Male circumcision for HIV prevention: from evidence to action?

Helen A. Weiss[a], Daniel Halperin[b], Robert C. Bailey[c], Richard J. Hayes[a], George Schmid[d] and Catherine A. Hankins[e]

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Introduction

An estimated 2.5 million people were newly infected with HIV in 2007, of whom two-thirds live in sub-Saharan Africa [1]. In the context of the urgent need for intensified and expanded HIV prevention efforts, the conclusive results of three randomized controlled trials (RCT) showing that male circumcision reduces the risk of HIV acquisition by approximately 60% [2–4] are both promising and challenging. Translation of these research findings into public health policy is complex and will be context specific. To guide this translation, we estimate the global prevalence and distribution of male circumcision, summarize the evidence of an impact on HIV incidence, and highlight the major public health opportunities and challenges raised by these findings.

Male circumcision prevalence

Male circumcision, one of the oldest and most common surgical procedures, is practised for religious, social and medical reasons. By reviewing nationally representative data sources and assuming that all Muslim and Jewish men are circumcised, we estimate that 30–34% of adult men are circumcised worldwide [5]. Overall, an estimated 68% of circumcised men are Muslim and 1% are Jewish, with coverage almost universal in the Middle East, north Africa, Pakistan, Bangladesh and Indonesia (Fig. 1). Male circumcision is also practised for non-religious reasons either neonatally or as a rite-of-passage to manhood; and is very common in west Africa, parts of central and eastern Africa, the United States, Republic of Korea, and the Philippines [5]. Within countries, prevalence can vary widely with religion, ethnicity and socioeconomic status [5,6].

Evidence that male circumcision reduces the risk of HIV infection

Biological evidence

Several plausible biological mechanisms could explain the increased risk of HIV and other sexually transmitted infections (STI) in uncircumcised men, including microtears and lesions in the mucosal surface of the inner foreskin and the longer survival of pathogens in the warm, moist subpreputial space. Most importantly, the inner foreskin is especially susceptible to HIV infection, as a result of a lack of keratinization and the high density of HIV target cells that are relatively accessible to infection compared with their deeper location under the keratinized surface of the outer foreskin and the glans [7,8].

From the [a]MRC Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London, UK, the [b]Harvard Center for Population and Development Studies, Harvard School of Public Health, Cambridge, Massachusetts, USA, the [c]Department of Epidemiology, University of Illinois at Chicago, Illinois, USA, the [d]Department of HIV/AIDS, World Health Organisation, Geneva, Switzerland, and the [e]Department of Evidence, Monitoring and Policy, Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva, Switzerland.

Correspondence to Helen A. Weiss, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK.

