Circumcision and HIV transmission

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Purpose of review

To review the recent literature on male circumcision and its effect on HIV acquisition.

Recent findings

The report from the randomized clinical trial of male circumcision in South Africa demonstrating a 60% protective effect in preventing HIV acquisition provided the first clinical trial evidence of efficacy of male circumcision in protecting men against HIV infection. This protective effect was consistent with both ecological and epidemiologic studies which also show a protective effect of 50–70% in men at high risk for HIV infection. Biological studies also demonstrate an increased number of HIV receptor cells in the mucosa of foreskin providing additional evidence of HIV susceptibility in the uncircumcised male. Male circumcision may also have a beneficial effect in preventing HIV acquisition in women and lowering selected sexually transmitted infections in both sexes.

Summary

The results of two ongoing randomized clinical trials of male circumcision in Kenya and Uganda are awaited with interest, however male circumcision should be carefully considered as a potential public health tool in preventing HIV acquisition. If other trials confirm the results of the South African trial, implementation of this surgical procedure will need to be carefully scaled up and integrated into other prevention programs with emphasis on surgical training, aseptic techniques, acceptability, availability and cultural considerations.

Keywords

AIDS, circumcision, epidemiology, HIV, prevention, transmission

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Abbreviations

DSMB Data Safety Monitoring Board
STI sexually transmitted infection

0951-7375

Introduction

Male circumcision is one of the oldest surgical procedures dating back to Egypt's sixth dynasty (2345–2181 BC) [1]. Male circumcision is the surgical removal of all or part of the prepuce (foreskin) of the penis, which is practiced as part of a religious ceremony performed shortly after birth, a traditional 'coming of age' ritual practiced at or after puberty in certain cultures, or as a medical procedure related to infections, injury, or anomalies of the foreskin. In some countries, such as the United States, it is considered a preventive medical procedure to reduce the frequency of urinary tract infections and phimosis in young boys and potentially to reduce the acquisition of sexually transmitted infections (STIs). Common among Muslim and Jewish men, rates of circumcision vary widely as a surgical practice among ethnic populations and by geographical location. For example, circumcision may be common (60–70%) among men in the United States, but is rare (1–5%) among men throughout Europe and Latin America. Data from the National Health and Nutrition Examination Survey (NHANES) [2] on the frequency of circumcision in men in the United States between 1999 and 2002 demonstrated that the overall prevalence of circumcision was 79%, but it varied by race/ethnicity: 41% in Mexican Americans, 78% in non-Hispanic blacks, and 89% in non-Hispanic whites. Among boys born in the 1980s, the prevalence of circumcision was 83%, a significant decrease from its peak of 91% in men born in the 1970s.

Epidemiological associations

Circumcision practices also vary widely by culture and religious beliefs throughout sub-Saharan Africa and Asia. It was this noted variance in circumcision practices in sub-Saharan Africa that caused investigators to note an initial association between HIV and the lack of male circumcision in the late 1980s. These studies, referred to as ecological studies, demonstrated a definitive geographic correlation of high HIV prevalence in areas where male circumcision is rare. Ecological studies, while highly supportive of an association between HIV acquisition and lack of male circumcision, have been faulted due to confounding of behavioral factors, religion, culture, and geography. Extensive epidemiologic studies were therefore conducted to examine the relationship between the practice of circumcision and HIV incidence. More than 40 epidemiologic studies have shown a significant association between lack of male circumcision and acquisition of HIV in men [3••,4••]. Several reviews have shown that the risk of HIV acquisition in uncircumcised heterosexual

men is 1.8–11.2 times higher than in circumcised men [5]. The protective effect appears to be strongest for higher-risk men, with a subanalysis of 16 studies of high-risk men showing that circumcised men were 70% less likely to contract HIV (relative risk 0.3). After adjustment for likely confounders, such as marital status, age, condom use, number of sexual partners, alcohol consumption, income and education, the strength of the association of HIV with lack of circumcision increases. Among men who have sex with men studied in the US, acquisition was increased twofold among uncircumcised men compared with circumcised men, although the population attributable risk was only 10% due to the high frequency of circumcision in the US male population [6•].

