Male circumcision as a preventive measure against HIV and other sexually transmitted diseases

Helen A. Weiss

Purpose of review

In 2005, 4.1 million people were infected with HIV. There is an urgent need to intensify and expand HIV prevention methods. Male circumcision is one of several potential approaches. This review summarizes recent evidence for the potential of male circumcision to prevent HIV and other sexually transmitted infections.

Recent findings

The first randomized controlled trial of adult male circumcision found a highly significant 60% reduction in HIV incidence among men in the intervention arm. Modelling this effect predicts that widespread implementation of male circumcision could avert 2 million HIV infections over the next decade in sub-Saharan Africa. The biological rationale is that the foreskin increases risk of HIV infection due to the high density of HIV target cells and lack of keratinization of the inner mucosal surface.

Summary

There is strong evidence that male circumcision reduces risk of HIV, syphilis and chancroid. If results are confirmed by two ongoing trials in sub-Saharan Africa, provision of safe male circumcision could be added to HIV prevention packages in high-incidence settings. This would also provide an opportunity for HIV-prevention education and counselling to young men at high risk of infection.

Keywords

HIV, male circumcision, sexually transmitted infections

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Infectious Disease Epidemiology Unit, London School of Hygiene & Tropical Medicine, London, WC1E 7HT, UK

Correspondence to Helen A. Weiss, Medical Research Council Tropical Epidemiology Group, Infectious Disease Epidemiology Unit, London School of Hygiene & 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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Abbreviations

CI	confidence interval
MSM	men who have sex with men
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
STD	sexually transmitted disease
STI	sexually transmitted infection

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Introduction

In 2005, 4.1 million people were newly infected with HIV, mostly through heterosexual intercourse [1]. This alarming number of infections highlights the urgent need to intensify and expand proven prevention methods, and further, to identify and implement new methods of HIV prevention. Male circumcision, one of the most common surgical procedures globally, is a potential new HIV prevention method, along with vaginal microbicides, pre-exposure prophylaxis with antiretrovirals, herpes suppressive therapy and HIV vaccines [2–4]. This paper reviews the recent evidence for a protective effect of male circumcision against HIV and other sexually transmitted infections (STIs).

Male circumcision and HIV infection

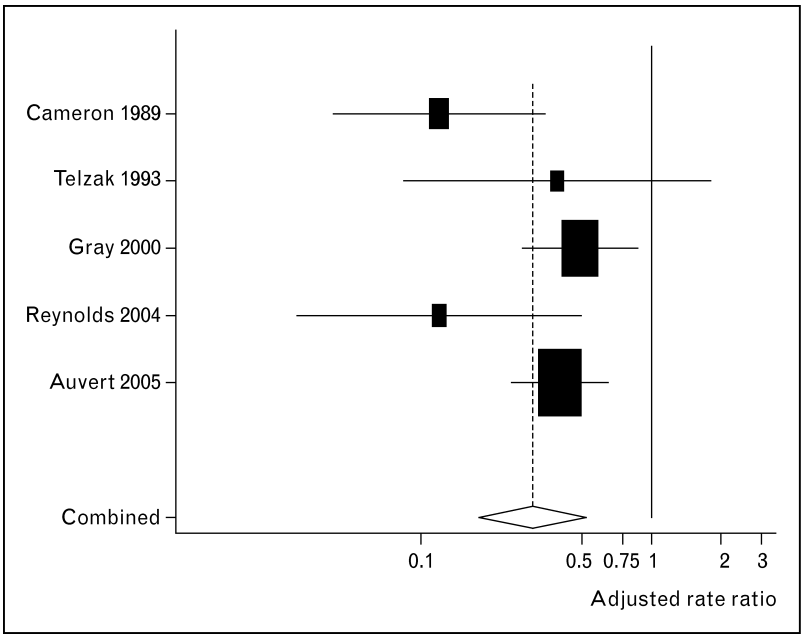
Systematic reviews of observational studies provide compelling evidence that circumcised men are at lower risk of HIV [5,6•]. The studies show a strong and consistent protective effect of male circumcision on HIV infection after adjustment for potential confounders [adjusted risk ratio (RR) = 0.56, 95% confidence interval (CI) 0.44–0.70 in general populations; adjusted RR = 0.29, CI 0.20–0.41 in high-risk populations] [5]. Observational studies are inherently limited by potential selection biases, however, and study quality was variable [6•]. To overcome these limitations, three randomized controlled trials (RCTs) of circumcision among consenting, healthy adult men in Uganda, Kenya and South Africa started in 2002–2003. In each trial, men were randomly assigned to receive circumcision immediately or to wait until the end of the trial, and were followed to assess HIV incidence. A further trial in Rakai, Uganda, is evaluating the impact of male circumcision on male–female HIV transmission.