Tel: +44 207 612 7872; fax: +44 207 636 8739; e-mail: helen.weiss@lshtm.ac.uk

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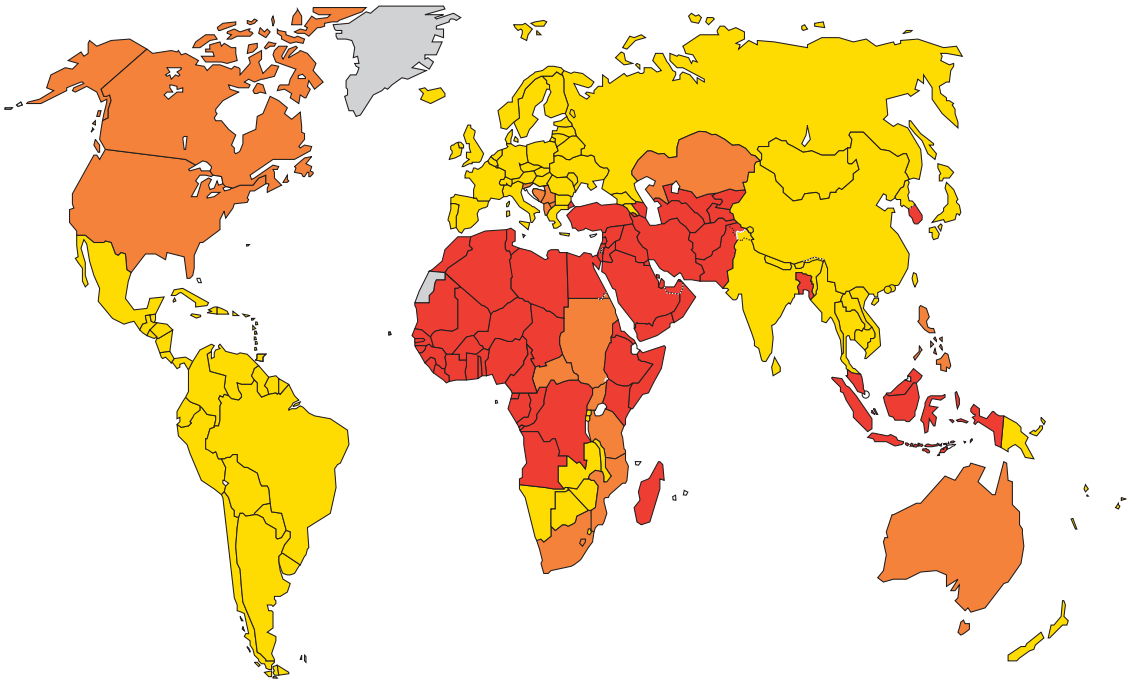

Fig. 1. Global map of male circumcision prevalence at country level, as of December 2006. No data; < 20% prevalence; 20–80% prevalence; > 80% prevalence. Source: World Health Organization. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Observational evidence

The hypothesis that male circumcision might protect against HIV infection was first suggested in 1986 [9,10], and was subsequently supported by ecological descriptions of areas with low prevalence of male circumcision and high HIV prevalence in sub-Saharan Africa in the late 1980s [11,12], and later across 118 developing countries [13]. Further evidence comes from two systematic reviews of observational studies comparing HIV risk between circumcised and uncircumcised men in the same populations [14,15]. One, restricted to sub-Saharan Africa, included 27 studies [14], and the other was a global review including 37 studies [15]. Circumcised men were consistently found to be at lower risk of HIV infection, and a meta-analysis of the 15 studies that adjusted for potential confounders showed this reduction to be large and highly statistically significant [adjusted risk ratio (RR) 0.42, 95% confidence interval (CI) 0.34–0.54] [14]. Subsequent studies have found similar significantly reduced risks among circumcised men [16–18].

Evidence from the randomized controlled trials

Although compelling, the observational data do not prove causality, and three RCT of circumcision among consenting, healthy adult men in Uganda, Kenya and South Africa were initiated in 2002–2003. Each trial was halted early after recommendations by independent Data and Safety Monitoring Boards in 2005–2006, when interim analyses found a highly significant reduced risk of HIV seroconversion among the men randomly assigned to circumcision [2–4].

In total, 10 908 uncircumcised, HIV-negative adult men were randomly assigned to intervention or control arms, and followed for up to 2 years (Table 1). Overall retention rates were high (86–92% at the end of follow-up, when men in the control arms were offered circumcision). HIV incidence was considerably lower in Uganda (1.33 per 100 person-years in the control arm) than in the other two sites (2.1 per 100 person-years; Table 1), possibly reflecting overall lower incidence in this population and the inclusion of older men in the trial.

Table 1 shows the cumulative risk among men who were HIV negative at enrolment, estimated using intention-to-treat Kaplan–Meier analysis. There have been no previous RCT of adult male circumcision [15], and to summarize the protective effects seen in the trials, we conducted a random-effects meta-analysis of results of these three trials, following the recommendations of the QUORUM statement for reporting trials as appropriate [19]. There was no evidence of heterogeneity between the trials ($P = 0.86$), and the summary rate ratio was 0.42 (95% CI 0.31–0.57; Fig. 2), corresponding to a protective effect of 58% (95% CI 43–69%), identical to that found in the observational studies (58%, 95% CI 46–66%) [14].