In Rakai, Uganda, among male partners of HIV-positive women in regular sexual relationships, 40 of 137 (29%) uncircumcised men and none of 50 (0%) circumcised men seroconverted over a 4-year period ($P < 0.001$) [7]. A similar association between circumcision and lack of seroconversion was found among Nairobi men attending STI clinics after a history of sex with seropositive commercial sex workers [8]. In India HIV prevalence was found to be seven times higher among uncircumcised men and was independent of acquisition of other STIs [9]. A 2004 population-based Kenya demographic and health survey found a fourfold higher HIV prevalence among uncircumcised men than circumcised men [10•,11,12].

In a recent study in Rakai, Uganda the effects of male circumcision on HIV and STD acquisition were examined in their female partners [13]. The incidence of female HIV acquisition was 6.6 per 100 person-years in wives of circumcised HIV-positive men compared with 10.3 per 100 person-years in wives of HIV-positive uncircumcised men. The risk of STDs in the female partners of circumcised versus uncircumcised men was also significantly reduced for trichomonas and bacterial vaginosis but not for chlamydia and gonorrhea. The sample size was too small to effectively examine the effect of decreasing acquisition of herpes simplex virus (HSV) or human papillomavirus. The risk for female genital ulcer disease was also reduced in wives of circumcised men but this was confounded due to the low prevalence and incidence of HIV in these wives.

Turner and coworkers [14] also addressed the role of men's circumcision status and women's risk for HIV in Zimbabwean and Ugandan women. Among 4448 women, 23.2% reported at baseline that their primary partner was circumcised. The hazard ratio for HIV acquisition comparing women whose primary partner was circumcised with women whose primary partner was uncircumcised was 0.75 (95% confidence interval (CI) 0.53–1.06). Following multivariate adjustment for country, recruitment population, age, and hormonal contraceptive use, the hazard ratio was attenuated. The study investigators concluded that crude analyses suggested that women partnered with circumcised men may be at lower HIV risk, but the association was weakened with adjustment for other risk factors, particularly age and recruitment population.

In a study by Drain and colleagues [15], the relationship between male circumcision prevalence, religion, and seven infectious diseases was evaluated using country-specific data among 118 developing countries. In their analysis, male circumcision was associated with lower HIV prevalence and lower cervical cancer incidence but not with reductions in HSV-2, syphilis, nor, as expected, hepatitis C, tuberculosis, or malaria. In multivariate analysis controlling for religion, circumcision was significantly associated with lower cervical cancer incidence and lower HIV prevalence independent of Muslim and Christian religion. Male circumcision was also strongly associated with lower HIV prevalence among countries with primarily sexual HIV transmission, but not among countries with primarily injecting drug user (IDU) transmission. These findings strengthen the reported biological link between male circumcision and STIs, including HIV and cervical cancer [16•,17,18].

Randomized clinical trials

Three randomized controlled trials were initiated to assess the safety and efficacy of male circumcision in reducing female-to-male HIV transmission in Kenya, Uganda, and South Africa. In Uganda, a randomized controlled trial of male circumcision of HIV-positive men is underway in order to examine the effect of male-to-female HIV transmission. The South African study in Orange Farm [19••] was stopped prematurely in mid-April 2005 on the recommendation of the study's Data Safety Monitoring Board (DSMB) and the male circumcision intervention was offered to the control group. Trial data were analyzed and demonstrated a 60% protective effect (95% CI 40–80%) for adult male circumcision. In that study a total of 3274 uncircumcised men, aged 18–24 years, were randomized to a control group or an intervention group with follow-up visits at 3, 12, and 21 months. Male circumcision was offered to the intervention group immediately after randomization and to the control group at the end of the follow up. The mean follow-up period was 18.1 months when the study was stopped prematurely by the DSMB. There were 20 HIV infections (incident 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 a rate ratio of 0.40 (95% CI 0.24–0.68%; $P < 0.001$). This rate ratio corresponds to a protection of 60%. When controlling for behavioral factors including sexual behavior, which

increased slightly in the intervention group, condom use and health-seeking behavior protection, the protective effect was 61% (95% CI 34–77%).

