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Publication date
2014

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Citation for published version (APA):
Hankins, C. A. (2014). *HIV prevention policy and programme planning: What can mathematical modelling contribute?* [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 5

Male circumcision for HIV prevention: from evidence to action?

Helen A Weiss, Daniel Halperin, Robert C Bailey, Richard J Hayes, George Schmid, Catherine A Hankins

AIDS 2008, 22: 567-574

EDITORIAL REVIEW

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]

AIDS 2008, **22**:567–574

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].

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Received: 21 July 2007; revised: 20 October 2007; accepted: 31 October 2007.

ISSN 0269-9370 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

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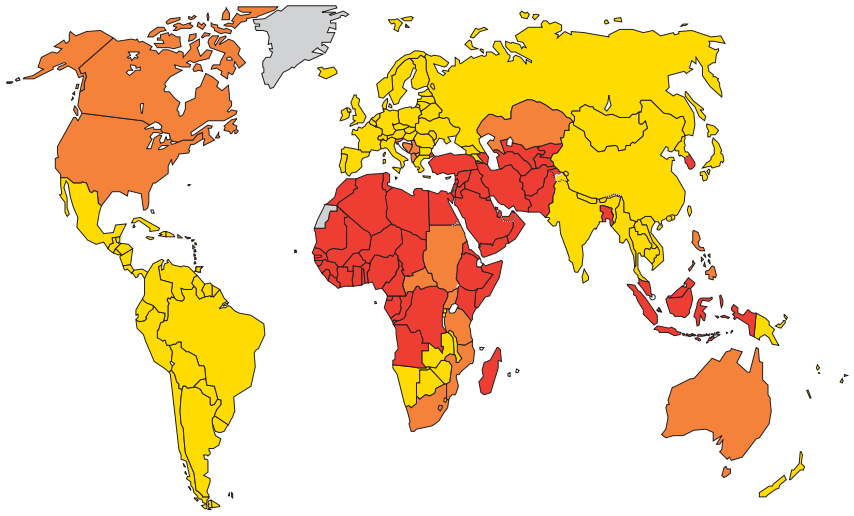

Fig. 1. Global map of male circumcision prevalence at country level, as of December 2006. No data; < 20% prevalence; 20–80% prevalence; > 80% prevalence. Source: World Health Organization. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion 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].

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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).

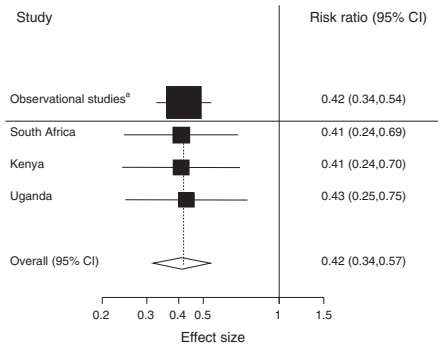

Fig. 2. Random-effects meta-analysis for the randomized controlled trials intention-to-treat analysis, with summary risk ratio for the observational data. CI, Confidence interval. [a]Risk ratio based on 15 studies that adjusted for potential confounders [14].

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

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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 predetermined 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

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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

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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

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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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Chapter 6

Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis

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Lancet Infectious Diseases 2009; 9: 669-77

Review

Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis

Helen A Weiss, Catherine A Hankins, Kim Dickson

Male circumcision provides long-term indirect protection to women by reducing the risk of heterosexual men becoming infected with HIV. In this Review, we summarise the evidence for a direct effect of male circumcision on the risk of women becoming infected with HIV. We identified 19 epidemiological analyses, from 11 study populations, of the association of male circumcision and HIV risk in women. A random-effects meta-analysis of data from the one randomised controlled trial and six longitudinal analyses showed little evidence that male circumcision directly reduces risk of HIV in women (summary relative risk 0·80, 95% CI 0·53–1·36). Definitive data would come from a further randomised controlled trial of circumcision among men infected with HIV in serodiscordant heterosexual relationships, but this would involve enrolling about 10 000 couples and is likely to be logistically unfeasible. As circumcision services for HIV prevention are scaled-up in high HIV prevalence settings, rapid integration with existing prevention strategies would maximise benefits for both men and women. Rigorous monitoring is essential to ensure that any adverse effects on women are detected and minimised.