Table 1. Summary of the three randomized controlled trials of male circumcision on HIV acquisition in sub-Saharan Africa.

	South Africa	Kenya	Uganda
Number enrolled	Control 1582 Intervention 1546	Control 1393 Intervention 1391	Control 2522 Intervention 2474
Age range (years)	18–24	18–24	15–49
Median age (IQR)	21 (19.6–22.5)	20 (19–22)	N/A
Age category (years)			
≤19	N/A	N/A	28.0%
20–24			27.5%
25–29			18.3%
≥30			26.2%
Setting	Peri-urban area	Urban area	Rural
Method of circumcision[a]	Forceps-guided method by local general practitioners	Forceps-guided method by study clinicians	Sleeve procedure by study clinicians
Visit schedule	3, 12 and 21 months	1, 3, 6, 12, 18 and 24 months	6, 12 and 24 months
Retention rate	92% at 21 months	86% at 24 months	90% at 24 months
Person-years of follow-up[b]	4693	4428	6744
HIV incidence in control arm	2.1 per 100 py	2.1 per 100 py	1.3 per 100 py
HIV cases (intervention:control)	20:49	19:46	22:45
Risk ratio (95% CI)[b]	0.41 (0.24–0.69)	0.41 (0.24–0.70)	0.43 (0.24–0.75)
Summary risk ratio (95% CI)[c]		0.42 (0.31–0.57)	

CI, Confidence interval; IQR, interquartile range; py, person-years.
[a]See WHO manual for further details (www.who.int).
[b]Intention-to-treat analysis among individuals who were HIV seronegative at baseline estimated with Kaplan–Meier analyses.
[c]Estimated with a random-effects meta-analysis.

The true biological protective effect of male circumcision, however, may be better estimated by an 'as-treated' analysis [20], which assigns person-time according to the actual circumcision status of participants. In each trial, not all men adhered to the arm they were randomly assigned to. For example, in the South African trial, 10.3% of men randomly assigned to the control arm had been circumcised outside the trial at month 21. This was greater than in the other trials (1.1–1.3%) perhaps because of the greater local availability of male circumcision services. In each trial, approximately 5–6% of men randomly assigned to be circumcised declined surgery. An 'as-treated' meta-analysis of the three trials shows a stronger effect than the intention-to-treat analysis (summary RR 0.35, 95% CI 0.24–0.54).

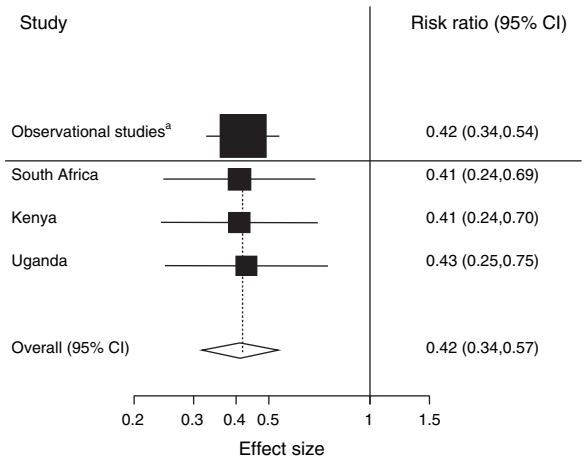

Fig. 2. Random-effects meta-analysis for the randomized controlled trials intention-to-treat analysis, with summary risk ratio for the observational data. CI, Confidence interval. [a]Risk ratio based on 15 studies that adjusted for potential confounders [14].

