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PERSPECTIVE

Adult male circumcision to prevent HIV?

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Summary While the HIV pandemic persists, and randomized clinical trials to evaluate the effectiveness of male circumcision as an HIV prevention measure are underway with initial results being released, there is still much debate on the implications of these studies as well as on the feasibility of such a measure. This paper summarizes and discusses the main findings of studies of the evidence underlying adult male circumcision to prevent HIV, explores its feasibility and the implication for policy and future research. While the existing biological and epidemiological evidence suggest potential reduction of the risk of HIV acquisition in circumcised men, additional evidence from randomized trials are needed to confirm this. Even if the findings are confirmed, the practical aspects of implementing adult circumcision would have to be carefully considered. The feasibility of such an intervention, particularly with respect to its cost-effectiveness, safety and acceptability, is still to be demonstrated.

Background

The control of infection with the human immunodeficiency virus (HIV) remains a major challenge to health systems worldwide. It is estimated that since the beginning of the epidemic in the early 1980s, close to 20 million people have died of HIV/AIDS.[1] Meanwhile about 40 million people are currently living with the virus and an estimated 4.8 million new infections occurred during the year 2003 alone.[1] The continuous increase in the number of new HIV cases, despite all the control measures being implemented so far, is an indication of the limited effectiveness of these measures. Efforts are being made to identify other control measures that could cost-effectively replace or complement the current control measures. Adult male circumcision is one such an alternative that has been suggested to help curb HIV transmission and acquisition. However, the evidence in support, as well as the feasibility, of adult male circumcision as an intervention to prevent HIV transmission, has been a subject of debate and disagreement within the scientific community. This paper summarizes and discusses the main findings of studies of the evidence underlying such an intervention, then explores its feasibility and the implications for policy and future research.

Biological evidence

The foreskin is thought to contain high concentrations of HIV-target cells including Langerhan cells, CD4+ T cells and macrophages.[2] Using ex-vivo organotypic culture of foreskin and cervical tissue biopsies, Patterson et al. showed that these foreskin target cells express predominantly the HIV-1 chemokine co-receptor CCR5, and are more susceptible to infection with HIV when compared to cervical tissue. Unfortunately, because their study did not include a comparison to

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tissue from the circumcised penis, it cannot be inferred that the foreskin increases the risk of HIV infection compared to skin from the penile shaft. Other HIV-specific co-receptors such as DC-SIGN (dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin) have been described to be co-expressed with CD4 and CCR5 on dendritic cells in the foreskin.[3]

Male circumcision could thus potentially reduce the risk of HIV acquisition and or transmission by reducing the number of HIV target cells in the penis. However, given that the immunological function of the foreskin has not been completely elucidated and that not all target cells are removed during circumcision[4] this biological evidence cannot be considered conclusive. Studies correlating higher target cell expression and higher infectivity in foreskins versus penile shaft skin are needed for this evidence to be more compelling.

Male circumcision could also potentially indirectly reduce the risk of HIV infection by reducing susceptibility to sexually transmitted infections (STIs) that increase the risk of HIV infection. The evidence that male circumcision reduces the risk of STI acquisition is however contradictory.[5] While some studies have reported lower acquisition rates of genital ulcer diseases,[6] and lower prevalence rates of human papillomavirus (HPV),[7] herpes simplex virus-2 (HSV-2), syphilis or chlamydia in circumcised men,[8] others found no significant protection from STIs (including herpes and syphilis).[5,9]

Evidence from epidemiologic studies

Epidemiologic studies of male circumcision and HIV transmission are quite numerous and diverse. This diversity is not limited to the design used, including ecological, cross-sectional and cohort studies, but also extends to the study population, the methods of ascertaining circumcision as well as the control for potential confounders. Thus careful considerations have to be made when summarizing these studies.

