that are not helpful for public discourse.

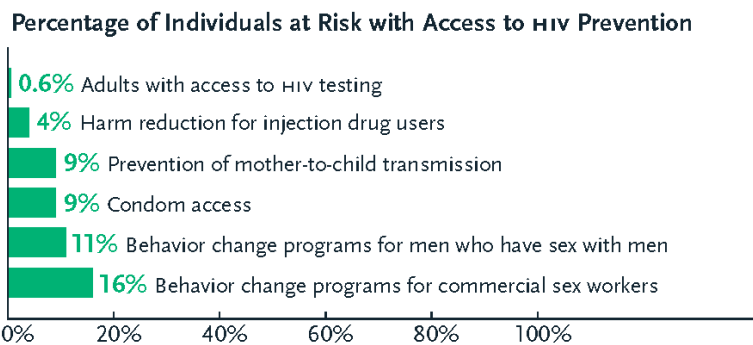
No single prevention technology or strategy will work on its own. All currently investigated strategies will require implementation in concert with one another. A vaccine providing 100% immunity is not likely to be developed in the short term, as fundamental questions about whether a highly effective preventive vaccine is even feasible remain unanswered. In the mean time, novel biomedical prevention strategies (such as microbicides, pre-exposure prophylaxis, etc) will be needed to effectively control the epidemic. As with MC, each of these strategies has the potential to lead to increased risk behavior. Caution should be emphasized so that the actual biomedical benefits of any investigational strategy are

not conflated with variables like risk behavior. Unlike other prevention strategies that are only as effective as the individual's ability to adhere to modified behavior or an ARV regimen, the protective benefits of male circumcision are disconnected from the actual risk behavior, making it an even more powerful strategy. The relative infection risk for each coital act remains the same. Increased risk behavior resulting from perceived protection of an intervention must be addressed in any strategy for rollout.

Any rollout must take into consideration the fact that male circumcision will be introduced into a relatively complicated prevention environment. The first complicating issue has been the (some would say unnecessary; others will say harmful) debate about abstinence, partner reduction, or condom use. The "abstinence, be faithful, use condoms" (ABC) approach to prevention has sparked debate about whether or not abstinence is better than partner reduction, and whether or not condoms provide sufficient protection against HIV and other STIs. The unfortunate consequence of this debate is that all three contribute to HIV prevention. Obviously, one cannot get HIV or an STI if one is abstinent, and delaying onset of intercourse may also render people less susceptible to HIV and other STIs. Older individuals' reproductive systems have matured to be more resistant to infection, and older individuals may be more capable of taking care of themselves emotionally and behaviorally. Reducing number of partners, especially concurrent partnerships, may reduce exposure to pathogens.

Nonetheless, some have seemed to pit one strategy against another, and disparage condoms in the process. This had lead to unnecessary confusion about the real and beneficial protective effect of condoms. The problem has been exacerbated by religious objections to condoms on the grounds that they might encourage promiscuity in an environment where abstinence and/or faithfulness within marriage should be supported (such discussions do not take into account that most women in sub-Saharan Africa, and perhaps in other regions, are put at risk for HIV and other STIs within the context of a marriage or committed relationship).

The second complicating issue is that the current prevention strategies--male and female condoms, prevention of mother-to-child transmission with ARVs, access to clean syringes and needles, voluntary counseling and testing for HIV, treatment for substance abuse (including substitution and maintenance chemotherapy for opiate abuse--have not been used widely at all. One could conclude that prevention has not worked because it has not been tried. The following chart, drawn from the work of the Global HIV Prevention Working Group and funded by The Bill and Melinda Gates Foundation, shows that fewer than one in five--just 4% to 16%--of people at high risk for HIV infection have access to effective prevention. The report goes on to state that access is particularly limited to populations known to be at especially high risk for infection, including sex workers, men who have sex with men, and injecting drug users (IDUs).



Sources: UNAIDS, 2006; USAID et al., 2004

The report also cites the fact that the current supply of condoms falls 50% short of the number required, and the number of condoms needed annually is expected to increase significantly as the population of reproductive-age individuals increases by nearly 25% in some countries between 2000 and 2015.

Within this context, it is entirely possible that male circumcision will be hailed as the great new intervention, compensating for the significant failures of prior strategies when in fact those strategies

were never fully implemented. The unfortunate circumstance may be that progress toward implementation of the other strategies falls to the wayside and all hopes are pinned on male circumcision. This would be ethically irresponsible because, as we have reported, the effect of male circumcision will be relative and not absolute.

Challenge #3: Defining Risk, Benefit, and Harm Reduction

Population acceptability, societal perception, and implications for gender dynamics, sexual practices and other issues should be factored into these discussions and given appropriate weight.

Beneficence is an ethical principle that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: 1) do no harm, and 2) protect from harm by maximizing anticipated benefits and minimizing possible risks of harm. Minimal risk for male circumcision is usually understood as minimal medical risk. The common risk/benefit analysis presented in discussions of male circumcision is framed typically in terms of the biological or medical well-being of the individual.

It would appear that the current studies, and those responsible for them, have limited their perspective of risk to “medical risk” and are providing limited consideration to possible negative social or gendered impacts. Placing the risk/benefit calculus in a framework that only considers, or even emphasizes, the medical harm minimizes the social, cultural, or psychological impacts that are a necessary part of any risk/benefit calculation.

Medical risk and adverse consequences require accurate and appropriate surveillance and documentation. It might be possible, for example, that a few sensational adverse consequences will attract media attention and headlines, and cause confusion, much in the way that some toxicities associated with ARVs sometimes are exaggerated both in terms of effects on individuals and the prevalence of those effects. Thus, it will be essential, if rollout occurs, that systems be set up to understand the range and prevalence of adverse effects, and the conditions associated with those effects, and that such information be used to improve the surgery for further use. If, for example, more adverse events are associated with a particular type of medical practitioner, or with traditional practitioners, then that information needs to be used to improve quality of outcomes lest individuals and populations be put at needless risk.

There are also several ethical issues that remain around the balance of expectations concerning local and international standards of care before and after trials—and who determines them. One issue is who should provide the needed treatments and services. Major ethical debates are currently circulating about whether public health interventions can or should provide treatment, and for how long, if participants are found to be HIV-infected.

Risk and risk aversion have different meanings to different groups of people. The concept of risk perception is socially constructed and culturally imbedded within groups, and individual risk perception is perceived through this sensibility(38-41). Policy statements pertaining to routine male circumcision are no exception. The social and economic factors that inform risk perception by the American Academy of Pediatrics, the British Medical Society, or any other developed country may not be congruent with those of societies within developing countries in which the risk of morbidity or mortality resulting from HIV infection (or a host of other opportunistic infections) is considerably higher. For example, the AAP may focus on the immediate health of a neonate because the adult risk of HIV is not high in the United States and access to ARV therapy is widespread. In developing countries where there is an incredibly high risk of HIV infection and access to life-saving drugs has not materialized, risk perception may dramatically differ from that of the U.S. Multilateral and bilateral organizations based in the United States and Europe should ensure that, when considering the risk/benefit calculus of interventions targeted to high prevalence

areas, harm reduction is understood in terms of regionally specific health risks. Equally important will be assurances from governments and community members that an MC intervention may have a positive impact; these assurances may play an important role in guiding policy.

Challenge #4: Placing Male Circumcision in a Combination Prevention Strategy Context

Ideally, what could happen is that the introduction of male circumcision can be used as impetus to gain support for the wider use of all prevention technologies and strategies, and that male circumcision causes us to focus on “combination prevention” and the need to evaluate the use of multiple prevention strategies in combination.

Consider the following letter published in *The New York Times* on December 19, 2006.

To the Editor:

Although I am encouraged by the discovery that circumcisions can significantly reduce the chances of transmitting the virus that causes AIDS, I am a concerned about how people living in the third world will react to this news.

We do still live in a world where men with AIDS in Cambodia have unprotected sex with virgin girls in the belief that it will "cure" them, as Nicholas D. Kristof noted in his Dec. 12 column.

I'm concerned that more men will be circumcised as a result of these studies, but that they will then live an even more promiscuous life. We ought not lose sight of the importance of condom education.

Edmund DeMarche, Brooklyn, Dec. 14, 2006

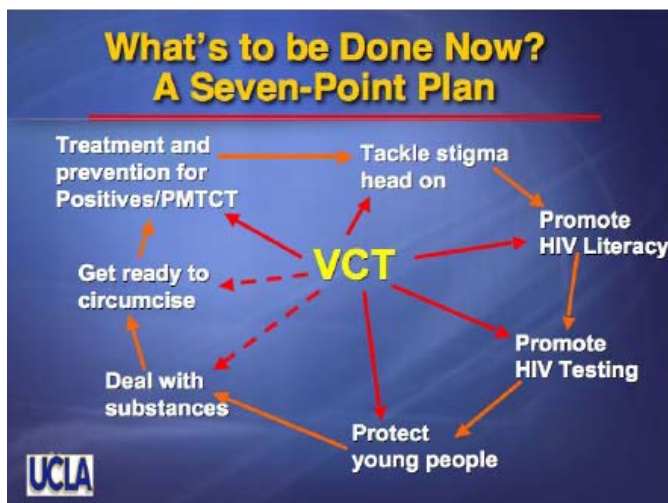
And another letter said:

How do you persuade a man to snip off a protective skin on the most sensitive part of his body? Condoms are infinitely safer than circumcision.

Marshall Guerra, Chicago, Dec. 14, 2006

One issue here is that condoms are pitted against male circumcision in a totally unnecessary contest. We need both prevention strategies. A second is the disparaging language (addressed below).

What is needed is a framework that place MC within the context of a broader framework of prevention strategies and that does not isolate the strategy, thereby reinforcing the notion that it has the potential to address the complexities of HIV prevention by itself.