Lancet Infect Dis 2009; 9: 669–77

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Introduction

Three randomised controlled trials and over 40 observational epidemiological studies have provided compelling evidence that male circumcision reduces the risk of heterosexual men becoming infected with HIV.[1–4] WHO-UNAIDS recommend that circumcision be added to present HIV-prevention strategies for HIV risk reduction in heterosexual men.[5]

Men who are not infected with HIV in high HIV-prevalence settings will directly benefit from expanded access to circumcision services, but the implications for women are less clear. Women are affected by circumcision as sexual partners and as parents.[6] Studies of the acceptability of circumcision in southern and east Africa done before trials showed that a majority of women interviewed (median 69%; range 29–87%) favoured circumcision for their partners, and 81% (range 70–90%) were willing to circumcise their sons, if it were safe and affordable.[7] A study from Mysore, India, also found that most women with uncircumcised sons (457 of 564; 81%) would definitely circumcise them if the procedure was offered safely and free of charge.[8]

A woman's risk of HIV infection depends on the prevalence of HIV infection among her male partners, the rate of forming partnerships, and the probability of becoming infected with HIV on exposure to an infected partner. Expanded male circumcision services will decrease the HIV prevalence in men, and mathematical modelling confirms that, in high HIV-prevalence settings, women will benefit from expanded circumcision services through a lower risk of exposure to men infected with HIV.[9] In the absence of a direct protective effect of circumcision on male-to-female transmission, these benefits will likely take several years to become evident, and will increase over time, with subsequent reductions in rates of mother-to-child transmission.[9,10] The effect of circumcision on the probability of becoming infected with HIV on exposure to an infected male partner will depend on whether there is a direct protective effect of circumcision on male-to-female transmission, as well as any effect of circumcision on HIV cofactors (ie, factors that affect HIV transmission probability) in either the man or the woman. Although there are few data on the direct effect of circumcision on male-to-female HIV transmission, randomised controlled trials show that circumcised men are at substantially lower risk of some cofactors (genital ulcer disease and possibly herpes simplex virus type 2).[11–13] There is increasing evidence that female partners of circumcised men also have a reduced risk of cofactors, including genital ulcer disease[14] and vaginal infections such as bacterial vaginosis and trichomonas infection.[14,15]

In this Review, we summarise the available epidemiological evidence of a direct effect of circumcision on male-to-female transmission of HIV, and discuss research and public health implications of our findings.

Methods

Search strategy and selection criteria

Inclusion criteria were epidemiological studies of the association of HIV prevalence or incidence in women as the outcome, with male partners' circumcision status as an exposure. We identified such studies by searching PubMed with the following search string: ("HIV seropositivity/epidemiology"[MeSH] or "HIV seropositivity/etiology"[MeSH] or "HIV seropositivity/prevention and control"[MeSH] or "HIV seropositivity/transmission"[MeSH] or "HIV infections/epidemiology"[MeSH] or "HIV infections/etiology"[MeSH] or "HIV infections/prevention and control"[MeSH] or "HIV infections/transmission"[MeSH] or HIV[MeSH] or hiv[text word]) and ("epidemiologic studies"[MeSH] or "seroepidemiologic studies"[MeSH] or "risk factors"[MeSH] or "odds ratio"[MeSH] or

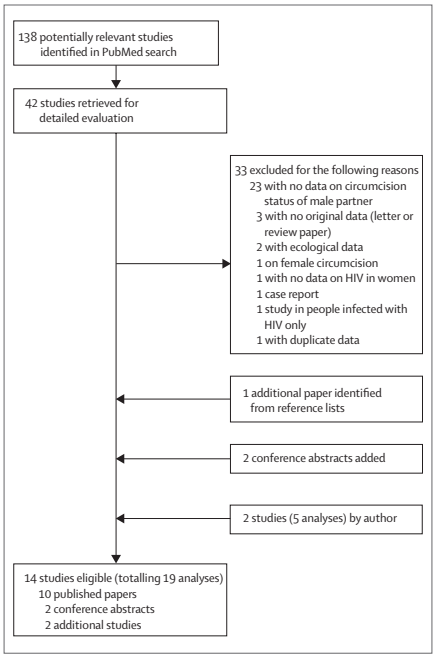

Figure 1: **Flow diagram of study selection process**

"prevalence"[MeSH] or "incidence"[MeSH] or "risk"-[MeSH] or "cross-sectional studies"[MeSH] or "epidemiologic methods"[MeSH] or prevalence[text word] or incidence[text word]) and (journal article[pt] or letter[pt]) and "humans"[MeSH] and "female"[MeSH] and ("circumcision, male"[MeSH] or circumcision[text word]).

The initial search, done on Nov 27, 2008, identified 121 papers. The abstracts of these 121 papers were read by two reviewers (HAW and Natasha Larke, London School of Hygeine and Tropical Medicine, London, UK), and 41 were potentially relevant (ie, the abstract showed that the study included measures of effect size for HIV risk factors for women). The search was updated on Aug 8, 2009, identifying a further 17 papers, of which one was potentially relevant. Two studies from conference presentations were also included.[16,17] Full copies of the 42 potentially relevant papers and two presentations were obtained, and one further paper[18] was identified through the reference lists of relevant papers. 33 of these papers were deemed ineligible, with the most common reason being that they did not contain data on circumcision status of the male partner (figure 1). Additional relevant analyses were obtained from two authors (Gray RH, Johns Hopkins University, Baltimore, USA, personal communication; Lingappa J, University of Washington, Seattle, USA, personal communication). Of the 14 eligible studies, two included three subanalyses (Gray RH, personal communication),[19] and one included two subanalyses (Lingappa J, personal communication). The final review contained data on 11 distinct study populations, and included 19 analyses.