This study provided the first experimental evidence of the efficacy of male circumcision in protecting men against HIV infection [20•,21]. The demonstration in this study of a causal association between HIV infection and male circumcision is consistent with protection suggested by metaanalysis of the observational studies but with a higher protective effect. A major limitation of this study is that participants were followed for only a short period of time due to the cessation of the study by the DSMB. Consequently, this study does not explore the long-term protective effect of male circumcision. Nevertheless, at least for the general population in South Africa where this study took place, the trial clearly documents the protective effect of circumcision, providing an efficacy rate analogous to what could be hopefully expected from a vaccine trial. The study does not directly address the impact of male circumcision on male-to-female HIV transmission nor were the investigators able to provide data on the effects on other STIs.

Since this study was limited to only one population in South Africa, the World Health Organization (WHO) and the United Nations Joint Programme on HIV/AIDS (UNAIDS) have recommended that planning for male circumcision in other areas including acceptability, feasibility, and training be initiated while awaiting the outcomes of the remaining two randomized control trials. The two further randomized controlled trials ongoing in the Rakai region of Uganda and the Kisumu region of Kenya will hopefully provide additional information regarding the efficacy of circumcision as a preventive procedure [22]. The Ugandan trial is in a rural setting and involves 5000 participants aged 15–49 years. The Kenyan trial involves 2784 men aged 18–24 years in an urban setting. The two trials are due to be completed in 2007 and an interim review of the data was conducted in June 2006 with continuation of the study with a planned analysis in December 2006.

Biological causality

Biological explanations for decreased susceptibility to HIV in circumcised men include the ability of the internal foreskin to absorb HIV more efficiently due to the greater presence of Langerhans cells and other HIV target cells, and the greater susceptibility of the foreskin in the uncircumcised men to tears, abrasions, and infections by STIs and subsequently HIV. Circumcision may also result in increased keratinization of the glands when not protected by the foreskin, resulting in a short drying period after sexual contact, reducing the life expectancy of HIV on the penis after sexual contact with an HIV-positive partner and reduction of total surface of the skin of the penis and reduction of target cells which are numerous in the foreskin. The finding of an increased frequency of Langerhans cells and macrophages present near the surface of the epithelium of the inner foreskin where there is no or minimal keratin barrier suggests a strong biological effect in susceptibility to HIV in uncircumcised men. Thus, it is plausible that circumcision reduces the risk of HIV acquisition through the penis by physically removing HIV-1 target cells positioned close to the mucosal surface of the inner foreskin. Primary infection is most likely to occur when there is little or no overlying protective layer of keratin, whereas in contrast in a circumcised man, keratinized epithelium covers the entire surface of the penis.

The results from Patterson *et al.* [23] suggest that men with a history of STIs have a higher density of HIV target cells on the inner mucosal surface of their foreskin than men with no STI history. Donoval *et al.* [24•] also quantified HIV-1 target cells in foreskin tissue obtained from men aged 18–24 years who were undergoing circumcision in Kisumu, Kenya. Unlike Patterson *et al.* [23], they did not find any differences in CD4+ cells between men with or without a history of STIs. Langerhans cells and macrophages, however, were more abundant in the group with a history of infection. The densities and positions of HIV 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. An elegant study by McCoombe and Short [25••] demonstrated that both the inner aspect of the foreskin and the frenulum are poorly keratinized and are richly supplied with HIV-susceptible cells. Of the cells tested, Langerhans cells are the most likely to be encountered as they are most superficial and have dendritic processes sampling a large epithelial surface area.