Such a framework was presented by Coates in the December 1, 2006 issue of the *Mail and Guardian* (Johannesburg). This is but one example; we encourage others to be developed:

For every person given antiretrovirals (ARVs) for HIV in South Africa, seven more become infected. If that continues, the health system will be completely overwhelmed. The advances of treatment in South Africa currently are groundbreaking. This must continue, expand and reach every person who needs drugs. Every HIV-infected person should know his or her status and be monitored so that treatment starts when he or she needs it. A good starting point would be a seven-point prevention plan, to counter the seven people that become infected for every ARV treatment. Promote HIV literacy: Received wisdom is that everyone knows about HIV and its transmission. The truth and the facts are muddled for many. That is partly the government's responsibility and partly because widespread information and messaging campaigns are imperceptible.

Goal 1: By 2010, 75% of adults score 100% on Aids literacy tests.

Promote HIV counseling and testing: People cannot plan their futures, take treatment or prevent transmission (including to babies) unless they know whether they have HIV. The biggest barriers to HIV testing are logistics and cost. We have found that bringing HIV testing to people--either through mobile or door-to-door testing--massively increases uptake. Mobile testing draws youth and especially young men.

Goal 2: By 2010, 75% of people have been tested for HIV at least once.

Protect young people: They are the future of South Africa. Access to accurate information, services and condoms are fundamental human rights. Young people vitally need them.

Goal 3: Prevalence of HIV among youth is reduced by 50% by 2010.

Prevent and treat substance use and abuse: Alcohol is probably a major driver of HIV transmission in South Africa, but other drugs such as tick and cat are spreading rapidly and could further fuel the pandemic.

Goal 4: What if every alcoholic beverage sold were accompanied by a condom? It would get the message across and demonstrate commitment to HIV prevention.

Get ready to circumcise: The results from Orange Farm's male circumcision study are the most hopeful we have had in HIV prevention since we found that ARVs can prevent mother-to-child transmission.

Goal 5: Circumcise 50% of men by 2010; advise 100% of parents of baby boys about circumcision and 75% opt for it.

Integrate prevention into treatment for HIV-positives: HIV can only spread from those who have it to those who don't. Treatment for HIV is wonderful, not only because it extends people's lives and brings hope, but also because it gives us the chance to interact with HIV positive people regularly.

Goal 6: By 2008, every HIV-infected patient is advised about safer sex at every clinic visit, every patient is offered a bag of condoms along with ARVs. An annual sexually transmitted infections check is offered to all HIV-infected patients.

Tackle stigma head-on: The popular paradigm is sad: if someone has HIV, they've been sleeping around and they bring shame on themselves and their families.

Goal 7: By 2010, 75% of South Africans regard HIV like any other disease, and that 75% of people with HIV disclose their status.

Challenge #5: Maintaining Broader Funding Commitments to Social and Behavioral Research and to Fighting Gender Inequality

The implications of MC would be helpful if, as a result of the ongoing MC clinical trials, the scientific community and those who support HIV/AIDS prevention were led to increase their commitment to all solutions to the HIV/AIDS epidemic, and the broader fight against social inequalities that fuel the epidemic, such as gender inequality.

There is no vaccine to solve gender inequality or change behaviors, and the potential ethical implications of this larger over-reliance on biomedical solutions at the expense of social justice and human rights missions can't be dismissed. Finally, given the cost of circumcisions, the difficulty for health systems to scale up, and the lack of current attention in the field on the clear interaction between biomedical solutions and social and behavioral effects of interventions, some consider it unethical not to further promote behavioral prevention interventions financially, and in national-level communications at the same time as results and calls for further mass MC may roll out.

Challenge #6: How Will Male Circumcision Benefit Women? How Can Male Circumcision Not Harm Women?

There are two separate issues that must be considered: (1) benefiting women; and (2) shifting the disease burden toward women is a potential problem that may occur because the critical threshold to herd immunity cannot be achieved. Groups that advocate a cautious approach to male circumcision interventions increasingly voice this concern. The issue is that interventions that do not include adequate behavioral/educational components to ensure that the protective benefits of circumcision are not interpreted as allowing increased risk behavior among men, may in fact increase the risk to women. HIV-positive men are almost twice as likely to infect a female partner as an HIV-positive woman is to infect a male partner(42, 43). As a result, reducing the male prevalence rate would indirectly benefit the susceptibility of female partners. Modeling studies by Williams et al suggest that if male circumcision were to reduce female-to-male transmission by 60% as the Orange Farm clinical trial reports, it would have a population-level impact that reduced transmission in both directions by 37%(24).

Although mathematical modeling suggests that lowering the overall incidence of female-to-male transmission will lower prevalence rates for men and women (see *Herd Immunity* discussion above), and other studies suggest that MC combined with controlled viral burden in HIV-positive men will reduce transmission to their female partners, the degree to which MC as a prevention intervention will benefit women--or potentially increase their risk of infection--is uncertain and is a growing concern among social and behavioral scientists and policymakers. Of primary concern is that the sense of protection individuals associate with MC may lead to increased risk behaviors. Such behaviors could both diminish the

protective benefits and effectively shift the disease burden further toward women by increasing their risk. This argument is often framed as comparatively gauging the effective risk reduction for men and women separately. A strategy affording infection reduction to men that is misperceived as allowing more frequent risk behaviors may exacerbate existing gender disparities and further shift the disease burden to women.

Less obvious, but equally important, is addressing the underlying issues of why so much attention is given to the potential disinhibition of sexual behavior for male circumcision as a prevention strategy? Although there is some evidence regarding sexual disinhibition, there are conflicting results in various settings. Addressing behavioral disinhibition will have to accompany all prevention technologies (PrEP; viral load suppression; microbicides; vaccines; and even condom use, as inconsistent/improper use is pervasive). Some behavioral concerns regarding male circumcision may in part be linked to existing power discourses that connote specific gender and reproductive rights issues, (ie, coercive sex). Behavioral disinhibition would not be sufficient grounds to slow a prevention strategy that has such high potential for population impact. Behavioral disinhibition should be addressed in structuring effective messaging as part of rollout; it should not be used to withhold this technology (which in itself is counter to ethical principles of beneficence). While these issues are complex and are intimately related to prevention strategies, caution should be taken in distinguishing and evaluating with equal value the absolute biomedical harm or benefits of any strategy and its social impact.

Challenge #7: MC and Religious and Cultural Practices in the African Context

Historically, circumcision appears to have been practiced at one time or another throughout most of Africa, with the exception of the central inland east extending from southern Sudan to South Africa. Myriad circumcising and non-circumcising ethnic groups exist in both North and sub-equatorial Africa with diverse social histories. The practice, even among currently circumcising groups, was by no means consistently adhered to over time.

For groups that were not circumcising at the time of Colonial contact, there are at least two explanations for abandonment of the practice. The first is a less understood abandonment of circumcision and initiation schools in areas of south Malawi, Mozambique, parts of Zambia and Zimbabwe before arrival of the Europeans(44). The second explanation is better understood and relates to the Zulu wars in southern Zimbabwe and South Africa. The Zulu king Chaka ordered his people to stop the practice due to the difficulty of conducting initiation schools during the continuous period of fighting in the early 1800s. Many other groups that were also drawn into the fighting also abandoned the practice. That some groups readopted circumcision practices after the period of warfare, Jeff Marck explains as "...the general shifting of traditions and adopting other groups' styles and formats after long periods of abandonment"(44). Although the example of abandonment during the Zulu wars can not be generalized to the entire continent of Africa, it does provide an example of how circumcision patterns shifted because of historical factors even prior to Colonial imposition.

Religious beliefs are closely linked to the acceptability of circumcision. Islamic groups universally circumcise males. Many investigators have suggested the link between lower HIV prevalence rates in North Africa and the predominance of Islam and associated circumcising practices. As previously discussed, associating male circumcision in North Africa with lower HIV prevalence rates may be more complicated as sexual behavioral patterns among Muslims may have significant impact on curbing the spread of HIV(11, 44). In Africa, predominantly Christian groups have widely varying beliefs and inconsistent practices regarding male circumcision. In mapping the context of existing practices and strategies for potential interventions, local religious institutions and leaders should be involved, particularly where Christianity is prevalent.

Challenge #8: When to Circumcise: Infants vs. Adolescents vs. Adults?

The age at which circumcision is performed poses multiple challenges. Neonatal circumcision is considerably safer and substantially less expensive than adolescent or adult circumcisions(14, 15, 18, 45-49). If male circumcision proves effective and is only rolled out to neonates, it would take at least a generation before a population-level impact occurs. An adult intervention raises significant questions regarding the capabilities of existing health systems, increased complexity of the procedure, higher complication rates, and expense. Managing complications, and the associated costs, in resource-poor settings also raises significant concerns. Age at which a circumcision intervention is introduced is highly dependent on locally available capacity and training of staff. Surgical techniques that are feasible in resource-limited settings would have to be rapidly developed, as would clear guidelines for practitioners.

Modeling studies suggest that, although male circumcision could have an immediate and dramatic impact on HIV transmission, the full impact on prevalence rates and deaths would only be apparent in 10 to 15 years(24). Complicating the issue are the official statements, such as those cited in this document, regarding the advisability of infant circumcision, especially when such surgeries do not have an immediately beneficial therapeutic effect and/or the preventive impact will not occur for years.

Challenge #9: Taking the Opportunity to Further Distinguish MC from Female Genital Mutilation

The demand for male circumcision might lead to increased demand for female circumcision², especially in places where both practices are being carried out. The human rights reversals that are implied by this situation is one in which decades of work that has been carried out on fighting the harm of FGM to girls and women could be rolled back with implications for gender equity, rights, health, sexuality, and the body. Certainly, the ethical implications of attempting to make parallels between HIV outcomes with male circumcision and female genital mutilation are numerous. We advice caution and call for: a) extreme care around definitions of practices; b) warding off inaccurate parallels between MC and FGM; c) calls for action, advocacy, and media communications that ensure that inappropriate parallels are not made that would undermine long fought battles at the intersection of gender equality, women's rights, and harmful health outcomes on the issue of FGM; and d) consideration of a possible reinvigoration of human rights violations against girls and women if inappropriate parallels are made and actions supporting FGM moved forward.