In the literature there are at least six systematic reviews and one meta-analysis of these studies.[10] Most of these reviews focused only on published studies, had unclear search strategies, or did not adequately assess for confounding.[10] The Cochrane review of male circumcision and HIV transmission[10] is one of the most recent reviews and appears to be the most extensive (as it includes previous reviews) and meticulous as it not only aimed at obtaining a summary measure but also evaluated the quality of studies included in the analysis. This review, carried out in 2003 and updated in 2004,[11] found no completed randomized clinical trial (RCT) and reported three ongoing RCTs. Sixteen general population studies were identified, of which the only cohort study showed a protective effect of male circumcision on HIV transmission (odds ratio OR = 0.58, 95% confidence interval (CI): 0.36, 0.96). The 14 cross-sectional studies found heterogeneous crude ORs ranging from 0.28 to 1.73. However nine of these reported adjusted ORs that ranged from 0.26 to 0.80. The only case-control study reported an OR of 1.9 (95% CI: 0.5, 7.2). A crude analysis of these general population studies suggests a variable effect of male circumcision, protective in some cases and causative in others. However, when stratified by method of ascertainment of circumcision, in most of the studies in which the researchers directly observed circumcision, a protective effect was shown, while in most of the others, either a null or a causative effect were shown. This suggests that misclassification of circumcision may be a serious cause of bias in studies of HIV transmission and male circumcision. It also suggests that circumcision may need to be complete for it to be effective.

The Cochrane review further reports the effect of male circumcision in high-risk groups. All the 18 studies (four cohort studies, 11 cross-sectional and three case-control studies) showed a protective effect suggesting that circumcision may be more effective in high-risk groups than the general population.

One of the most interesting studies of circumcision and HIV, because of its size and the fact that it studied both HIV transmission and acquisition in discordant couples, was that carried out in Rakai, Uganda.[12] In this cohort study of 5507 men Gray et al. reported a crude protective effect of circumcision (risk ratio (RR) = 0.61) and a statistically non-significant effect of post-pubertal circumcision of 0.83 (95% CI: 0.35, 2.03). However, one may argue on the validity of clinical significance instead of statistical significance in the interpretation of this effect (that is a close to 20% reduction in HIV transmission which in some settings may be substantial). It is also worthwhile to note that, due to the relatively small number of people who had post-pubertal circumcision in this study, this estimate suffers from a low precision as evidenced by the wide confidence interval. Gray et al., in their analysis of 187 discordant couples, found a reduction of HIV acquisition in circumcised men (0 seroconversion/50 couples in which the male was circumcised compared with 40 seroconversions/137 couples in which the male was uncircumcised). Male circumcision also seemed to reduce the male-to-female transmission of HIV when the viral load was low (less than 50 000 copies/ml).

Two more recent studies have addressed the topic with specific considerations for confounding and visual ascertainment of circumcision. The first was a prospective study of 2298 male patients in an STI clinic in India[9] in which a protective effect of circumcision was found only for HIV (adjusted RR = 0.15) and not for other STIs (syphilis, gonorrhea, HSV). This suggests, as the authors conclude, a biological, rather than a behavioral, explanation of the effect of circumcision. However there is no mention of the age at circumcision in this study. In a meticulously implemented cross-sectional study of 845 men in Kenya, Agot et al. found that after controlling for religion, sexual risk and age, uncircumcised men where 1.5 times more likely to be HIV infected than their circumcised counterparts.[13] Age at circumcision did not seem to make a difference.

The evidence from observational studies seems to be in favor of circumcision having at least some effect in specific high-risk groups. However, this evidence is not compelling as it is based exclusively on observational studies that are very subject to selection bias and thus limited in their generalizability. Furthermore, few of these studies address the issue of when to circumcise (at birth, puberty, or adulthood).

Some authors caution that the observed effect of circumcision may be due to confounding from religious and cultural differences, sexual behaviors and hygiene practices, arguing that circumcised men tend to be from religions that lead them to have behaviors that reduce their risk.[9] Though there is this possibility for residual confounding, it is worth noting that because circumcision is protective, confounding caused

by other protective factors will be upwards (that is cause an increase in the risk or odds ratio), towards the null and adjusting for them will actually (as seen in most of the studies) result in estimates that are more protective. Thus skepticism based on confounding will be valid only for non-protective risk factors like age.

Three randomized clinical trials are being conducted in sub-Saharan Africa to better understand the evidence from observational studies. The results of the RCT conducted in South Africa were recently made available.[14] These show a 63% reduction in the risk of acquiring HIV infection over 21 weeks of follow-up in circumcised, 18—24 year-old males. The incidence rate in the intervention group was 0.7 per 100 person years while in the control group it was 2.2 per 100 person years — a crude incidence rate ratio of 0.35 (95% CI: 0.20, 0.60). The other two RCTs (in Uganda and Kenya) are still to be completed.