An alternative hypothesis for protection in circumcised men was suggested recently by Wawer *et al.* [26•] in Rakai, Uganda. In a metaanalaysis, Wawer *et al.* found HIV acquisition in circumcised compared with uncircumcised men was 0.29 (95% CI 0.20–0.41) in men with high-risk behaviors compared with an adjusted relative risk of 0.56 (95% CI 0.44–0.70) in the general male population. One hypothesis for why circumcision is more protective in high-risk men is because the procedure may reduce the risk of genital ulcer disease, a cofactor for HIV acquisition. Wawer *et al.* [26•] also suggested that the urethral meatus represents a small area of vulnerable mucosa and in circumcised men experiencing recurrent exposure to low-dose HIV, antigenic stimulation by repeat subinfectious inoculums may induce a mucosal immune response enhancing protection over and above the reduced risk afforded by removal of the foreskin *per se*. The induction of this mucosal immunity has been observed in highly

exposed but uninfected members of HIV-discordant couples and in commercial sex workers among whom there were enhanced mucosal CD8 T-cell responses and HIV-1-specific immunoglobulin A [27,28]. Thus, circumcision may protect men by three possible mechanisms: an anatomical mechanism consequent on the removal of all vulnerable foreskin mucosa; the reduction of cofactors such as genital ulcer disease; and the induction of a mucosal immune response in the presence of repeated antigen stimulation [26•].

Acceptability

Twelve published studies and two unpublished manuscripts found reasonable acceptability of circumcision in Botswana, Kenya, Malawi, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe ranging from 29 to 80% (mean 60%) [29,30•,31]. Men were asked whether they would choose circumcision for themselves and their sons and women were asked about acceptability for their husbands and sons. In Botswana, a 1 h information session increased acceptance rates from 60 to 80%. In Malawi 32 focus group discussions were conducted with 159 men and 159 women aged 16–80 years. Acceptability was lowest in the north where the practice was little known, higher in younger participants, and higher in central and southern districts where male circumcision is practiced by a minority Muslim group. Barriers to circumcision include fear of infection and bleeding, cost, and pain. Facilitators include hygiene, reduced risk of STI, religion, medical conditions, and enhanced sexual pleasure. If male circumcision services are introduced in Malawi, acceptance is likely to vary by region but many parents and young men would use the services if they were safe, affordable, and confidential. These studies in which most of the uncircumcised African men express interest in becoming circumcised if performed safely and affordably highlighted the potential of the procedure as a population-level intervention to reduce HIV spread. Nevertheless, cultural practices may persist as barriers to male circumcision in certain selected areas such as in India and Asia, where the procedure is rarely practiced.

Safety and complications

Complications of circumcision include excessive bleeding, infection, excessive pain, too much skin removed, anesthetic complications, penile damage or amputation, cosmetic complications, erectile dysfunction, psychobehavioral complications, HIV infection from nonsterilized instruments and possibly death if appropriate treatment of complications is not provided [32]. It should be noted from most studies, however, that serious complications are rare. Complications have been reported by fewer than 4% of the participants in the South African, Kenyan, and Ugandan trials, and none of the complications were life-threatening or serious. However, it is likely that complications could increase if circumcision is scaled up and performed in areas under nonsterile conditions or by practitioners with little experience [33•]. In Zambia 16% of men are circumcised and HIV prevalence overall is 16% [34]. According to their survey, meeting the existing demand for circumcision services is hampered by a shortage of skilled providers; lack of dedicated space for health education, counseling, and surgery in existing health facilities; shortage of supplies; high cost, especially in the private sector; and the fact that this 'elective' procedure is given low priority by healthcare providers [35]. Recommendations have been made for circumcision services to be prioritized and made part of a package that includes male reproductive health services.