The World Health Organization (WHO) describes the different types of FGM as follows:

- Type I - excision of the prepuce, with or without excision of part or all of the clitoris;
- Type II - excision of the clitoris with partial or total excision of the labia minora;
- Type III - excision of part or all of the external genitalia and stitching/narrowing of the vaginal opening (infibulations);
- Type IV - pricking, piercing or incising of the clitoris and/or labia; stretching of the clitoris and/or labia; cauterization by burning of the clitoris and surrounding tissue;
- Scraping of tissue surrounding the vaginal orifice (angurya cuts) or cutting of the vagina (gishiri cuts);
- Introduction of corrosive substances or herbs into the vagina to cause bleeding or for the purpose of tightening or narrowing it, and any other procedure that falls under the definition given above.

² Throughout this document we refer to female circumcision as female genital mutilation in compliance with World Health Organization's standard nomenclature.

The WHO reports that up to 80% of FGMs globally involve excision of the clitoris and the labia minora(50). The practice is conducted by several different cultures and religious groups. There are dramatic differences between FGM and male circumcision. FGM is partly structured to control a woman's sexuality and reposition it to focus on the male partner's pleasure. Removal of the clitoris eliminates the woman's ability to orgasm; and stitching the vaginal canal to make it smaller is carried out, in part, to increase male sexual pleasure due to tightening. Although significant medical and psychological morbidity has been documented, the perception of FGM by women in cultures that widely practice it varies. The importance of the practice as a group identifying marker and its cultural significance should be considered thoroughly when developing interventions intended to either eradicate the practice or minimize its severity (51). Comparisons to MC do significant violence to the global movement to eliminate the most severe forms of the practice. Male circumcision as an initiation practice is most often intended to signify either group affiliation or the transition from adolescents to adult status. From a cultural perspective, the intent is not to curtail or control the practice of one's sexuality. From a medical perspective, while circumcision may affect male sexual pleasure to a limited degree, circumcision as a public health measure is, at least in part, intended to keep men's sexual ability intact while providing protective benefits from disease.

Other than an unfortunate similarity in the naming of the procedures, male circumcision and female circumcision/FGM have no common health benefits. Male circumcision has been proven to reduce the risk of several sexually transmitted diseases, penile cancer, UTIs and a host of other diseases. FGM has no medical benefits and, in fact, may promote disease. The most severe forms of FGM are associated with tetanus infection, UTIs, gangrene, uterine infections, and other complications. In regards to HIV, UNAIDS has a clear position that, "There is no evidence or observational data that (female circumcision) would reduce the risk of HIV transmission; biologically, it is more likely to increase the likelihood of HIV transmission." Several recent studies of circumcised Tanzanian women have demonstrated the increased susceptibility to bacterial vaginosis and HSV-2, which are positively linked with HIV infection(52-54). The only biological-based similarity is that both procedures modify or remove sensitive tissues of the sexual organs.

Several possible components could be added to male circumcision interventions to ensure that participants do not believe similar benefits are gained from FGM. One possibility is to introduce joint counseling services for men and their female partners during the consent process. Additionally, male circumcision could be integrated as part of reproductive health services that provide both the circumcision procedure and family planning that distinguishes FGM from MC.

Challenge #10: Assessment and Surveillance of Safety and Complications

In developed countries it is difficult to accurately report complication rates as they vary widely depending on the type of study, setting, person performing the surgery, and most importantly, how complications are defined. This problem is compounded in resource-limited settings where multiple confounding factors may be present and basic sentinel surveillance is often limited. Limited data exists on the safety of male circumcision in resource-poor regions with high HIV prevalence. The procedure, whether conducted by traditional circumcisers or in medical facilities, is often conducted under suboptimal conditions, increasing the risk of immediate and future complications. Nevertheless, there is limited data suggesting that safe procedures utilizing accessible resources could be established in resource-limited settings. In a recent article, Krieger et al working in the Kisumu district of Kenya demonstrated that standard procedures for safe and acceptable MC services could be established in developing countries(55). The study used locally trained staff to conduct the procedures, and all supplies and instruments were locally obtained. In the United States, two large retrospective studies are often cited. The first, conducted by Wiswell et al reviewed the records of 136,086 boys from 1980-1985 for complications over the first month of life and found a 0.19% rate of complications, the majority being relatively minor(49).

The second study conducted by Christakis et al retrospectively reviewed the circumcision status of 354,297 neonates, of which 37% were circumcised, over 9 years (1987-1990) (56). The study reported a 0.20% complication rate, but also advised that although the procedure is relatively safe, “modest medical benefits may be offset by its complications.” The most common complications in both these studies were post-circumcision bleeding and infection. The major limitation to both of these studies is neither monitor or report complications after the newborn is discharged from the hospital. A longitudinal study following 500 New Zealand children from birth to 8 years post-circumcision reported an 11% complication rate (vs. 18.8% for uncircumcised males)(18). Although circumcision appears to provide a lifetime of numerous medical benefits, it is not without risk. The assessment of personal and public health benefit verses relative risk may differ dramatically by regionally specific confounding factors. In regions where high HIV prevalence rates expose the population to risks that have devastating impact on entire societies, the risks associated with MC may be outweighed by the potential lives saved. There is an urgent need to conduct further research on locally specific risks in resource-limited settings and to establish country plans for surveillance of procedures and complications.

Challenge #11: Health Systems Challenges

Implementation of male circumcision will be difficult and will strain the resources of health systems in many countries, especially those that need it the most. Prevention of mother-to-child transmission (PMTCT) is still accessible to only 9% of mothers who need it, rising from 5% in 2003 to the current figure in 2005. Blood safety remains an important issue in several sub-Saharan African countries, and infection via occupational exposure (because safer devices or even clean needles and syringes are not accessible) also continues to occur.

Several issues emanate from this reality. The first is the need to continue to build and develop health systems in countries that most need it. HIV/AIDS has provided the opportunity to do so, especially given the aggressive targets for getting people onto ARVs.

But the second is the need to do so without distorting or diminishing resources from other critical aspects of the medical care system. The modeling done by Williams et al projecting thousands of new infections averted and overall reduction of prevalence rates were based on the results of the Orange Farm trial(24). With the release of the recent data from the Uganda and Kenya trials confirming the protective benefits found in Orange Farm, the Williams modeling gains further strength. The implications of averted new infections and reduced prevalence rates are that resources currently committed to combating HIV would be freed. While this is true, it will take time, as Williams points out that it would take approximately 10 years to reach the initial threshold of 2 million averted new infections and 20 years to reach approximately 6 million averted new infections (see discussion above, *Potential Benefits to Populations*). Each year would increase averted infections, presumably freeing funds. This means that substantial resources would initially need to be invested from international agencies to accommodate scale up of MC interventions and that funds could be re-allocated to other health systems needs as prevalence drops.

Immediate resource allocation will require comprehensive analysis as reduction in HIV prevalence could have a potential dramatic impact on available health system resources in the future. While achieving high rates of circumcision might be beneficial, it should not be at the cost of other disease prevention strategies such as antenatal care, malaria control, nutrition, etc. Since an internationally agreed-upon public health goal is for all women to give birth in health facilities, offering male circumcision in clinics to babies would at least not divert national resources from current efforts to build systems and might be a strategy that has multiple benefits. It might mean, however, that women have to remain longer in those settings and adequate resources will be essential to ensure that the goals might be met.

A major issue has to do with the need to ensure that there are sufficient personnel available to perform circumcisions, and whether or not the procedure necessarily needs to be performed by a physician, or whether medical officers, nurses or others can perform the surgery. Basic competency levels and certification that personnel are able to meet these standards must be established. An important issue highlighted in several XVI International AIDS Conference (Toronto, 2006) venues was the paucity of skilled health care personnel and the lack of proper medical training, even to perform the current tasks. Skilled, trained health care personnel are desperately needed to accommodate treatment needs in the context of wide-scale distribution of ARVs and appropriate follow-up treatment and care, particularly given the need for more widespread HIV testing scale up. In some contexts, many health workers received their medical training prior to the emergence of HIV, and therefore have little or no knowledge of the diagnosis and treatment of HIV and HIV-related illnesses. For some who received training after the onset of the epidemic, but prior to the availability of ARVs in their region, many still believe that HIV/AIDS is an invariably terminal and unmanageable condition. Those aware of ARVs may lack the knowledge to administer them properly.

In other contexts, community-based workers who may be lacking “formal” health-care training are delivering the highest standard of care. Volunteers have played important roles in counseling and care, but investment is needed to bridge the gap and maintain consistency in quality of care for the long term, since altruism alone may be inadequate in providing sustained motivation for volunteer involvement in long-term health programs, particularly in high-burden settings where volunteers may be subject to many of the same environmental conditions contributing to disease(57).

The South African (Orange Farm), Kenyan, and Ugandan MC randomized clinical trials all employed highly trained medical staff in controlled environments to perform the surgical procedure. As would be expected, complications in these controlled settings are relatively low; Orange Farm, the only trial of the three to report results, reported a 3.8% complication rate. Low complication rates may be significantly higher outside a controlled clinical trial environment. Questions pertaining to safety, human resources, and adequate medical training in resource-poor environments remain a high concern. A recent study in Ibadan, Nigeria reported a 20.2% complication rate among a cohort of 322 circumcised male infants ranging in age from 8 days to 13 months in which circumcisions were performed by nurses (55.9%), doctors (35.1%), and traditional circumcisers (9%)(58). Over eighty percent of these circumcisions were performed in a hospital setting. Other studies in Nigeria and Kenya cite complications rates (of varying severity) ranging from 12-17.5% in hospital settings.

Returning to Williams’ modeling, any initial intervention will take time (nearly a decade) before a dramatic impact is seen on population-level prevalence. It is unlikely that a rapid response that will achieve sufficient coverage to avert millions of new infections over the next decade can be achieved without a scale up that does not solely rely on physicians or nurses.

Health Care Infrastructure. For men who undergo an important initiation into manhood when circumcision is performed by a “traditional” surgeon (as is the case for many men in South Africa), there may be important reasons to provide solid training to those outside of the medical establishment to support important cultural rites of passage and their continuation. It is unethical not to further promote behavioral prevention interventions. What if demand outstrips capacity? Where will men get this done? What are the ethical implications of putting forward a practice and suggesting it *en masse* if families have to eventually decide, due to lack of health care capacity, which person they will or will not circumcise?