Randomized controlled trial of adult male circumcision in Orange Farm, South Africa

Results of the RCT in the Orange Farm area in South Africa were published in 2005 [7••]. In this trial, 3128 HIV-negative men aged 18–24 years were randomized to immediate or delayed circumcision. Men in both arms received individual counselling on sexually transmitted disease (STD)/HIV prevention at each visit, and were encouraged to attend voluntary counselling and testing, including access to antiretroviral therapy when it became nationally available in 2004. The trial was stopped following a recommendation by the Data and Safety Monitoring Board when interim analyses found men in the intervention arm at strongly reduced risk of HIV infection (rate ratio = 0.40, CI 0.24–0.68; $P<0.0001$). The estimated

Figure 1 Rate ratios and 95% confidence intervals showing the association of male circumcision and HIV infection in longitudinal studies of heterosexual men

The black square and horizontal line correspond to relative risk and 95% confidence interval for each study. The size of the black square reflects the weight of each trial. The diamond represents the combined relative risk and 95% confidence interval.



protective effect was even stronger (rate ratio = 0.24, CI 0.14–0.44) when data were re-analysed by actual circumcision status (i.e. allowing for men randomized to be circumcised but who chose not to be, or vice versa). The effect size in this trial is similar to that in previous cohort studies (Fig. 1) [7••,8–11], which are generally less susceptible to bias than cross-sectional studies.

Potential impact and cost-effectiveness of male circumcision on HIV spread in Africa

Based on the effect estimate found in the RCT, full coverage of male circumcision in sub-Saharan Africa would avert an estimated 2.0 (1.1–3.8) million new HIV infections and 0.3 (0.1–0.5) million deaths over the next 10 years [12••]. This means that male circumcision would be equivalent to an intervention (such as a vaccine or increased condom use) that reduces transmission in both directions by 37%. As expected, the impact would be greatest where there is highest HIV incidence and lowest rates of circumcision, and would be even more dramatic if (as must be the case) male circumcision were combined with other prevention strategies.

Preliminary calculations indicate that the cost-effectiveness of male circumcision for HIV prevention in sub-Saharan Africa compares favourably with other interventions such as improved STD treatment and school-based educational interventions [13]. Based on the South African data, each 1000 adult circumcisions in that population would avert an estimated 308 HIV infections in men and women over 20 years, at a cost of $181 (95% CI $117–306) per HIV infection averted [14]. Although these calculations incorporated costs of the procedure and treatment of adverse events, training or health infrastructure improvements were not included, and further work is needed in this area.

Recent observational evidence on male circumcision and HIV

Two recent longitudinal studies have provided additional observational data on the association of male circumcision and HIV incidence. One, a study of HIV acquisition among 745 Kenyan truck drivers [15••], estimated female–male HIV transmission probabilities per coital act. This study estimated HIV-1 infectivity taking into account multiple concurrent partnerships of different types. Overall infectivity was significantly higher for uncircumcised than for circumcised men (1.28% compared with 0.51% risk per contact; $P = 0.04$). Lack of circumcision significantly affected risk of HIV transmission in men at high risk, such as those with genital ulcer disease during follow-up (infectivity ratio 4.3, $P = 0.04$). This evidence of a stronger protective effect of circumcision among higher risk men is consistent with results from previous observational studies [5,6•], and may be due to an indirect effect through protection against other STIs [16••].

The major strength of this study is the prospectively collected sexual behaviour data, which minimize reporting bias, and the data on concurrent partnerships, which allows estimation to be closer to HIV transmission

patterns in populations than those from studies of HIV-1 serodiscordant couples. Notably, the estimated rate in uncircumcised men is substantially higher than the female–male transmission rate per sexual contact estimated from discordant couples in Uganda (0.13%) [17] but is lower than the estimated rate among young male military conscripts in Thailand (5.96%) [18]. A limitation of the study was that HIV-1 infection status and disease status of sex partners was unknown and is likely to affect infectivity as transmission probabilities are higher during acute HIV infection [19].