The Ugandan trial reported efficacy in subgroups, and in general found greatest efficacy among men at higher risk (those with two or more partners during follow up, non-marital sexual partners, reporting transactional sex or having a history of genital ulcers); i.e. approximately 70% risk reduction. These results agree with previous observational data suggesting a stronger protective effect in high-risk populations (summary RR 0.29, 95% CI 0.20–0.41) compared with general populations (RR 0.56, 95% CI 0.44–0.70) [14]. The Ugandan and Kenyan trials found that circumcised men were at approximately half the risk of self-reported or clinically diagnosed genital ulcer disease (GUD) during the trial. This suggests that the stronger protective effect in high-risk groups may be caused partly by circumcision protecting against other STI, especially GUD [21], thus providing additional indirect protection against HIV [22]. Models based on the Kisumu data estimate that approximately 10–20% of the HIV infections prevented by male circumcision were caused by efficacy against STI [23].

In the Kenyan and Ugandan trials there was little evidence of a protective effect until 6–12 months after randomization. In contrast, in South Africa, a protective effect was seen within 1–3 months (RR 0.23, 95% CI 0.05–1.04). These differences may be due to chance, or differences in behaviour such as the resumption of sex before complete wound healing (which can take up to 6 weeks). Also, in the Kenyan trial, four men in the circumcision arm seroconverted within a month of randomization, and

assuming a short period of abstinence after surgery, are likely to have been already infected at baseline. Pooled analyses of the trial data focusing on early seroconvertors would help determine when and how protection begins.

What are the implications of the trials stopping early? Larger than expected treatment effects that result in trial termination may be due to chance, but the risk of overestimating the treatment effect decreases when the number of events is over approximately 200 [24]. After the South African trial was published, it was suggested that inferences from the trial may be weak because the study was stopped early [25]. There are, however, several reasons why early termination is unlikely to bias the trial results. First, all three trials had conservative pre-determined stopping rules that were met. Second, the consistency of the results and indication of a somewhat stronger effect of the intervention over time in two of the trials argues that, if anything, the early stopping may have underestimated the effect. Third, the overall number of events is greater than the suggested threshold of 200 [24]. Finally, the observed effect in each of the male circumcision trials is not larger than expected, but is identical to that seen in previous observational studies.

The findings of the male circumcision trials are in contrast to the recent disappointing results of other trials of HIV prevention tools, including the cellulose sulfate microbicide, the female diaphragm and gel, herpes simplex virus suppressive therapy and, most recently, an adenovirus-5-based HIV vaccine [26–29]. These results highlight the need to expand services for confirmed HIV prevention strategies including safe adult male circumcision.

Public health relevance of the trial results

Responding to the conclusive evidence that male circumcision offers significant protection for men from HIV infection, several countries are planning to introduce or expand safe male circumcision programmes, including Kenya, Zambia, Swaziland and Rwanda. International funding agencies are also backing this strategy, with programmes such as the US President's Emergency Plan For AIDS Research (PEPFAR) providing funds to complement domestic funding for expanded circumcision services. Furthermore, the Agence Nationale de Recherche sur la SIDA (ANRS), the Bill and Melinda Gates Foundation and the US National Institutes of Health are supporting operational and related research.

Among the major concerns about the expansion of male circumcision services for HIV prevention are surgical complications, the potential for men to increase their risky sexual behaviour if they believe themselves to be fully protected, the optimal messages to relay about offering male circumcision services to men who are HIV seropositive, and the costs and opportunity costs of expanding services in often overstretched health systems. The trials provide initial insights into these issues; however, further operational research is needed to evaluate these concerns in the 'real world'.

Complications of male circumcision

Adolescent or adult circumcision requires suturing and can cause bleeding and, more rarely, haematoma or sepsis. Comparing the adverse event rates in the three trials is complex, as different definitions and criteria were used. In the Kenyan trial, adverse events possibly, probably or definitely related to circumcision occurred in 23 of 1334 circumcised participants (1.7%). All adverse events were mild or moderate and resolved with treatment within hours or days. In the South African trial, the adverse event rate was 54 per 1495 (3.6%) in HIV-negative men. In Uganda, the risk of an adverse event related to surgery was higher, at 7.6% (178/2328). This may be attributable to differences in adverse event case management. The risk of moderate adverse events related to surgery was 3% and there were five severe adverse events (0.2%). All of these events were successfully managed and resolved.