In addition, we reviewed data from the Demographic and Health Surveys (DHS) project[20] to obtain self-reported prevalence of male circumcision, and national population-based surveys done from 2001–05.[21]

	Level of evidence	Number of analyses
Randomised–controlled trial[15]	+ + + +	1
Longitudinal studies of serodiscordant couples[16,17]	+ + +	2
Longitudinal studies among women only[19,22]	+ +	4
Cross-sectional studies among women[18,23,24]	+	3
Cross-sectional studies among couples (Gray; Lingappa)[25–28]	+	9
Ecological data	+	..

Table 1: **Summary of studies contributing to association of HIV infection and male partners' circumcision status**

Data extraction and analysis

11 studies contained relevant information and data were extracted by HAW and CAH. The data extracted included study design, study population, location, circumcision prevalence, HIV prevalence among women by circumcision status of their partner, and measures of effect. Unadjusted risk ratios (RRs) and 95% CIs were calculated from data given in the papers. Adjusted measures of effect were also extracted. To our knowledge, none of the studies included men infected with HIV on antiretroviral treatment, either because they were done before availability of treatment, or because such men were ineligible for the studies.

The association of male circumcision and HIV risk in women is best estimated from longitudinal studies, which, unlike cross-sectional studies, are able to distinguish the temporal sequence of exposure and infection with HIV (table 1). Specifically, in cross-sectional studies of couples we do not know which partner was infected first, and such information is essential to estimate the effect of circumcision on male-to-female transmission. For this reason, the primary analysis was restricted to longitudinal studies. Random-effects meta-analysis was used to assess between-study heterogeneity, and to calculate the summary RR and 95% CI. For consistency, unadjusted measures of effect for cross-sectional studies are presented as prevalence ratios, even if an odds ratio (OR) is presented in the original paper. The meta-analysis was done using the adjusted measure of effect ratio if available, otherwise the unadjusted measure was used. All analyses were done with Stata 10.1.

	Setting (year of study)	Study population	% with circumcised partner	HIV rate among women with circumcised partners	HIV rate among women with uncircumcised partners	Unadjusted RR* (95% CI)	Adjusted RR (95% CI)
Randomised controlled trial							
Wawer (2009)[15]	Rakai, Uganda	Female partners of men infected with HIV	58%	17/92 (18%)	8/67 (12%)	1·58 (0·68–3·66)	1·49 (0·62–3·57)†
Couples cohort							
Baeten (2009)[16]	14 sites in east and southern Africa	Female partners of men infected with HIV	34%	2·04 per 100 person-years	3·47 per 100 person-years	0·59 (0·31–1·13)	0·60 (0·31–1·16)
Reynolds (2006)[17]	Rakai, Uganda (1994–2004)	Female partners of men infected with HIV	13%	6·6 per 100 person-years	10·3 per 100 person-years	0·67 (0·45–1·00)	..
Cohort							
Turner (2007)[19]	Uganda (low risk; 1999–2004)	Family planning clinic attenders	36%	1·53 per 100 person-years	1·20 per 100 person-years	1·28 (0·69–2·35)	1·33 (0·72–2·47)‡
Turner (2007)[19]	Uganda (high risk; 1999–2004)	Sexually transmitted diseases clinic attenders and sex workers	37%	0·84 per 100 person-years	3·23 per 100 person-years	0·26 (0·06–1·16)	0·16 (0·02–1·25)‡
Turner (2007)[19]	Zimbabwe (1999–2004)	Family planning clinic attenders	10%	4·57 per 100 person-years	4·19 per 100 person-years	1·10 (0·64–1·87)	1·12 (0·65–1·91)‡
Kapiga (1998)[22]	Dar es Salaam, Tanzania (1991–95)	Family planning clinic attenders	98%	2·6 per 100 person-years	9·2 per 100 person-years	0·28 (0·09–0·89)	0·29 (0·09–0·97)§
Cross-sectional							
Allen (1991)[18]	Kigali, Rwanda (1986–87)	Women attending prenatal and paediatric clinics	34%	132/456 (29%)	275/887 (31%)	0·93 (0·78–1·11)	..
Chao (1994)[23]	Butare, Rwanda (1989–1991)	Antenatal clinic attenders	5%	75/307 (24%)	442/5286 (8%)	2·78 (2·23–3·47)	2·1 (1·5–2·9)¶
Hunter (1994)[24]	Nairobi, Kenya (1989–1991)	Family planning clinic attenders	91%	165/3930 (4%)	43/373 (12%)	0·36 (0·26–0·50)	0·34 (0·24–0·50)‖