Incorporating trained and certified traditional circumcisers and nurses should be considered. It is likely that traditional circumcision practices will continue, regardless of regulatory mandates limiting them(35, 36). It is also conceivable that if circumcision receives the same level of acceptability reported from studies, and health care systems are incapable of meeting demand, unregulated and unsafe circumcisions

may rise dramatically. The ability to incorporate these providers into scale up provides several advantages including the reduced strain on existing health care systems, a more rapid scale up, and the ability to regulate and monitor circumcision conducted in a cultural context. Equally important will be engaging traditional circumcisers and potentially incorporating the complex social dynamics associated with traditional ceremony into a population-level intervention that could avert millions of deaths. Finally, as discussed above (see *Acceptability*), religious and cultural leaders have substantial influence on circumcision practices and, as Westercamp recommends, should be consulted prior to any intervention. They could present significant barriers if they are not engaged in scale up (33).

Challenge #12: Placing Male Circumcision Within a Broader Context of Sexual and Reproductive Health and Beyond the Constraints of HIV Alone

The intensification of linkages between sexual and reproductive health (SRH) and HIV/AIDS is not simply a service issue but is at the core a policy and program issue as well. These linkages are complex and involve family planning, maternal and infant health, management of STIs, and management of other sexual and reproductive health (SRH)-related issues on the one hand, and HIV/AIDS prevention, treatment, care, and support on the other.

Areas where key linkages need to be made include VCT, the promotion of safer sex, STI management, tending to the SRH of people living with HIV/AIDS (PLWH/A), tending to the primary health care of PLWH/A, integrating HIV/AIDS prevention and care into maternal and reproductive health, examining SRH and safer sex between discordant couples, and optimizing other connections between HIV/AIDS and SRH (eg, gender-based violence, female condoms). The challenge here is to place the discussion and advancement of male circumcision within this broader context and not restrict the discussion to HIV/AIDS alone.

Male circumcision provides the additional benefit for partners intending to have children. It provides a level of protection against HIV, STIs, and HPV while allowing for pregnancy.

Challenge #13: Perceptions of Inequitable Power Relations between the North and the South and Reinvigorations of Essentialized Notions of Male Sexuality

The power relations implied by the way in which developed countries are carrying out trials in developing countries for a practice that has finally been declared medically unnecessary for babies in the West may be tainted with unfortunate accusations of new forms of colonialism(59). While these accusations are relatively few, and have come from adamant opponents to routine MC, they have the potential to distract from important questions of scale up. Nevertheless, there are significant ethical concerns pertaining to MC randomized trials. Trials are being carried out consistently in Africa, when several other countries, including the inner-city United States, clearly have significant epidemics. While they may not be as severe as many regions in Africa experiencing generalized population-wide epidemics, they are nonetheless local epidemics. What are the ethical issues around “exporting” a rejected practice from the West (eg, AAP, BMA, Australia, New Zealand, Canada, etc) to the South, while not calling for implementation of it in the West too?

The ethical principle of justice asks questions about who ought to receive the benefits of research and bear its burdens. This is an issue of social justice, in the sense of considering fairness in distribution or what is deserved. An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly. Thus, some may argue that the principle of justice would center on whether particular racial and ethnic minorities or individuals in particular regions of the world are being systematically selected for participation in MC trials simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to

the problem being studied. As the medical, prevention, public health, and advocacy communities are perched to hear the results of upcoming trials, these issues will undoubtedly and increasingly come to the fore.

Thus, the ways in which developed countries are carrying out trials in developing countries for a practice that has been declared medically unnecessary for the West may also invariably reinvigorate racist perceptions of sexuality and African masculinity in regions where the trials are not conducted. Specifically, MC trials have already likely reinvigorated perceptions that the epidemic is largely “heterosexualized”—that men’s sexual behavior is problematic and “excessive”—only to be contained by medical surgery and an essentializing notion of male sexuality. No matter how acceptable MC may be internally to communities in various regions, the gaze of external audiences might stigmatize men in regions not experiencing the severity of the sub-Saharan African generalized epidemic. Perceptions of race are fluid, and racial formation is influenced by both proximal (local) and global factors. Diasporic communities of African men, their descendants, and men whose ancestry is of the global South are influenced and shaped by the gaze of the West on Africa. That is, the assumed relationship that men of color in the Global South have to their own (and others’) bodies and sexuality under a suggested roll out of MC—that some men are more moral and can contain themselves while others need surgery on their genitals so as to not impose damage on the populace—may become part of the public perception and this stigmatizing effect has been left out of studies and commentaries on trials thus far. While individuals in other nations will not bear the ethical brunt of the implications of the science in this way, men in the Global South may not be able to avoid it, and trials might exacerbate erroneous perceptions that men are perpetrators of the disease and responsible for it. Additionally, there is a need to investigate how MC as a HIV prevention strategy may affect social and cultural meanings about the role of the penis in constructing men’s sense of themselves and their sexuality.

Challenge #14: Avoiding Stigma Associated with Male Circumcision or the Lack of It

Remarks at the XVI International AIDS Conference in Toronto in 2006 placed the importance of female-initiated methods of HIV/STI prevention (and especially microbicides) at center stage. The comments were important and useful, and it was refreshing to see major leaders talking about equity, prevention, female-controlled methods, and condoms. The choice of words revived a familiar and important discourse that was not critically examined deeply enough at the conference. The resurgence of an individualist innocence discourse brought to the fore the need to advance rights-based approaches to HIV prevention and care without falling into the trap of morality, judgment, and blame.

This innocence discourse, long used to set apart babies, hemophiliacs, faithful wives, and orphaned children as deserving of protection and health services, might be a way to make condoms (and other prevention strategies) palatable to politicians and others. However, such discourse may perpetuate stigma, minimize structural factors that affect both women’s and men’s HIV risks, and does not deal with issues of marginalized populations (eg, MSM, commercial sex workers, and IDUs).

Lurking just below the surface in many presentations is the belief or perception that people in certain countries or regions are more promiscuous, more callous, less empathic, or less moral. For numerous reasons, some are framed as more damaged from their past and present environments than others. All too quickly, this can slide into discussions of morality, “excessiveness,” or personal responsibility. The ensuing conversations about sexuality may be too individualized (or group-based) and become a justification for racism and inequitable judgments on populations from the Global South (or inner cities of the North). Also lurking below the surface is the attitude and expectation that people living with HIV should abstain or minimize sexual activity and refrain from pursuing a full sex life, including procreation.

In this context, the questions are these: Will those men who choose not to become circumcised be branded as risky? Will they be assumed to have HIV infection? Will they be stigmatized as individuals not willing to do all that they can to reduce the spread of HIV? Will parents of young women want certification of circumcision in the male partners of their daughters?

Further, the need remains to better understand sexual behaviors and sexuality in diverse populations, as well as the needs of sexual minorities, especially in places where discrimination, stigma, and legal sanctions are practiced. Any discussion of male circumcision, and its advisability for specific populations, needs to be placed in this context.

Challenge #15: Avoiding Discourse That Brands Men as Perpetrators of Infection

In the present context, the challenge is this: Will advancement of male circumcision further brand men as perpetrators? Will male circumcision be seen as “the answer” to the need to change conceptions of masculinity in society? Will efforts to modify male social norms and behaviors be given short shrift in the desire to advance male circumcision more generally?

There were new and important emphases at the Toronto AIDS conference placed on structural inequities facing women and how to adequately respond with new interventions at this level (eg, educational and economic interventions, property rights, continued legal reform). But most sessions referred to gender as a women’s issue, and there were few sessions on gender relations, men, and masculinity. Even fewer sessions examined the role of racism in the exacerbation of the epidemic. Some of the discourse and research framed “problems” related to the epidemic as the fault of individual men instead of examining a system of interlocking race, class (or caste), age, and gender relations. Overall, particularly strong vilification of African men occurred throughout the conference.

Improving gender equality will go a long way toward resolving some of the most powerful dynamics of HIV transmission. It will remain important to examine the disenfranchisement that both women and men face, and to develop programs to fight structural inequities. Vigilance will be required in order to avoid the trap of individualizing problems/solutions that pit men and women against one another. A rights-based agenda can advance women’s status and reduce their HIV/AIDS risks, and hence a women’s empowerment agenda needs to be advanced.

However, it also remains vital that discourse and research find a more accurate way to describe men and masculinities, particularly as these intersect with race, class/ caste, sexuality, and nationality, in order to take a comprehensive gender relations agenda forward. One writer for *The Toronto Globe and Mail* said, “...changing the behaviour of African men is probably hopeless.” These kinds of stereotypes of African men serve to entrench both a highly racialized perspective on African males’ sexuality, moral depravity, and common modes of thought about gender, rather than advancing these discussions. African men are being portrayed as vectors, unconcerned about others and spreading disease along with violence and neglect for families.

What Research Needs to Be Conducted?

We provide here a list of ideas, in no particular order, about research initiatives that might be undertaken to address some of the challenges articulated above. We anticipate expanding this list as people reading this and other reports consider these issues and challenges.