These trial data indicate that adult male circumcision can be safely undertaken in limited-resource settings when performed in a clinical setting by experienced, well-trained providers. Similar conclusions were found from a recent review of complications of male circumcision in Anglophone Africa [30]. When male circumcision is undertaken in un-antiseptic conditions, however, by inexperienced providers with inadequate instruments, or with poor aftercare, serious complications or even death can result [31]. It is possible that unmet demand for male circumcision may result in an increase in non-medical circumcision services offered by untrained individuals as a means of income generation, with a heightened risk of significant harm. To assist in preventing these problems, WHO/UNAIDS/JHPIEGO have produced a manual for performing adult male circumcision under local anaesthesia [32]. National policies, however, are needed to maximize the safety, efficiency, and availability of male circumcision service provision.

Behaviour change after male circumcision

The adoption of, or increase in, unsafe sex practices ('risk compensation') after adult circumcision could potentially offset the protective effect of male circumcision [33]. The Rakai trial found no differences in sexual behaviour during the trial by circumcision status. The South African trial showed a significantly increased mean number of sex acts between 4 and 21 months among men in the circumcision arm, but not an increase in the number of sexual partners or a change in condom use. In the Kenyan trial there was a decline in reported risk-taking behaviour

during the 24 months of follow-up in both arms. At 24 months, however, significantly fewer men in the control arm reported unprotected sexual intercourse (46 versus 51%) and these men were also more likely to report consistent condom use (41 versus 36%). There was also a tendency for a greater proportion of the uncircumcised men to report practising sexual abstinence at 24 months (18 versus 14%).

Although reassuring, these trial data may not be generalizable. The trials provided the highest standards of preventive care, with men receiving intensive, individual counselling and without knowing that circumcision reduced their risk of HIV. The challenges of expanding services within already overstretched health systems include the need to provide adequate counselling to convey the message that male circumcision is a risk-reduction strategy that provides partial protection only.

The only data published on sexual behaviour after adult male circumcision outside a clinical trial setting support the RCT findings. In a cohort study of 648 men in western Kenya [34], of whom half had elected to become circumcised, circumcised men were no more likely to report risky sexual behaviour (number of unprotected sex acts, number of non-spousal partners, inconsistent condom use) during the 12 month period post-circumcision than uncircumcised men. Results were unchanged when the postoperative period was excluded. This study suggests that, within the context of adequate counselling on risk reduction, circumcised men did not increase their risky behaviour, but again this study was conducted before dissemination of the RCT findings. Further follow-up studies of men choosing to be circumcised are needed as male circumcision services are expanded and perceptions by individuals and communities evolve. In addition further work evaluating strategies to optimize counselling and communication messages, including among men already circumcized, in resource-poor settings is urgently needed.

Cultural acceptability of male circumcision in non-circumcising African communities

Concerns about the cultural acceptability of male circumcision in Africa now seem unwarranted. Thirteen acceptability studies from nine countries in sub-Saharan Africa have shown that 29–81% (median of 62%) of uncircumcised men wished to become circumcised, 50–79% of women favoured circumcision for their partners, and 50–90% of men and women would circumcise their sons [35]. The lowest level of acceptability among uncircumcised men (29%) was from a study in eastern Uganda in 1997 [36], before male circumcision was more widely perceived as possibly being associated with HIV protection. More recently, the pre-trial data from Rakai indicated that 60% of men were willing to be circumcised [personal communication: Ron Gray] to gain perceived HIV protection. Otherwise, more than half of uncircumcised men in the regions studied were willing to become circumcised. The main barriers to acceptability were cost, fear of pain, and safety concerns, with improved hygiene, perceived lower risk of STI and other health benefits the main facilitators [35]. These data suggest that culture and ethnicity are not major barriers to the acceptability of male circumcision in most of sub-Saharan Africa.