*The risk ratio shown is the prevalence ratio for cross-sectional studies and incidence rate (or hazard) ratios for the cohort studies and the randomised controlled trial. †Hazard ratio adjusted for age and condom use in past year. ‡Hazard ratio, adjusted for age, age at coital debut, contraceptive method, husband's employment status, education, number of partners in past 3 months, and a product-interaction term between time and number of partners in past 3 months. §Rate ratio, adjusted for age, marital status, number of reported sexual partners in past year, gonorrhoea, candidiasis, and history of alcohol consumption during follow-up. ¶Odds ratio, adjusted for age, education, marital status, income, cigarette smoking, age at first pregnancy, number of previous pregnancies, oral contraceptive use, past sex work, number of reported non-marital sexual partners in past 5 years, and history of sexually transmitted diseases. ‖Odds ratio, adjusted for age, marital status, education, number of pregnancies, age at first sex, number of abortions or miscarriages, number of lifetime sexual partners, number of partners in the past year, sex for gifts or money, sex during menstruation, history of injection in past 6 years, history of blood transfusion in past 6 years, and current sexually transmitted disease diagnosis.

Table 2: **Summary of studies of the association of HIV infection in women and partners' circumcision status**

Results

Randomised controlled trial data

Good randomised controlled trials are the gold standard of epidemiological evidence (table 1). Only one trial of male circumcision has investigated the effect on women becoming infected with HIV.[15] This trial, which enrolled men infected with HIV with no evidence of immunosuppression, with uninfected female partners, was done in Rakai, Uganda, in parallel with the trial among men not infected with HIV.[3] Recruitment into the trial was stopped at interim analysis on the recommendation of the data safety monitoring board. This decision was on the basis of the futility of continuing to recruit because fewer serodiscordant couples had been enrolled concurrently than anticipated, decreasing the power to detect a protective effect. Couples were followed for up to 24 months, and 17 (18%) of 92 women in the intervention arm became infected with HIV during follow-up compared with eight (12%) of 67 women in the control arm (adjusted hazard ratio [HR] 1·59, 95% CI 0·62–3·57; table 2).[15] There was some evidence that recently circumcised men infected with HIV who resumed sexual activity early might be more likely to transmit HIV in the first 6 months after surgery than those who wait until complete wound healing, but the numbers are too small to be conclusive. Among the 18 couples in the intervention arm who resumed sex more than 5 days before certified wound healing there were five seroconversions (27·8%), compared with six among 63 couples (9·5%) who first had sex after this time (p=0·06). This latter figure is similar to the seroconversion risk among couples in the control arm (six of 68; 8·8%).[15] Since the trial was stopped early, the effect of circumcision on new HIV infections in female partners might have become stronger over time as the relative effect of any increased transmission among couples resuming sex before complete wound healing would be greatest in the first few months after circumcision. However, overall, this trial provides no evidence of benefit or harm of male circumcision on women becoming infected with HIV.

Population-based longitudinal studies among serodiscordant couples

The most informative observational designs to detect an effect of circumcision on women becoming infected are

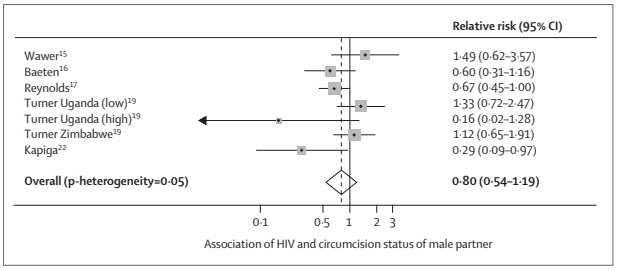

Figure 2: **Meta-analysis of longitudinal studies of the association of partner's circumcision status and HIV risk in women**

Weights are from random-effects analysis. Studies with boxes to the left of the vertical line at 1 favour circumcision and studies to the right favour non-circumcision.

longitudinal studies among monogamous HIV-serodiscordant couples with the male partner infected with HIV and the female partner uninfected. To our knowledge, data from only two such studies are available.[16,17] In the Rakai community cohort study of 343 HIV-serodiscordant couples with the male partner infected with HIV, participants were followed from 1994 to 2004.[17] An updated analysis of data presented in a previous publication[27] found that circumcision was associated with a borderline lower risk of women becoming infected with HIV (RR 0·67, 95% CI 0·45–1·00; table 2). In an earlier analysis of the cohort, based on 224 couples, the overall RR was 0·41 (95% CI 0·10–1·14),[27] and circumcision had a substantially greater protective effect in couples where the men had viral loads below 50 000 copies per mL. However, there was no difference by viral load in the updated analysis (Gray RH, personal communication).

The recently completed Partners in Prevention trial[16] of herpes suppressive treatment also provides data on the effect of male circumcision on HIV transmission to female partners. This multicentre study recruited 3408 HIV-serodiscordant couples in 14 African sites. Among these, 1096 couples had a male partner who was infected with HIV and there was at least one follow-up visit of the female partner. Viral sequencing was used to determine whether incident HIV infections had happened within the partnership. There was some evidence that the female partners of circumcised men infected with HIV were less likely to become infected with HIV, although this was not statistically significant (adjusted RR 0·60, 95% CI 0·31–1·16; table 2).