1. What is the effect of male circumcision on female partners—not just related to HIV, but also sexually transmitted infections (STIs), cervical cancer, female pleasure, and female perceptions of sexual viability of the male partner?
2. There are often few ethical guidelines on the social and behavioral effects of biomedical trials—only medical effects and adverse events are examined. Social and behavioral effects need to be defined, and studies need to be carried out on the positive and negative consequences related to study participation.
3. Is penile hygiene as good as MC? Clinical trials that include a penile hygiene study arm should be conducted. These studies should also conduct analyses of feasibility, required resources, and infrastructure requirements.
4. Although much cost analysis, particularly in the United States, has been conducted to project the cost savings from averted HIV infection, STIs, and urinary tract infections (UTIs), there is a lack of data projecting the costs of treating circumcision-related complications. How will complications be addressed in resource-poor settings?
5. The development of models that include cost analysis for training practitioners in resource-poor settings is urgently needed. Modeling should project the cost of equipment and its maintenance, and the treatment of complications. These projections should be comprehensive modeling strategies including PMTCT, condom provision, voluntary counseling and testing (VCT), and treatment.
6. Interventions that combine reproductive health services, HIV VCT, and male circumcision should be explored.
7. Should MC rollout begin, it is essential that surveillance systems be put into place to track who is presenting for services, incidence of adverse events, and disinhibition in circumcised populations.
8. Qualitative studies that shed light on people’s understanding of protection afforded by male circumcision—both for males and females—will be essential. It will be important to repeat these over time as events change. The perspective of parents will also need to be included.
9. Prevention models that include male circumcision, but do not focus on it exclusively, are needed to elucidate how male circumcision can be incorporated into a broader prevention framework.
10. Legal research is needed to understand barriers and facilitators of male circumcision, and the protections necessary to maximize benefits and reduce harms.
11. Stigma remains a central impediment in HIV prevention. Understanding how male circumcision reduces or enhances stigma will be essential.

Ethical Issues for Future Research

As human subjects protections committees (HSPPCs) or institutional review boards (IRBs) are only beginning to define what the social and behavioral effects of participation in a biomedical trial are (with emphasis only on “adverse events”), the field should attempt to be ethically ahead of the curve on these

issues and not wait for protests that may soon follow (a letter of caution has already been written by many leading thinkers in the field to the WHO asking for immediate consideration of ethical issues such as these to be taken into account).

Ethical Issues Related to Informed Consent

There is anecdotal information that men in several areas of high HIV prevalence are eager to be circumcised. One rather large ethical implication of these trials for future research involves the question of how consent is given by men. In some instances, researchers' may have meetings with community leaders—often including traditional, tribal, and political leaders—who then lead discussions with men, who subsequently volunteer.

But the actual question remains as to whether individuals within a village can maintain the ability to individually refuse participation while the village is being strongly encouraged to participate from its leaders. Additionally, the extent to which full disclosure about the risks and benefits are being offered to men at the group or individual level (particularly given the lack of sociocultural, gendered, tribal, or other cultural factors in the definition of risk/benefit calculation). The extent to which men feel coerced or pressured into volunteering have not been evaluated.

Ethical Implications for Past, Present, and Future Trials

Circumcision does not have a strong history of being systematically and ethically examined prior to claims being made about its ability to resolve health problems. The historical record shows that it has been claimed to prevent hydroencephalitis, persistent masturbation, epilepsy, insanity, tuberculosis, spinal paralysis, hip dysplasia, STIs, penile cancer, cancer of the tongue, and more.

IRB Principles of Respect for Persons, Beneficence, and Justice

Recognized principles that guide the ethical conduct of research are respect for persons, beneficence, and justice. To what extent are these being adequately considered in the current trials?

Respect for persons is an ethical principle that requires that individual autonomy be respected and that persons with diminished autonomy be protected. Here, it is clear that autonomy refers to requirement that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.

Some ethical issues linked to respect for persons and autonomy include:

1. Prior comments we have made concerning the way in which researchers seek the consent of participants are relevant here. The process through which consent is being obtained in MC trials is not being critically examined, particularly given the differential relationship that individuals from non-Western countries can have to the medical establishment (eg, individual consent vs. group or village level decision-making processes).
2. If recommendations are made for mass MC for neonates, the medical establishment will be recommending a permanent surgical procedure for a child who does not have the right to decide something about their own body, the consequences of which would not even be relevant until they are sexually active.

3. Full evaluation of risks and benefits is needed in order to say that one responded with informed consent to voluntarily participate. Yet, risks and benefits that we have delineated throughout this document are not currently fleshed out beyond medical risk.
4. Autonomy should also be respected in terms of respecting the fact that individuals who are HIV tested in trials may not want to receive their results. At the same time, researchers should track the behaviors of such individuals, as it is known that such individuals engage in higher risk behavior.
5. Language issues—are consent forms clear? Do people understand what is being said?

Beneficence is an ethical principle that entails an obligation to protect persons from harm. The principle of beneficence can be expressed in two general rules: (1) do no harm; and (2) protect from harm by maximizing anticipated benefits and minimizing possible risks of harm. Some ethical issues related to beneficence:

1. What are the risks—medical risks and beyond—and are they worth the benefits? Furthermore, since we do not know how behavioral factors will interact with medical aspects of risk, how can we accurately ensure protection under the principle?
2. Stigma is an issue related to both beneficence and justice. After all, entire communities may be stigmatized by the mere fact that large, well-publicized HIV/AIDS research is being conducted in them. Previous issues raised in this document about perceptions of male sexuality, masculinity, racism, and beliefs that certain men are responsible for the perpetration of disease while others are not are highly relevant.
3. Are there reductions in sexual pleasure, sexual functioning, and changed self- or sexual-concept for men? Are these, on balance, worth the benefits? How shall this be decided and by whom?
4. Properly weighing risks/benefits not just to men but also to women will remain an important ethical and practice issue.
5. As has been noted, there is no consensus on how to properly balance expectations concerning local and international standards of care before and after trials—and who decides. Who should provide the needed treatments and services is a key issue. Major ethical debates are currently circulating about whether public health interventions can or should provide treatment, and for how long, if participants are found to be HIV -infected.

The principle of **justice** asks questions about who ought to receive the benefits of research and bear its burdens. As we have noted, this is an issue of social justice, in the sense of considering fairness in distribution or what is deserved. An injustice occurs when some benefit to which a person is entitled is denied without good reason, or when some burden is imposed unduly.

Some ethical issues related to justice:

1. As we have noted, are men from particular areas of the world--or particular racial and ethnic minorities—being systematically selected for participation in MC trials simply because of their easy availability, their compromised position, or their manipulability, rather than for solid reasons directly related to the problem being studied?
2. Are poor communities able to bear the burdens of research and can they truly benefit from it despite the complexities of poverty or a lack of infrastructure?
3. With the exception of adverse events, inadvertent positive and negative consequences of research participation are not generally tracked. These could be defined and tracked in order to adequately assure adherence to principles of justice—and define new ones if needed.
4. Relatively privileged researchers may feel motivated to contribute to the reduction of social inequality through health research but this may be carried out at the expense of local communities, as Western definitions can exacerbate situations on the ground. Key to the local research experience might be the way in which “risk,” “benefit,” or “acceptable” are defined for communities that may or may not be adequate for the region.
5. Some believe that researchers from rich countries contribute to sustaining poverty in poor countries (eg, through exploitation of cheap labor, unsound trade rules, requiring debt payments that are not payable, histories of colonialism) and thus they have an ethical obligation to transfer resources (and not just public health requirements or suggestions) to reduce gross injustices(60).
6. Studies have elucidated how power relations between developing and developed countries have resulted in the misperception that Western science and its interventions are perceived by study participants as definitively “working”, even when, for example, candidate microbicides may be investigated for acceptability and not efficacy(61). No matter how clear informed consent may be concerning risks/benefits, levels of protection, and the need for behavioral change, individuals might feel that an intervention that comes from Western science is one that unequivocally “works.” True dangers therefore exist that misperceptions will occur regarding the partial protection afforded by MC. Qualitative research needs to be conducted to investigate men’s and women’s perceptions of protection afforded over the long run.

Standards of Care

Determining what the standard of care should be during and after clinical trials can be complex, particularly when examining the differential resources available to resource-rich and resource-poor countries (and middle-income countries). Debates about standards of care required in placebo arms of drug trials initially emerged in 1999, and were modified and rewritten in 2000 due to ethical debates about randomized controlled trials of PMTCT. At the time, placebo-controlled study arms were being used, rather than comparing the experimental regimen to another that was either a) an acceptable standard treatment around the world or b) a local standard treatment. Debates raged about whether control arms should be constituted according to “the highest standard in the world,” “the highest standard of care practically attainable in the country in which research is being carried out,” or “placebo control.” At first, the World Medical Association proposed that placebos should be used in trials by arguing that the standard of care should not be the “highest in the world” but rather “the highest standard of care practically attainable in the country in which research is being carried out.” However, other arguments emerged to underscore that the standard of care that is “practically attainable” might mean anything from state-of-the-art to clearly substandard treatment; on the lower end, this could certainly violate the

principle of beneficence known as “do no harm.” As a result of these debates, in October 2000 in Helsinki, the World Medical Association released a new version of the Declaration to argue that placebo arms were prohibited in “situations of local scarcity” if the “best current method” existed elsewhere. Relevant issues related to standards of care in MC trials involve debates about what will constitute standard of care during and after trials, and who will decide.

Some relevant issues are:

1. There are several ethical issues that remain about local and international standards of care before and after trials and for potential rollout. Who should provide HIV and non-HIV treatment and care services for trial participants in resource-limited health systems is a major issue. Ethical debates are also focusing on whether public health interventions can or should provide treatment, and for how long, if participants are found to be HIV-positive. In countries where ARV rollout is incomplete, what if MC trial participants are among the few in their communities who receive ARV treatment?
2. The above relates to the question of how dual standards of care shall be dealt with. In short, it is not uncommon for trial participants to receive more or better access to health care than others in their communities due to their participation in research. This can result in problems within families, communities, and health systems. Some argue that this can lead to “undue inducement” to participate in research and that large payments for trial participation should not be made to participants, as this might further exacerbate undue inducement and interfere with the principle of autonomy.
3. A basic principle of standard of care is that researchers or sponsors of trials should make successful interventions available to the host country after research is completed.
4. Some believe that researchers from resource-rich countries have an ethical obligation to transfer resources to improve the overall standard of care in health systems (and not just offer public health suggestions) to reduce gross injustices in resource-poor countries(60). The argument is that sustainable improvements in health come from improvements in the health care system--researchers from resource-rich countries are ethically obligated to improve standards of care in the health care system where research occurs. How this would actually happen is not clear.
5. Several opportunities may exist to improve standards of care in health systems. For example, there is the opportunity to integrate male circumcision within broader male sexual, reproductive health, and HIV prevention strategies. Needs assessments and capacity building assistance in various contexts is much needed on this and various other standard-of-care improvements.