In the light of these findings from epidemiological studies and considering that close to 5 million new cases of HIV were estimated for the year 2003[1] and that some other measures (like condoms) being used to curb HIV never needed proof from an RCT, one wonders if it would not be right to start implementing adult male circumcision as a public health intervention. The decision would have been easier to make if the evidence from epidemiological studies was unequivocal and if the intervention was going to be easy and feasible. As discussed above the evidence from observational studies is not so compelling and the only RCT result available is yet to be replicated.

The feasibility of male circumcision as a public health intervention to prevent HIV

For male circumcision to be implemented as a public health intervention it will have to be acceptable to the community in which it is being implemented, be easily implemented and cost-effective.

Acceptability

Circumcision is traditionally done for religious, ethnic, or medical reasons.[15] The greatest challenge facing this intervention is the paradoxical situation by which it will be least acceptable in communities that need it the most (traditionally non-circumcising communities) and it will be most acceptable in communities in which it is likely to be least effective because people already practice it. Studies of the community acceptance in Kenya,[16,17] South Africa[18,19] and Botswana[20] have reported acceptability rates of 51—61% in uncircumcised men. These rates may seem acceptable if the method was really effective and not costly. The stigma associated with circumcision in some communities, the fear of pain and bleeding, reduced sexual pleasure and limited access to health facilities may, however, hamper the effective number of people who may accept the procedure once it is proposed.

Correlated with acceptability, is the risk of a false perception of security from circumcision that may arise if it is offered to people. In one study in South Africa, 30% of circumcised men believed that circumcised men could safely have sex with multiple partners.[21] This risk is in fact also existent for other measures like vaccines, or drugs and could be lessened by an effective information and education system as an adjunct to these measures. Caution has to be taken to make sure that communities do not perceive circumcision as 'The' way to prevent HIV.

Simplicity and safety

Circumcision has generally been regarded as a surgical procedure, needing trained personnel and facilities, and at risk of complications such as bleeding and infection. There is a scarcity of data on the frequency of complications following adult circumcision, particularly for developing countries. A study in Turkey reported close to 85% of men having complications when circumcised in non-medical settings; this compared to 2% when circumcision was conducted by licensed surgeons.[22] Eleven percent of 249 consecutive men of all ages having circumcisions in sterile conditions in hospitals in Nigeria and Kenya developed complications.[23]

It is worth noting that technologies have recently been developed that allow for the use of a single-use disposable device, requiring little training and practically no surgical instruments. If confirmed to be effective and safe these could potentially cut down both the risk of adverse outcomes and the cost, while improving acceptability. Also, providing circumcision in medical settings as opposed to traditional settings will probably reduce the risk of potential adverse outcomes.

Cost—benefit

To the author's knowledge, there has been no published study of the cost-effectiveness of adult male circumcision to prevent HIV. Potentially, the cost of the procedure itself as well as the cost of training health personnel, information, education and communication as well as for maintaining the health facilities will need to be considered. The use of modern techniques as opposed to traditional surgery may however reduce cost. In high HIV-prevalence settings the relative cost of averting a case of HIV infection as opposed to having to manage that case will probably be in favor of the intervention. Other benefits that may result from a public health intervention that includes adult male circumcision, include the opportunity to bring men in contact with the healthcare system and increase awareness of the HIV pandemic, to increase voluntary counseling and testing, to increase the acceptability of neonatal circumcision and also the benefit of reducing other penile infections such as HPV (which could be transmitted to their female partners and cause cervical cancer) or penile cancer. Data on the cost—benefit of adult male circumcision are needed to guide policy.

Other considerations

In addition to the considerations above, the implementation of such an intervention will have to carefully consider legal, ethical, and human rights issues.[24] The opportunity cost from reducing resources to other programs, age at circumcision, circumcision in hospitals versus traditional settings, management of complications and how to deal with concurrent female genital mutilation that is being prohibited, are examples of issues that need to be tackled.

Conclusion

Adult male circumcision could potentially reduce the transmission efficiency of HIV and thus reduce the reproductive rate of HIV in a population. Therefore, it could eventually be one of the tools used in preventing HIV within a comprehensive HIV control program. However, because of its limited feasibility, more evidence on its effectiveness is needed so as to increase its acceptability (both in the population and the scientific community) as well as to justify the addition, and/or displacement of meager resources from other strategies, towards its implementation.

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