We included the trial data and the longitudinal observational studies[15–17,19,22] in a random-effects meta-analysis. The summary RR was 0·80 (95% CI 0·54–1·19; figure 2). Since there was some evidence of heterogeneity (p=0·05), this summary estimate should be interpreted cautiously.

Population-based observational studies among women

We identified seven observational analyses among women that included their male partners' circumcision status as a risk factor for infection with HIV (table 2). All studies were from sub-Saharan Africa, three studies were cross-sectional, and four were longitudinal. Each of these studies relied on the women's reports of their partners' circumcision status, and hence the studies are susceptible to misclassification of circumcision status. Results were inconsistent, with two studies finding a significant protective effect of having a circumcised partner,[22,24] one finding a significant adverse effect,[23] and four not finding a significant association.[18,19] The adjusted measures of effect are generally similar to the unadjusted measures, indicating relatively little confounding. The study found a significantly increased HIV prevalence among 5690 partners of circumcised men that attended antenatal clinics in the Butare region, Rwanda, revealing an HIV prevalence of 75 (24·4%) of 307 among women with circumcised partners and 442 (8·4%) of 5286 among women with uncircumcised partners (adjusted OR 2·1, 95% CI 1·5–2·9).[23] The association was similar in higher-risk and lower-risk women, with higher-risk women defined as those who reported having more than one sexual partner in the past 5 years or having had sex to support themselves. Notably, the 2005 Rwanda DHS survey[20] also found slightly higher HIV prevalence among self-reported circumcised men (3·5% prevalence among circumcised men, 2·1% prevalence among uncircumcised men).

Including these cross-sectional studies in women[18,23,24] made little difference to the summary RR (OR 0·81, 95% CI 0·54–1·22) but increased the between-study heterogeneity (p<0·001) as expected, since it is to be expected that estimates from longitudinal studies would be more accurate, since partners' reported (or observed) circumcision status at the time of HIV seroconversion is known.

Cross-sectional observational studies among couples

We identified nine cross-sectional analyses on circumcision prevalence among HIV-serodiscordant couples (Gray RH, personal communication; Lingappa J, personal communication).[25–28] These cross-sectional data provide weaker evidence than randomised controlled trials or longitudinal studies because it is unknown which partner in seroconcordant couples became infected first, and whether transmission happened within the partnership. Table 3 summarises circumcision prevalence in seroconcordant couples infected with HIV (M+F+), serodiscordant couples with male partner that is infected (M+F–), serodiscordant couples with a female partner that is infected (M–F+), and seroconcordant couples that are not infected with HIV (M–F–). Given the partial protection of male circumcision against men becoming infected with HIV, we would expect a higher prevalence of circumcision in serodiscordant couples with a female index case (M–F+) than in seroconcordant couples that are infected with HIV. Similarly, if circumcision protects against women becoming infected by male partner

	Setting (year of study)	Circumcision prevalence in HIV seroconcordant couples	Circumcision prevalence in M–F+ serodiscordant couples	Circumcision prevalence in M+F– serodiscordant couples	RR for circumcision among M–F+ *vs* M+F+ couples (95% CI)	RR for circumcision among M+F– *vs* M+F+ couples (95% CI)	RR for circumcision among M–F+ *vs* M+F– couples (95% CI)
Rakai cohort 1994–98[27]	Rakai, Uganda (1999)	..	50/187 (27%)	29/224 (13%)	..	..	2·07 (1·36–3·13)
Rakai cohort 2003 (Gray)	Rakai, Uganda (2003)	22/154 (14%)	12/71 (17%)	23/118 (19%)	1·18 (0·62–2·25)	1·36 (0·80–2·33)	0·87 (0·46–1·63)
Rakai cohort 2004 (Gray)	Rakai, Uganda (2004)	29/169 (17%)	22/75 (29%)	22/119 (18%)	1·71 (1·05–2·77)	1·08 (0·65–1·78)	1·63 (0·97–2·73)
Rakai cohort 2005 (Gray)	Rakai, Uganda (2005)	38/184 (21%)	31/92 (34%)	24/115 (21%)	1·63 (1·09–2·44)	1·01 (0·64–1·59)	1·61 (1·02–2·55)
Partners in Prevention baseline data (Lingappa)	Southern Africa (2004–05)	..	300/816 (37%)	81/346 (23%)	..	..	1·57 (1·27–1·94)
Partners in Prevention baseline data (Lingappa)	Eastern Africa (2004–05)	..	956/1488 (64%)	300/763 (39%)	..	..	1·63 (1·48–1·80)
Carael[25]	Kigali, Rwanda (1986)	34/124 (27%)	Unknown/10	Unknown/4	..	..	..
De Gourville[26]	Trinidad and Tobago (1992–94)	4/34 (12%)	2/20 (10%)	5/16 (31%)	0·85 (0·17–4·23)	2·66 (0·82–8·58)	0·32 (0·07–1·44)
Malamba[28]	Kampala, Uganda (1998)	3/49 (6%)	24/102 (24%)*	24/102 (24%)*	..	..	..