Conclusions: Possible Steps Forward

Because the Kenya and Uganda MC trials replicated the results of the already completed Orange Farm study, at least in providing evidence that HIV infection is reduced for males who are circumcised vs. those who are not, immediate steps should be taken to engage stakeholders in formulating assessment of potential MC scale up. It remains an open question as to whether or not the evidence will be similarly strong to support the hypothesis that circumcising HIV-infected men reduces transmission to their partners.

Because all three trials presented similar and convincing data, the pressure will begin mounting for broad implementation of male circumcision, especially in high-prevalence areas such as sub-Saharan Africa,

parts of India, and perhaps Eastern Europe. Questions will arise regarding the benefits of male circumcision for concentrated epidemics—such as are occurring in the United States, many parts of Spanish-speaking Latin America, Europe, Australia, New Zealand, and China—and especially when these epidemics involve primarily men who have sex with men, where the main risk is from receptive anal intercourse. Questions will continue to arise about the benefits of infant vs. adolescent or adult circumcision. Controversies will continue to rage as to whether male circumcision is mutilation, or whether it is justified for health, religious, and cultural reasons.

Because there may be a disconnect between the MC lobbying forces in Europe and the United States and those voices from the areas most impacted by HIV, it is important to ensure comprehensive inclusion of all positions, and that these positions are identified by local origin and are evidence based.

We have presented challenges to ensure comprehensive coverage of medical, social, and structural issues related to MC as a prevention strategy. The challenges are not intended to discourage the use of male circumcision for HIV prevention nor are the challenges intended to slow the development of potential interventions. Indeed, if the effectiveness of male circumcision in real practice approaches the results from the three clinical trials, the practice can potentially avert thousands of new infections and dramatically reduce prevalence of infection in entire populations.

Further, we do not present these challenges as a “social science” reaction to a decidedly medical HIV prevention strategy. All advances in HIV prevention are welcome and encouraged.

Rather, we present these challenges to ensure that the discussion regarding the evolution and rollout of male circumcision reflects the full range of issues that should be considered for individuals and for populations. We believe that there are benefits to this kind of discussion that will strengthen policy and application. We think it essential that laws, policies, and programs reflect the full reality of concerns and issues, especially for a practice as radical and potentially helpful as male circumcision.

Next steps:

- We encourage broad dissemination of this and similar monographs as a way to stimulate discussion of the points made. Articles should also be prepared for the scientific literature, and for general readership, to ensure dissemination and discussion of the ideas.
- Encourage the development of national strategic plans for countries with the highest prevalence rates. These plans should include assessment of current capacity, the development of a single sentinel surveillance and reporting mechanism, clear guidelines on basic standards of care, plans for complication triage, measurable targets, cost analyses, and specific assessment of internal ethnic group practices.
- Engagement of traditional practitioners and religious groups should be paramount. The development of national plans should include them. Ongoing research on the ethnic and cultural dynamics of scale up should be encouraged.
- Additional modeling should be done. The important modeling done by Williams et al relies on only the Orange Farm data and assumes high uptake. Modeling projections that estimate varying degrees of uptake and additional factors such as combination prevention strategies (MC + ARVs or MC + condoms) should be undertaken.
- In preparation for scale up, widespread public information campaigns should be developed that describe the risks and benefits.

- The development of regionally specific “tool kits” for ministries of health that outline standards, triage, and surveillance techniques. These kits would include manuals and modules for training of practitioners as well as “training of trainers.”
- Technical support for country-level scale up should be sought from NGOs and multilaterals.
- One or more think tanks might be beneficial to flesh out ideas, test them with larger groups of people, and to modify the points made here and add to them. Such think tanks should involve key opinion leaders. It might be useful to think of global events, as well as regional or country-level meetings, that could serve as opportunities to stimulate thinking and discussion.
- From these think tanks could emerge briefings for policymakers, program planners, and implementers. Obviously, such efforts should coincide with those of the multilateral and bilateral implementing agencies (WHO, UNAIDS, World Bank, PEPFAR, USAID, DFID, etc), so that people charged with making funding and programmatic decisions are not receiving contradictory advice. Nonetheless, we would hope that briefings would allow for the full range of issues to be raised in these discussions so that programs and policies can be advanced that take into account all of the necessary information and perspectives.
- International standards for MC should be developed that are flexible enough to respond to local need.
- It would be useful to stimulate research on some of the specific topics outlined, and especially to encourage country- and regional-level research that will have applicability for local advocacy, legal and policy issues, sexual and reproductive health, and religious and cultural perspectives.
- Specific focus needs to be given to ethical discussion, studies, and guidelines, as these issues are among the most difficult in the field of HIV prevention, especially regarding male circumcision in the context of research and in practice.
- We also encourage a focus on stigma, as it is possible that male circumcision could have a beneficial effect on HIV/AIDS stigma. It is also possible that male circumcision could result in increased stigma for individuals who do or do not undergo the surgery.
- The feasibility of comprehensive reproductive services targeting both men and women that include the provision of MC and associated counseling and messaging, as well as family planning, STI counseling, the provision of condoms, contraceptive devices, and VCT services should be considered.
- We think it would be useful to track media coverage of the issue. If one searches Google for “male circumcision,” an extremely varied array of viewpoints are found. Many of these take the perspective that male circumcision is genital mutilation. Media coverage of the issue might illuminate the various ways that people are thinking about the issue, and also highlight confusions that might be generated in populations.

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Annotated Bibliography of Key Literature

(Wiswell and Geschke 1989; Moses, Bradley et al. 1990; Christakis, Harvey et al. 2000; Gray, Kiwanuka et al. 2000; Quinn, Wawer et al. 2000; Schoen, Wiswell et al. 2000; Siegfried, Muller et al. 2003; Auvert, Taljaard et al. 2005; Christoffersen-Deb 2005; Cohen 2005; Malone 2005; Schoen 2005; Siegfried, Muller et al. 2005; Wawer, Reynolds et al. 2005; CDC 2006; Donoval, Landay et al. 2006; Fergusson, Boden et al. 2006; Westercamp and Bailey 2006; Williams, Lloyd-Smith et al. 2006)

Auvert, B., D. Taljaard, 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.

BACKGROUND: Observational studies suggest that male circumcision may provide protection against HIV-1 infection. A randomized, controlled intervention trial was conducted in a general population of South Africa to test this hypothesis. **METHODS AND FINDINGS:** A total of 3,274 uncircumcised men, aged 18-24 y, were randomized to a control or an intervention group with follow-up visits at months 3, 12, and 21. Male circumcision was offered to the intervention group immediately after randomization and to the control group at the end of the follow-up. The grouped censored data were analyzed in intention-to-treat, univariate and multivariate, analyses, using piecewise exponential, proportional hazards models. Rate ratios (RR) of HIV incidence were determined with 95% CI. Protection against HIV infection was calculated as $1 - RR$. The trial was stopped at the interim analysis, and the mean (interquartile range) follow-up was 18.1 mo (13.0-21.0) when the data were analyzed. There were 20 HIV infections (incidence rate = 0.85 per 100 person-years) in the intervention group and 49 (2.1 per 100 person-years) in the control group, corresponding to an RR of 0.40 (95% CI: 0.24%-0.68%; $p < 0.001$). This RR corresponds to a protection of 60% (95% CI: 32%-76%). When controlling for behavioural factors, including sexual behaviour that increased slightly in the intervention group, condom use, and health-seeking behaviour, the protection was of 61% (95% CI: 34%-77%). **CONCLUSION:** Male circumcision provides a degree of protection against acquiring HIV infection, equivalent to what a vaccine of high efficacy would have achieved. Male circumcision may provide an important way of reducing the spread of HIV infection in sub-Saharan Africa. (Preliminary and partial results were presented at the International AIDS Society 2005 Conference, on 26 July 2005, in Rio de Janeiro, Brazil.).

CDC (2006). Male Circumcision and Risk for HIV Transmission: Implications for the United States, Centers for Disease Control and Prevention.

This fact sheet summarizes information in 4 areas of male circumcision: (1) male circumcision and risk of HIV transmission; (2) male circumcision and other health benefits; (3) risk associated with male circumcision; and (4) status of HIV infection and male circumcision in the United States

Christakis, D. A., E. Harvey, et al. (2000). "A trade-off analysis of routine newborn circumcision." *Pediatrics* 105(1 Pt 3): 246-9.

BACKGROUND. The risks associated with newborn circumcision have not been as extensively evaluated as the benefits. **OBJECTIVES.** The goals of this study were threefold: 1) to derive a population-based complication rate for newborn circumcision; 2) to calculate the number needed to harm for newborn circumcision based on this rate; and 3) to establish trade-offs based on our complication rates and published estimates of the benefits of circumcision including the prevention of urinary tract infections and penile cancer. **METHODS.** Using the Comprehensive Hospital Abstract Reporting System for Washington State, we retrospectively examined routine newborn circumcisions performed over 9 years (1987-1996). We used International Classification of Diseases, Ninth Revision codes to identify both circumcisions and complications and limited our analyses to children without other surgical procedures performed during their initial birth hospitalization. **RESULTS.** Of 354, 297 male infants born during the study period, 130,475 (37%) were circumcised during their newborn stay. Overall 287 (.2%) of circumcised children and 33 (.01%) of uncircumcised children had complications potentially associated with circumcision coded as a discharge diagnosis. Based on our findings, a complication can be expected in 1 out every 476 circumcisions. Six urinary tract infections can be prevented for every complication endured and almost 2 complications can be expected for every case of penile cancer prevented. **CONCLUSIONS.** Circumcision remains a relatively safe procedure.

However, for some parents, the risks we report may outweigh the potential benefits. This information may help parents seeking guidance to make an informed decision.

Christoffersen-Deb, A. (2005). "'Taming tradition': medicalized female genital practices in western Kenya." *Med Anthropol Q* **19**(4): 402-18.