Due to the potential complications and the uncertainty of benefit to a low-risk population, scaling up circumcision as a preventive measure worldwide has met with some controversy [36,37•,38,39•]. Fox and Thomson [40•] argue strongly that it is ethically inappropriate to subject children whether male or female to the acknowledged risk of circumcision and contend that there is no compelling legal authority for the common view that male circumcision is lawful. They criticize the continued professional willingness to tolerate the nontherapeutic, nonconsensual excision of healthy tissue, arguing that in this context both professional guidance and law are uncharacteristically tolerant of risk inflicted on young children given the absence of clear medical benefits. Although published after the results of the trial of the South African circumcision trial, the authors fail to address the scientific evidence supporting the public health effect of circumcision. Instead, they quote Benatar and Benatar's [41] conclusion following a review of the literature that none of the scientific evidence 'is anywhere near conclusive'. It is likely that papers such as this and others [42] will continue until the results of the other two trials are completed and the effect of circumcision is documented in populations other than the completed trial on South Africa.

Circumcision as an HIV prevention intervention

Mathematical models of implementing male circumcision in countries with high incidence rates also suggest marked reductions in HIV infection in men with subsequent decreased transmission rates to women in a cost-effective manner [43••]. Moses and colleagues [44] presented two mathematical models regarding the public health impact of male circumcision on HIV prevention. With varying assumptions ranging from 50 to 80% uptake of circumcision in a population in which 90% of men were uncircumcised, the introduction of male circumcision resulted in large and sustained declines in HIV prevalence over time among both men and women. In a random mixing model, decreases in HIV prevalence of up

to 60% among men and 30% among women were calculated. The authors concluded that large-scale uptake of circumcision services in African countries where circumcision is rarely practiced and HIV prevalence is high could lead to a substantial reduction in HIV prevalence over time in both men and women. Lloyd-Smith and coworkers [45] also used mathematical models to measure the potential impact of circumcision on the AIDS epidemic in Africa. In summary, they found that increased circumcision coverage could avert 2.0 million new HIV infections and 0.3 million deaths in the period 2005–2015 in sub-Saharan Africa. In the following 10 years it could avert a further 3.7 million new infections and 2.7 million deaths, with one quarter of all incident cases prevented and deaths averted occurring in the country of South Africa. Full circumcision coverage is predicted to increase the proportion of infected people that are women from about 52% to about 58%. Using a conservative estimate, circumcision is equivalent to an intervention such as a vaccine or increased condom use that would reduce transmission from male to female and female to male by 37%. Thus, while the protection of HIV-negative people would be immediate, the full impact of circumcision on HIV-related illness and death would not be felt for 10–20 years.

Kahn and coinvestigators [46] conducted a cost-effectiveness model based on the completed South African circumcision trial. At full male circumcision coverage, each 1000 circumcisions would avert an estimated 308 infections over 20 years, two-thirds in men and one-third in women. The cost is US$181 per HIV infection averted, with net savings of US$2.4 million. Cost-effectiveness is sensitive to the cost of male circumcision and of averted HIV treatment, the protective effect of circumcision, and HIV prevalence. With HIV prevalence of 8.4%, the cost per HIV infection averted is US$550 and net saving is US$753 000. In settings in sub-Saharan Africa with higher HIV prevalence among the general population, adult male circumcision appears to be cost-effective when adjusted for averted HIV medical cost savings.

Conclusion

Research over the past 20 years has demonstrated a strong association between HIV infection and the lack of male circumcision in sub-Saharan Africa, Asia, and the United States. The completion of one randomized clinical trial of male circumcision demonstrated a 61% protective effect against HIV acquisition in South Africa, necessitating the early termination of the trial and offering circumcision to the control arm. Two additional randomized controlled trials in Uganda and in Kenya are still underway and recommendations regarding the integration of male circumcision as a preventive measure have been postponed pending the results of the remaining trials. If these two trials result in a significant protective effect due to circumcision, it is likely that widespread male circumcision could lead to a strong reduction in the spread of HIV in high incidence areas such as sub-Saharan Africa. There are concerns that still need to be addressed, however, such as the change in sexual behavior, surgical complications such as infection and bleeding and acceptance of a surgical procedure for prevention of HIV. Consequently, if male circumcision is to be introduced widely pending the results of the two remaining trials, it will be crucial to design programs that provide a balance between promotion of male circumcision as an HIV prevention tool and providing all individuals with the full spectrum of other HIV prevention practices.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 90).

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