*Data are for all serodiscordant couples, since the sex of the index partner was not given.

Table 3: **Summary of studies of male circumcision status among cross-sectional studies of serodiscordant HIV couples**

infected with HIV, one would expect a higher circumcision prevalence in M+F– couples than in concordant couples infected with HIV.

Circumcision prevalence in both M+F+ and M–F+ couples was available for only four studies, of which three were cross-sectional analyses from the Rakai population-based cohort (Gray RH, personal communication). In Rakai, the prevalence of circumcision is higher in M–F+ couples than among seroconcordant couples infected with HIV, as expected, but there is little difference in circumcision prevalence between M+F– couples and seroconcordant couples infected with HIV, suggesting little effect of circumcision on women becoming infected with HIV. The fourth informative study, from Trinidad and Tobago, was a small study, but found circumcision prevalence similar in M+F+ (four of 34; 12%) and M–F+ (two of 20; 10%) couples, and circumcision prevalence higher in M+F– couples (five of 16 [31%]; RR 2·66, 95% CI 0·82–8·58 compared with M+F+ couples; de Gourville, WHO, Geneva, Switzerland, personal communication).

In summary, the cross-sectional studies of circumcision status in couples are not informative with regard to the effect of circumcision on women becoming infected with HIV.

Ecological data

Figure 3 shows the correlation of country-level male circumcision prevalence with national HIV prevalence (2001–05) among men and women aged 15–49 years, for all countries in sub-Saharan Africa with available data.[20,21,29] HIV prevalence in both men and women is highest in countries in southern Africa where fewer men are circumcised (Zimbabwe, Zambia, South Africa, and Malawi). HIV prevalence is also high in Lesotho, where 48% of men report being circumcised but the true figure is thought to be much lower than this since generally the foreskin is not removed during initiation.[30] In other countries, the correlation between the prevalence of HIV in adult women and male circumcision suggests a clear population-level benefit of circumcision to women, most likely through a reduced HIV prevalence in men and hence low risk of exposure.[20,21]

Discussion

Our Review finds little epidemiological evidence of a direct protective effect of male circumcision on women becoming infected with HIV, although such an effect cannot be ruled out. We do, however, see that in sub-Saharan Africa, HIV prevalence in women is lower in countries with high levels of male circumcision. This is likely due to reduced exposure to HIV among women in settings where male circumcision is widespread.

The most rigorous study designed to directly estimate the effect of circumcision on women becoming infected is the randomised controlled trial from Rakai, Uganda.[31] However, because of the small numbers of partners enrolled concurrently and early termination of the trial, this trial does not provide evidence for or against an effect of circumcision on women becoming infected with HIV. Nevertheless, this trial does indicate a biologically plausible potential increased risk to female partners of circumcised men infected with HIV if sexual intercourse resumes before complete wound healing. Although mathematical modelling shows that this will have little population-level adverse effect because of the brevity of this healing period,[9] this finding is clearly of concern for individual women, highlighting the need for careful counselling about the importance of abstaining from sex until complete wound healing. Whenever possible, female partners should also attend pre-circumcision counselling to reinforce this message. Another potential concern for women is that circumcised men might increase their risk-taking behaviour if they believe