Sociocultural issues of expanding male circumcision services

As a practice having strong sociocultural resonance, and an occasionally controversial history in some parts of the world, the expansion of male circumcision services evokes challenges, including human rights, ethical and legal issues [37–39]. The protection and promotion of human rights is integral to all aspects of HIV prevention and care, and all male circumcision services must ensure that the procedure is carried out safely, under conditions of informed consent and without discrimination. Further research will be needed in different settings to obtain a better understanding of the attitudes and the meaning of circumcision among different groups, and to develop appropriate education and counselling messages.

Neonatal circumcision is a simpler, cheaper, and safer procedure than adult circumcision [5], and for reasons of safety and cost, countries may decide to include neonatal circumcision, under parental consent, as a longer-term HIV prevention strategy. This would have the additional benefit of greatly reducing the risk of urinary tract infections in the first year of life [40].

Potential population-level impact of male circumcision in sub-Saharan Africa

Modelling indicates that expanded services can have a marked population-level effect on HIV incidence in a very cost-effective manner. The population-level impact could be greater than the individual-level efficacy if a large proportion of men become circumcised, and, assuming full coverage, male circumcision could avert 2.0 (95% CI 1.1–3.8) million new HIV infections and 0.3 (95% CI 0.1–0.5) million deaths over the next 10 years in sub-Saharan Africa, and 3.7 million (95% CI 1.9–7.5) new HIV infections and 2.7 (95% CI 1.5–5.3) million deaths in the following 10 years [41]. A modelling study based on scenarios in Nyanza province in western Kenya, and Botswana, also found that male circumcision programmes resulted in large and sustained declines in HIV prevalence over time [42].

An alternative way to asses the population-level impact of the widespread coverage of male circumcision is by looking again at the ecological correlations discussed earlier, which represent a natural experiment. Countries with very high or universal coverage of male circumcision have, without

exception, relatively low and stable HIV prevalence which has never exceeded approximately 6%. The importance of male circumcision in 'containing' the HIV epidemic was highlighted in the Four Cities' Study [43], which found higher levels of reported risk-taking behaviour in Yaounde, the capital city of Cameroon, where prevalence has been fairly stable at below 7% for many decades, compared with Kisumu, Kenya and Ndola, Zambia where HIV is more prevalent. The authors concluded that biological co-factors for HIV transmission, notably male circumcision and herpes simplex virus type 2 infection, were likely to be key factors in the HIV epidemic in sub-Saharan Africa and this has been confirmed in subsequent modelling of the data [44].

Cost-effectiveness of male circumcision for HIV prevention in sub-Saharan Africa

Cost-effectiveness data from the Ugandan and South African trials indicate that male circumcision is likely to be a cost-effective, even cost-saving, intervention [33,45]. The South African estimate was modelled for Gauteng Province, where HIV prevalence is 25.6%, and the majority of men are uncircumcised. In this setting, assuming full coverage of male circumcision, and using cost data from the trial, the cost per HIV infection averted was US$181 (80% CI US$117–306), with net savings of US$2.4 million over 20 years (US$2411 per circumcision) [45]. Similar findings were seen in Kisumu, where it is estimated to cost $200 per HIV infection averted [personal communication, N. Nagelkerke]. In contrast, in Rakai, Uganda, with an HIV incidence of 1.2 per 100 person-years, assuming 60% efficacy against female-to-male, but not male-to-female transmission, and 75% coverage, 39 surgeries would be needed to prevent one HIV infection over 10 years, at a cost of US$2631 per HIV infection averted over 10 years [46]. Lifetime costs of HIV infections were not included in that study and thus potential cost savings were not calculated. As the benefits of circumcision are likely to be lifelong, and economies of scale should decrease costs, male circumcision is very likely to be a cost-effective intervention.