This article considers the question of female genital practices at the hands of health workers in western Kenya. Recent articles in *Medical Anthropology Quarterly* have critically engaged with the biomedical arguments condemning such practices. This article studies the case of medicalized circumcision in which biomedical concerns over health risks have become incorporated in their vernacular practice. Although some suggest that medicalization may provide a harm-reduction strategy to the abandonment of the practice, research in one region challenges this suggestion. It argues that changing and conflicting ideologies of gender and sexuality have led young women to seek their own meaning through medicalized practice. Moreover, attributing this practice to financial motivations of health workers overlooks the way in which these "moral agents" must be situated within their social and cultural universe. Together, these insights challenge the view that medicine can remain neutral in the mediation of tradition.

Cohen, J. (2005). "HIV/AIDS. Prevention cocktails: combining tools to Stop HIV's spread." *Science* **309**(5737): 1002-5.

Donoval, B. A., A. L. Landay, et al. (2006). "HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections." *Am J Clin Pathol* **125**(3): 386-91.

Numerous epidemiologic studies have found significant associations between lack of circumcision and HIV-1 acquisition in men. To our knowledge, this is the first study of human foreskin tissue that examines biologic mechanisms that increase susceptibility of uncircumcised African men to HIV-1. Foreskin specimens from 20 men with and 19 men with no history of sexually transmitted infections were examined for HIV-1 target cells. Most Langerhans cells were found in the epithelium; most CD4+ T cells and macrophages were in the submucosa. There were no differences in HIV-1 target cells between men with and those without history of sexually transmitted infections. However Langerhans cells and macrophages were more abundant in the group with a history of infection. The densities and positions of HIV-1 target cells in the foreskin tissue of these Kenyan men indicate that the inner mucosal surface of the human foreskin contains cells that make it highly susceptible to HIV infection.

Fergusson, D. M., J. M. Boden, et al. (2006). "Circumcision status and risk of sexually transmitted infection in young adult males: an analysis of a longitudinal birth cohort." *Pediatrics* **118**(5): 1971-7.

OBJECTIVES: Previous research suggests that male circumcision may be a protective factor against the acquisition of sexually transmitted infections; however, studies examining this question have produced mixed results. The aim of this study was to examine the association between circumcision status and sexually transmitted infection risk using a longitudinal birth cohort study. **METHODS:** Data were gathered as part of the Christchurch Health and Development Study, a 25-year longitudinal study of a birth cohort of New Zealand children. Information was obtained on: (1) the circumcision status of males in the cohort before 15 years old, (2) measures of self-reported sexually transmitted infection from ages 18 to 25 years, and (3) childhood, family, and related covariate factors. **RESULTS:** Being uncircumcised had a statistically significant bivariate association with self-reported sexually transmitted infection. Adjustment for potentially confounding factors, including number of sexual partners and unprotected sex, as well as background and family factors related to circumcision, did not reduce the association between circumcision status and reports of sexually transmitted infection. Estimates of the population-attributable risk suggested that universal neonatal circumcision would have reduced rates of sexually transmitted infection in this cohort by 48.2%. **CONCLUSIONS:** These findings suggest that uncircumcised males are at greater risk of acquiring sexually transmitted infection than circumcised males. Male circumcision may reduce the risk of sexually transmitted infection acquisition and transmission by up to one half, suggesting substantial benefits accruing from routine neonatal circumcision.

Gray, R. H., N. Kiwanuka, et al. (2000). "Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. Rakai Project Team." *Aids* **14**(15): 2371-81.

BACKGROUND: Male circumcision is associated with reduced HIV acquisition. **METHODS:** HIV acquisition was determined in a cohort of 5507 HIV-negative Ugandan men, and in 187 HIV-negative men in discordant relationships. Transmission was determined in 223 HIV-positive men with HIV-negative partners. **HIV**

incidence per 100 person years (py) and adjusted rate ratios (RR) and 95% confidence intervals (CI) were estimated by Poisson regression. HIV-1 serum viral load was determined for the seropositive partners in HIV-discordant couples. RESULTS: The prevalence of circumcision was 16.5% for all men; 99.1% in Muslims and 3.7% in non-Muslims. Circumcision was significantly associated with reduced HIV acquisition in the cohort as a whole (RR 0.53, CI 0.33-0.87), but not among non-Muslim men. Prepubertal circumcision significantly reduced HIV acquisition (RR 0.49, CI 0.26-0.82), but postpubertal circumcision did not. In discordant couples with HIV-negative men, no seroconversions occurred in 50 circumcised men, whereas HIV acquisition was 16.7 per 100 py in uncircumcised men (P = 0.004). In couples with HIV-positive men, HIV transmission was significantly reduced in circumcised men with HIV viral loads less than 50000 copies/ml (P = 0.02). INTERPRETATION: Prepubertal circumcision may reduce male HIV acquisition in a general population, but the protective effects are confounded by cultural and behavioral factors in Muslims. In discordant couples, circumcision reduces HIV acquisition and transmission. The assessment of circumcision for HIV prevention is complex and requires randomized trials.

Malone, P. S. (2005). "Circumcision for preventing urinary tract infection in boys: European view." *Arch Dis Child* **90**(8): 773-4.

Moses, S., J. E. Bradley, et al. (1990). "Geographical patterns of male circumcision practices in Africa: association with HIV seroprevalence." *Int J Epidemiol* **19**(3): 693-7.

To ascertain whether male circumcision might explain some of the geographical variation in human immunodeficiency virus (HIV) seroprevalence in Africa, we investigated the association between the practice of male circumcision at a societal level and HIV seroprevalence. Male circumcision practices for over 700 African societies were identified, and HIV seroprevalence in general adult populations from 140 distinct locations in 41 countries was obtained. In locations where male circumcision is practised, HIV seroprevalence was considerably lower than in areas where it is not practised. This study supports the hypothesis that lack of circumcision in males is a risk factor for HIV transmission.

Quinn, T. C., M. J. Wawer, et al. (2000). "Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group." *N Engl J Med* **342**(13): 921-9.

BACKGROUND AND METHODS: We examined the influence of viral load in relation to other risk factors for the heterosexual transmission of human immunodeficiency virus type 1 (HIV-1). In a community-based study of 15,127 persons in a rural district of Uganda, we identified 415 couples in which one partner was HIV-1-positive and one was initially HIV-1-negative and followed them prospectively for up to 30 months. The incidence of HIV-1 infection per 100 person-years among the initially seronegative partners was examined in relation to behavioral and biologic variables. RESULTS: The male partner was HIV-1-positive in 228 couples, and the female partner was HIV-1-positive in 187 couples. Ninety of the 415 initially HIV-1-negative partners seroconverted (incidence, 11.8 per 100 person-years). The rate of male-to-female transmission was not significantly different from the rate of female-to-male transmission (12.0 per 100 person-years vs. 11.6 per 100 person-years). The incidence of seroconversion was highest among the partners who were 15 to 19 years of age (15.3 per 100 person-years). The incidence was 16.7 per 100 person-years among 137 uncircumcised male partners, whereas there were no seroconversions among the 50 circumcised male partners (P<0.001). The mean serum HIV-1 RNA level was significantly higher among HIV-1-positive subjects whose partners seroconverted than among those whose partners did not seroconvert (90,254 copies per milliliter vs. 38,029 copies per milliliter, P=0.01). There were no instances of transmission among the 51 subjects with serum HIV-1 RNA levels of less than 1500 copies per milliliter; there was a significant dose-response relation of increased transmission with increasing viral load. In multivariate analyses of log-transformed HIV-1 RNA levels, each log increment in the viral load was associated with a rate ratio of 2.45 for seroconversion (95 percent confidence interval, 1.85 to 3.26). CONCLUSIONS: The viral load is the chief predictor of the risk of heterosexual transmission of HIV-1, and transmission is rare among persons with levels of less than 1500 copies of HIV-1 RNA per milliliter.

Schoen, E. J. (2005). "Circumcision for preventing urinary tract infections in boys: North American view." *Arch Dis Child* **90**(8): 772-3.

Schoen, E. J., T. E. Wiswell, et al. (2000). "New policy on circumcision--cause for concern." *Pediatrics* **105**(3 Pt 1): 620-3.

Siegfried, N., M. Muller, et al. (2005). "HIV and male circumcision--a systematic review with assessment of the quality of studies." *Lancet Infect Dis* 5(3): 165-73.

This Cochrane systematic review assesses the evidence for an interventional effect of male circumcision in preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse. The review includes a comprehensive assessment of the quality of all 37 included observational studies. Studies in high-risk populations consisted of four cohort studies, 12 cross-sectional studies, and three case-control studies; general population studies consisted of one cohort study, 16 cross-sectional studies, and one case-control study. There is evidence of methodological heterogeneity between studies, and statistical heterogeneity was highly significant for both general population cross-sectional studies ($\chi^2=132.34$; degrees of freedom [df]=15; $p<0.00001$) and high-risk cross-sectional studies ($\chi^2=29.70$; df=10; $p=0.001$). Study quality was very variable and no studies measured the same set of potential confounding variables. Therefore, conducting a meta-analysis was inappropriate. Detailed quality assessment of observational studies can provide a useful visual aid to interpreting findings. Although most studies show an association between male circumcision and prevention of HIV, these results may be limited by confounding, which is unlikely to be adjusted for.

Siegfried, N., M. Muller, et al. (2003). "Male circumcision for prevention of heterosexual acquisition of HIV in men." *Cochrane Database Syst Rev*(3): CD003362.