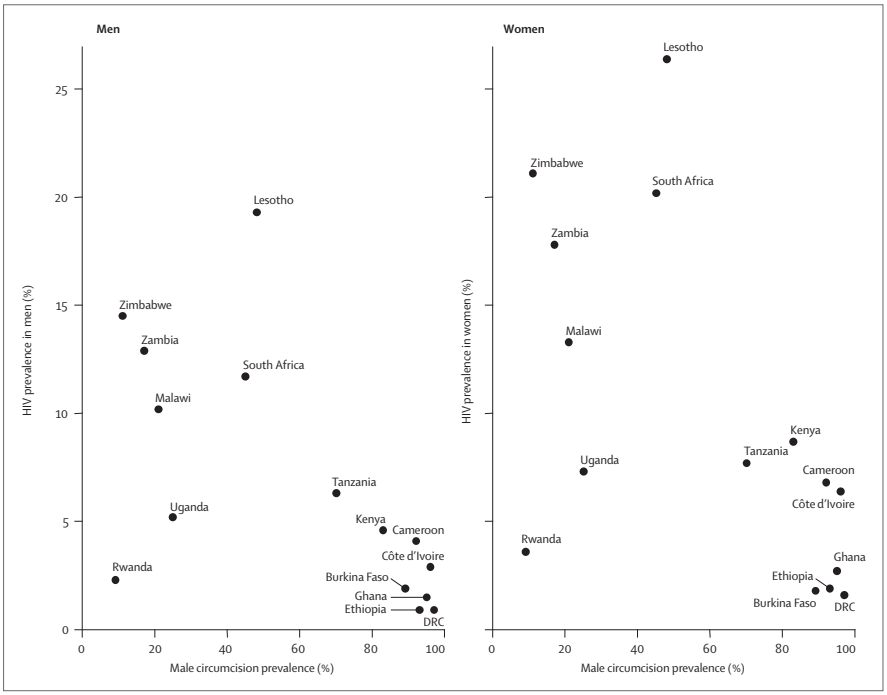

Figure 3: **Correlation of HIV prevalence in adult men and women with male circumcision prevalence**
Male circumcision prevalence from DHS data[20] and HIV prevalence in adults from population-based surveys.[21] DRC=Democratic Republic of Congo.

themselves to be fully, rather than partly, protected. To our knowledge, there are no data on risk behaviour after circumcision among men infected with HIV and there is no evidence of risk compensation in newly circumcised men that are not infected.[1–3,32]

The two longitudinal observational studies among serodiscordant couples suggest a modest reduced risk of becoming infected with HIV (RR 0·67, 95% CI 0·45–1·00; RR 0·60, 95% CI 0·31–1·16), and further data from similar study designs are needed, for example from HIV-vaccine studies in serodiscordant couples. Observational studies that follow women but not their male partners have several fundamental limitations to exploring the association of male circumcision and female risk of becoming infected with HIV. First, there is the likely misclassification of reported circumcision status of the partner where this has not been directly observed. Several studies have shown that self-reported circumcision status by men can be inaccurate.[33,34] If such misclassification was non-differential with respect to HIV status of the female partner, this would tend to bias any true association towards the null. With respect to how true the reports are of partners' circumcision status, one study[19] did sensitivity analyses to adjust for misclassification of circumcision status, and found that reporting errors were unlikely to have obscured an association between male circumcision and women's risk of HIV.[19] Second, female partners of circumcised men are less likely to be exposed to HIV infection because of lower prevalence in circumcised men, and hence an observed lower risk of HIV incidence in female partners of circumcised men might simply reflect a lower HIV prevalence in their male partners. Third, the cross-sectional studies provide limited information because when each woman became infected with HIV is unknown, so the present partner might not be the one who infected her. This is less of a problem in longitudinal studies where few women reported multiple partners during the period of seroconversion, and analyses can be restricted to women reporting one partner during follow-up. For example, when women with multiple partners were excluded from one study, there was little change in effect.[19] In our Review, these studies found inconsistent results, and this is likely because of these limitations.

Possible biological mechanisms for an effect of circumcision on reducing HIV transmission between

	Rate ratio	Person-years needed	Number of M+F– HIV-serodiscordant couples to recruit
3	0·80	31 522	19 701
4	0·80	23 641	14 776
6	0·80	15 761	9850
8	0·80	11 821	7388
3	0·75	19 613	12 259
4	0·75	14 710	9194
6	0·75	9806	6129
8	0·75	7355	4597

*Sample size needed for individually randomised trials of male circumcision to reduce HIV incidence in women. Assuming 90% power, 95% significance level, 2 years follow-up, 20% loss of person-years. In the Rakai trial, the retention rate in men infected with HIV was 81% in the intervention arm and 86% in the control arm. Retention of female partners was 92%. Retention was probably assisted as many participants were in the Rakai Community Cohort Surveillance Study.

Table 4: **HIV incidence per 100 person-years in placebo group translated into sample size needed for randomised trials***

men and women include an effect of circumcision through reduced risk of HIV cofactors such as genital ulcer disease and other sexually transmitted infections in men infected with HIV or the female partner uninfected with HIV,[14,15,35] or a direct biological mechanism (eg, if HIV were transmitted directly from the foreskin). However, most transmission of HIV between men and women is thought to happen through seminal fluid, and recent data from a study among men who have sex with men indicate that cell-free HIV RNA in the seminal fluid, rather than proviral DNA within lymphocytes in the semen might lead to HIV transmission.[36] Although it seems unlikely that circumcision will affect seminal HIV viral load, this hypothesis could be investigated further. For example, seminal viral load could be compared among circumcised and uncircumcised men. Several studies have collected semen samples, including studies of human papillomavirus and circumcision status.[37] Data from the three male circumcision HIV acquisition trials can also be used to investigate the role of circumcision in modifying the natural history of HIV infection, and subsequent male-to-female infectivity. For example, men who are circumcised before becoming infected with HIV might have a lower bolus of exposure because of a smaller mucosal surface area susceptible to infection, and hence lower blood plasma viral set point and seminal viral load compared with uncircumcised men or men who became infected with HIV before circumcision. Unfortunately, seminal viral loads are not available from these trials, but plasma viral setpoint could be compared with circumcision status among HIV seroconvertors.[38]

Given the limited evidence of a possible direct effect of circumcision on women becoming infected with HIV, it is worth considering whether another randomised controlled trial of circumcision among men infected with HIV and their uninfected partners is warranted and feasible. There are several reasons why it would be desirable to know whether male circumcision provides partial protection against male-to-female transmission of HIV, and if so, by how much.