Relevance of findings for female partners

We do not know whether male circumcision reduces the risk of male-to-female HIV transmission. Observational data from Uganda had previously suggested that circumcision reduced the risk of HIV transmission [18], but recent data from Uganda and Zimbabwe suggest little protective effect [47]. An RCT of the impact of male circumcision in protecting against male-to-female HIV transmission in Rakai, Uganda, was stopped at an interim analysis in December 2006 as there was little chance of eventually finding a statistically significant impact [48], although a protective effect cannot be ruled out, and the reduced risk of GUD among circumcised men would be expected to reduce the risk of transmission. Indirectly, women living in high HIV prevalence settings with low male circumcision prevalence will benefit if there is a reduction in HIV incidence among men who are circumcised, especially in programmes achieving wide coverage [41]. This is because women would have a lower probability of encountering a sexual partner with HIV infection. In addition, as for men, there are direct non-HIV-related benefits to female partners of circumcised men, most notably a lower risk of human papillomavirus infection and cervical cancer [13,49] and also possibly a lower risk of *Chlamydia trachomatis* [50]. If male circumcision services are expanded without appropriate and sufficient individual counselling, however, there is the potential for increased difficulty for women to negotiate safer sex behaviour if their male partners believe themselves to be protected from infection [51]. Whenever possible, female partners should be included in the education and counselling of men undergoing circumcision to provide support for adherence to postoperative care instructions to minimize the risk of transmission through the early resumption of sexual intercourse.

There are also concerns regarding the potential for confusion between conflicting messages for male circumcision and female genital mutilation/cutting (FGM/C), sometimes called female circumcision, in which parts of the external sexual organs of girls are removed. There are no known health benefits associated with FGM/C. Although in nearly all areas of Africa where men are not traditionally circumcised there is also no practice of FGM/C, it is critical that the promotion of male circumcision clearly distinguishes it from FGM/C.

Relevance of findings for men who have sex with men

Reported sex between men was uncommon in the three African trials, and the implications of the trial findings for men who have sex with men (MSM) are unclear. HIV transmission from penile–anal intercourse is predominantly to the receptive partner [52], a risk unlikely to be directly modified by his circumcision status. It is, however, biologically plausible that male circumcision provides partial protection against HIV acquired through insertive anal intercourse, as it does for vaginal–penile intercourse. There are few observational studies [53–56] and no RCT of the impact of circumcision on HIV transmission among MSM, and results are unclear. Definitive evidence may come only from an RCT among MSM. Meanwhile, the message for all men, regardless of sexual orientation or circumcision status, must be that practising safer sex behaviours, including correct and consistent condom use, is the best way to avoid infection.

In conclusion, randomized controlled trials have provided final conclusive evidence that male circumcision provides approximately 60% protection against the heterosexual acquisition of HIV in men. Male circumcision provides only partial protection against HIV and it is essential that services are embedded within comprehensive HIV prevention programmes, with strong counselling

messages and community campaigns conveying the message that the procedure will reduce, but not eliminate, HIV risk. If prudently developed, the increased provision of accessible safe voluntary adult male circumcision services could also increase opportunities to educate men about reproductive and sexual health topics, including hygiene, sexuality, gender relations and the need for ongoing combination HIV prevention strategies.

The endorsement of male circumcision for HIV prevention by the World Health Organization and UNAIDS will probably increase the demand for safe adult male circumcision services in settings with high rates of heterosexual HIV transmission. Several agencies have begun to fund the expansion of services, and individual countries are deciding whether this would be an appropriate addition to their HIV prevention programmes, considering the local epidemiology of HIV, cultural acceptability and feasibility of scaling-up the procedure. Close monitoring and evaluation of these programmes will be needed to ensure that effective counselling and follow-up takes place and that service expansion brings benefits to other health programmes. For reasons of safety, cost and feasibility, countries may also decide to promote neonatal circumcision as a long-term strategy.

In summary, male circumcision provides a much needed addition to the current HIV prevention armamentarium. It is not a new, untested or unknown technology, but possibly the oldest, and certainly the most common, surgical procedure known. The evidence from the trials is conclusive, and the challenges to implementation must now be faced.

Conflicts of interest: None.

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