BACKGROUND: The findings from observational studies, reviews and meta-analyses, supported by biological theories, that circumcised men appear less likely to acquire human immunodeficiency virus (HIV) has contributed to the recent ground swell of support for considering male circumcision as a strategy for preventing sexually acquired infection. We sought to elucidate and appraise the global evidence from published and unpublished studies that circumcision can be used as an intervention to prevent HIV infection. **OBJECTIVES:** 1) To assess the evidence of an interventional effect of male circumcision for preventing acquisition of HIV-1 and HIV-2 by men through heterosexual intercourse 2) To examine the feasibility and value of performing individual person data (IPD) meta-analysis **SEARCH STRATEGY:** We searched online for published and unpublished studies in The Cochrane Library (issue 2, 2002), MEDLINE (April 2002), EMBASE (February 2002) and AIDSLINE (August 2001). We also searched databases listing conference abstracts, scanned reference lists of articles and contacted authors of included studies. **SELECTION CRITERIA:** We searched for randomized and quasi-randomized controlled trials of male circumcision or, in their absence, observational studies that compare acquisition rates of HIV-1 and HIV-2 infection in circumcised and uncircumcised heterosexual men. **DATA COLLECTION AND ANALYSIS:** Independent reviewers selected studies, assessed study quality and extracted data. We stratified studies based on study design and on whether they included participants from the general population or high-risk groups (such as patients treated for sexually transmitted infections). We expressed findings as crude and adjusted odds ratios (OR) together with their 95% confidence intervals (CI) and conducted a sensitivity analysis to explore the effect of adjustment on study results. We investigated whether the method of circumcision ascertainment influenced study outcomes. **MAIN RESULTS:** We identified no completed randomized controlled trials. Three randomized controlled trials are currently underway or commencing shortly. We found 34 observational studies: 16 conducted in the general population and 18 in high-risk populations. It seems unlikely that potential confounding factors were completely accounted for in any of the included studies. In particular, important risk factors, such as religion and sexual practices, were not adequately accounted for in many of the included studies. **General population study results:** The single cohort study (N = 5516) showed a significant difference in HIV transmission rates between circumcised and uncircumcised men [OR = 0.58; 95% CI: 0.36 to 0.96]. Results for the 14 cross-sectional studies were inconsistent, with point estimates for unadjusted odds ratios varying between 0.28 and 1.73. Six studies had statistically significant results, four in the direction of benefit and two in the direction of harm. The test for heterogeneity between the cross-sectional studies was highly significant ($\chi^2 = 77.59$; df = 13; P-value < 0.00001). Nine studies reported adjusted odds ratios with eight in the direction of benefit, ranging from 0.26 to 0.80. Use of adjusted results tended to show stronger evidence of an association although they remained heterogeneous ($\chi^2 = 75.2$; df = 13; P-value < 0.00001). Only one case-control study was found (N = 51) which had a non-significant result [OR = 1.90; 95% CI: 0.50 to 7.20]. **High-risk group study results:** The four cohort studies identified found a protective effect from circumcision with point estimates for unadjusted odds ratios varying from 0.10 to 0.39. Two of these studies had statistically significant results. Two studies reported adjusted odds ratios, both protective with one being significant. The chi-square test for between-study heterogeneity was not significant ($\chi^2 = 5.21$; df = 3; P-value = 0.16). All eleven cross-sectional studies reporting unadjusted results found benefit from circumcision, eight of which had statistically significant results.

Estimates of effect from studies reporting unadjusted results found benefit from circumcision, eight of which had statistically significant results. Estimates of effect varied from an unadjusted odds ratio of 0.10 to 0.66. Between-study heterogeneity was significant with the chi-square = 29.77; df = 10; P-value = 0.0009. Four of these studies reported adjusted odds ratios ranging from 0.20 to 0.59 and all were significant. One additional cross-sectional study only reported an adjusted odds ratio in the direction of benefit which was statistically significant. All three case-control studies found a protective effect of circumcision on HIV status, two being statistically significant. Point estimates varied from unadjusted odds ratios of 0.37 to 0.88. One reported an adjusted odds ratio showing a significant protective effect. Adverse effects: No studies reported on the adverse effects of circumcision. In most studies, circumcision had taken place during childhood or adolescence before the studies commenced. REVIEWER'S CONCLUSIONS: We found insufficient evidence to support an interventional effect of male circumcision on HIV acquisition in heterosexual men. The results from existing observational studies show a strong epidemiological association between male circumcision and prevention of HIV, especially among high-risk groups. However, observational studies are inherently limited by confounding which is unlikely to be fully adjusted for. In the light of forthcoming results from RCTs, the value of IPD analysis of the included studies is doubtful. The results of these trials will need to be carefully considered before circumcision is implemented as a public health intervention for prevention of sexually transmitted HIV.

Wawer, M. J., S. J. Reynolds, et al. (2005). "Might male circumcision be more protective against HIV in the highly exposed? An immunological hypothesis." *Aids* **19**(18): 2181-2.

Westercamp, N. and R. C. Bailey (2006). "Acceptability of Male Circumcision for Prevention of HIV/AIDS in Sub-Saharan Africa: A Review." *AIDS Behav.*

Based on epidemiological, clinical and experimental evidence, male circumcision (MC) could have a significant impact on the HIV epidemic in selected areas. We reviewed studies of the acceptability of MC in sub-Saharan Africa to assess factors that will influence uptake of circumcision in traditionally non-circumcising populations. Thirteen studies from nine countries were identified. Across studies, the median proportion of uncircumcised men willing to become circumcised was 65% (range 29-87%). Sixty nine percent (47-79%) of women favored circumcision for their partners, and 71% (50-90%) of men and 81% (70-90%) of women were willing to circumcise their sons. Because the level of acceptability across the nine countries was quite consistent, additional acceptability studies that pose hypothetical questions to participants are unnecessary. We recommend pilot interventions making safe circumcision services available in conjunction with current HIV prevention strategies and evaluating the safety and acceptability of circumcision.

Williams, B. G., J. O. Lloyd-Smith, et al. (2006). "The potential impact of male circumcision on HIV in Sub-Saharan Africa." *PLoS Med* **3**(7): e262.

BACKGROUND: A randomized controlled trial (RCT) has shown that male circumcision (MC) reduces sexual transmission of HIV from women to men by 60% (32%-76%; 95% CI) offering an intervention of proven efficacy for reducing the sexual spread of HIV. We explore the implications of this finding for the promotion of MC as a public health intervention to control HIV in sub-Saharan Africa. METHODS AND FINDINGS: Using dynamical simulation models we consider the impact of MC on the relative prevalence of HIV in men and women and in circumcised and uncircumcised men. Using country level data on HIV prevalence and MC, we estimate the impact of increasing MC coverage on HIV incidence, HIV prevalence, and HIV-related deaths over the next ten, twenty, and thirty years in sub-Saharan Africa. Assuming that full coverage of MC is achieved over the next ten years, we consider three scenarios in which the reduction in transmission is given by the best estimate and the upper and lower 95% confidence limits of the reduction in transmission observed in the RCT. MC could avert 2.0 (1.1-3.8) million new HIV infections and 0.3 (0.1-0.5) million deaths over the next ten years in sub-Saharan Africa. In the ten years after that, it could avert a further 3.7 (1.9-7.5) million new HIV infections and 2.7 (1.5-5.3) million deaths, with about one quarter of all the incident cases prevented and the deaths averted occurring in South Africa. We show that a) MC will increase the proportion of infected people who are women from about 52% to 58%; b) where there is homogenous mixing but not all men are circumcised, the prevalence of infection in circumcised men is likely to be about 80% of that in uncircumcised men; c) MC is equivalent to an intervention, such as a vaccine or increased condom use, that reduces transmission in both directions by 37%. CONCLUSIONS: This analysis is based on the result of just one RCT, but if the results of that trial are confirmed we suggest that MC could substantially reduce the burden of HIV in Africa, especially in southern Africa where the prevalence of MC is low and the prevalence of HIV is high. While the protective

benefit to HIV-negative men will be immediate, the full impact of MC on HIV-related illness and death will only be apparent in ten to twenty years.

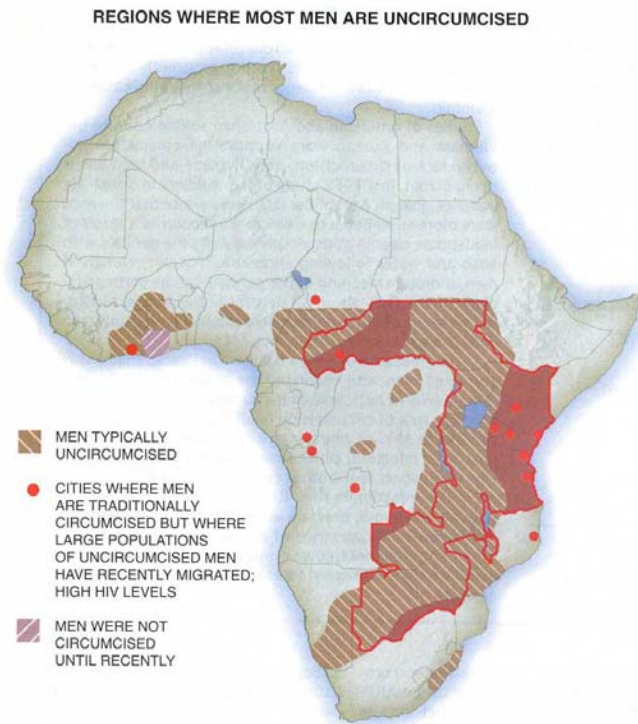
Wiswell, T. E. and D. W. Geschke (1989). "Risks from circumcision during the first month of life compared with those for uncircumcised boys." Pediatrics **83**(6): 1011-5.

The records of 136,086 boys born in US Army hospitals from 1980 to 1985 were reviewed for indexed complications related to circumcision status during the first month of life. For 100,157 circumcised boys, there were 193 complications (0.19%). These included 62 local infections, eight cases of bacteremia, 83 incidences of hemorrhage (31 requiring ligature and three requiring transfusion), 25 instances of surgical trauma, and 20 urinary tract infections. There were no deaths or reported losses of the glans or entire penis. By contrast, the complications in the 35,929 uncircumcised infants were all related to urinary tract infections. Of the 88 boys with such infections (0.24%), 32 had concomitant bacteremia, three had meningitis, two had renal failure, and two died. The frequencies of urinary tract infection (P less than .0001) and bacteremia (P less than .0002) were significantly higher in the uncircumcised boys. Serious complications from routine prepuce removal are rare and relatively minor. Circumcision may be beneficial in reducing the occurrence of urinary tract infections and their associated sequelae.

Maps

Circumcision Prevalence

(Caldwell, 2006) (67)



HIV Prevalence

UNAIDS HIV Prevalence, 2005