First, without this information, it is not possible to provide fully informed advice on benefits or harms of circumcision to men infected with HIV and their partners. Second, in terms of public policy, the size of the cost-saving and long-term health benefits of circumcision depend on the likely protection afforded to women. Third, further data are needed on personal risks and benefits of circumcision in men infected with HIV who choose to become circumcised.

However, a randomised controlled trial of circumcision among men infected with HIV and their uninfected female partners will be challenging, and sample size calculations on the basis of the summary efficacy of 20% from our meta-analysis suggests that it would need to identify, recruit, and retain about 10 000 HIV serodiscordant M+F– couples in a stable partnership with the man's CD4 count above 250 cells per µL, and both partners willing for the man to be circumcised, willing to participate in the trial, of legal age to provide informed consent, and intending to remain in study area for 2 years (table 4). This would involve screening many tens of thousands of couples to identify those eligible, which might not be logistically feasible. Further, it could be argued that another randomised controlled trial of circumcision, albeit in men infected with HIV, would potentially cause confusion if it is not understood that the new trial intends to answer a different scientific question. Such confusion could possibly delay scale-up of services if people perceive that male circumcision is still being tested as a strategy to prevent HIV.

There would also be some ethical concerns around a randomised controlled trial. In settings where circumcision is becoming the norm, asking half the men to remain uncircumcised until the end of the trial could be stigmatising. By contrast with other studies of serodiscordant couples, the trial would enrol only men infected with HIV with female partners that are uninfected. Participation would then imply that the men were infected with HIV, which again could be potentially stigmatising for them. These issues were less pertinent for the Rakai trial as it happened at the same time as the trial among men without HIV, and included men who chose not to know their HIV status.

Finally, the implications of such a trial are not straightforward. The Rakai trial showed that circumcised men infected with HIV benefited from a reduced risk of genitourinary disease,[35] and their female partners had lower risks of *Trichomonas vaginalis*,[15] so it is not clear that circumcision should be denied to men infected with HIV, even if there is no direct reduction in risk from men to women. Denying circumcision to men infected with HIV on their request when it is not medically contraindicated could imply their HIV status, potentially increasing stigma towards them and conflating

Review

Search strategy and selection criteria

These are described in detail in the Methods section.

circumcision status with HIV serostatus in the community.

Male circumcision for the prevention of HIV is at present being expanded in several settings, and evidence of a direct benefit to women would potentially increase funding, commitment, acceptance, and support for scale-up. Women will benefit both from a reduced HIV prevalence in men, and lower rates of some other sexually transmitted infections, but also likely lower risks of human papillomavirus, cervical cancer, and vaginal infections.[14,39] Although any direct reduction in the risk of women becoming infected with HIV because of circumcision would substantially enhance the overall effect of male circumcision programmes and lead to faster reductions in the incidence of HIV in women, this Review found no firm evidence for such a direct effect.

Conclusions

Although at a population-level, widespread male circumcision will benefit women by reducing their risk of exposure to HIV, there are insufficient data to know whether circumcision directly reduces risk of women becoming infected with HIV. A definitive answer would come from a randomised controlled trial of circumcision among heterosexual men infected with HIV in serodiscordant relationships, but such a trial is likely to be unfeasible. At present, circumcision services are being expanded for the prevention of HIV in several settings in southern and eastern Africa, and rapid scale-up of these services, integrated with existing prevention options (male and female condoms, treatment for sexually transmitted infections, testing, and counselling) would maximise the benefits to both men and women. Expansion of male circumcision services needs to include rigorous monitoring and evaluation to ensure that there are no adverse consequences for female partners of circumcised men.

Contributors

HAW designed the search strategy, did the systematic review and meta-analysis, and wrote the first draft of the paper. CAH and HAW extracted the data. KD and CAH commented in detail on the drafts and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

We thank the participants of a teleconference on the feasibility of a randomised controlled trial among men infected with HIV (Bertran Auvert, Bob Bailey, Connie Celum, Ron Gray, Daniel Halperin, George Schmid, Maria Wawer, and Richard White). We thank Bob Bailey, Ron Gray, Daniel Halperin, and Richard Hayes for written comments on an earlier draft; Natasha Larke for help with identifying relevant abstracts; and Jared Baeten, Connie Celum, Ron Gray, Esther de Gourville, Tom Lutalo, and Jai Lingappa for additional analyses and generously allowing use of their unpublished data. HAW received funding from the World Health Organization to do this work.

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