A second prospective study of male circumcision and HIV incidence has added to the sparse literature on the impact of circumcision among men who have sex with men (MSM) [20•]. The study, of 3257 high-risk MSM in six US cities enrolled from 1995–1997, found that lack of circumcision was associated with twice the risk of HIV seroconversion after adjusting for socioeconomic and recent sexual behavioural variables [odds ratio (OR) = 2.0, CI 1.1–3.7]. These findings are similar to those of a previous study among MSM [21] (OR = 2.0, CI 1.0–4.0). Biologically, less protection might be expected among men practising insertive, rather than receptive, anal intercourse, but a study of 63 recently infected HIV positive MSM in Australia found no evidence of this [22].

Male circumcision is now included in Demographic and Health Surveys (DHS), and analysis of the association with HIV using DHS data and AIDS Indicator Surveys in seven sub-Saharan African countries found a significant association in one country only (Tanzania) [23]. In contrast, the earlier systematic review found a significant protective effect in six out of nine population-based cross-sectional studies that adjusted for confounding [6•]. The inherent limitations of cross-sectional studies may contribute to this discrepancy [6•]. For example, men may become infected before being circumcised, especially in countries where the median age of circumcision is in the late teens or later, such as in South Africa [24], Lesotho [25] and Tanzania [26]. Further, important differences in behaviour between circumcised and uncircumcised men are unlikely to be sufficiently adjusted for in these studies, especially in countries where circumcision is the norm, such as Burkina Faso, Cameroon and Ghana, and finally, misclassification of self-reported circumcision status [27,28] is likely to underestimate any association.

Male circumcision was significantly associated with lower HIV prevalence (and lower cervical cancer incidence) after adjusting for religion in a recent ecological analysis of 118 developing countries in sub-Saharan Africa [29]. This evidence is strengthened by the finding that male circumcision was strongly associated with lower HIV prevalence among countries with primarily sexual HIV transmission ($P<0.001$), but not among countries with primarily nonsexual HIV transmission ($P=0.77$).

Biological rationale for increased risk of infection

For men acquiring HIV heterosexually, the virus enters through the penis, and several factors will influence risk of acquisition, including the type, density and distribution of HIV-1 target cells in the penis, and the degree of keratinization of the epithelium [30••].

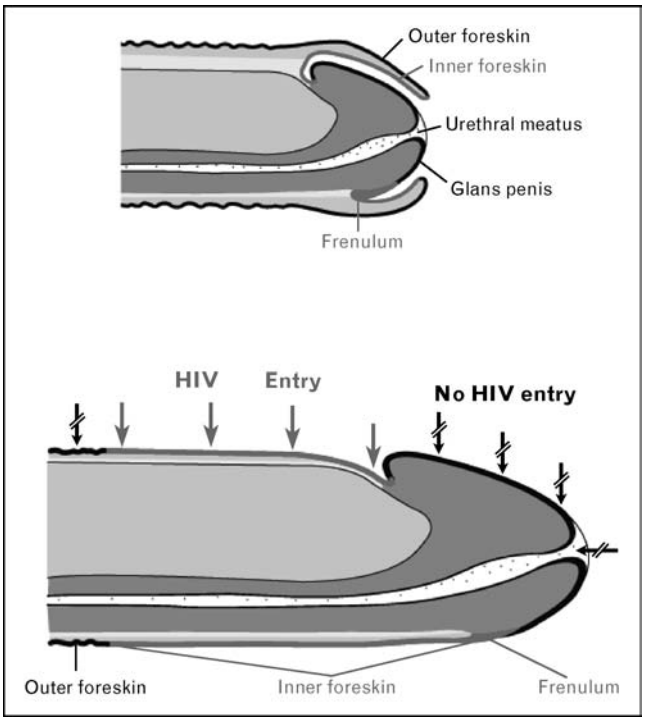
Unlike the glans penis and the outer surface of the foreskin, the inner mucosal surface of the foreskin is thinly keratinized [31••], and hence susceptible to minor trauma and abrasions which facilitate entry of pathogens (both bacterial and viral) [32]. Also, the preputial sac under the foreskin may provide a warm, moist environment to enable pathogens to replicate, especially when hygiene is poor [33].

The foreskin may also increase risk of HIV infection specifically as tissue from the inner surface of the foreskin mucosa contained higher proportions of HIV-1 target cells than cervical tissue [34]. Further, a recent study showed that the density of HIV-1 target cells in the inner foreskin was similar to that in the glans penis and outer foreskin, but those in the inner foreskin were closer to the epithelial surface than those situated elsewhere in the penis, due to the lack of keratin [31••]. In an uncircumcised man, the cells in the inner foreskin and frenulum are directly exposed to vaginal secretions during heterosexual intercourse, and this superficial location of the HIV-1 target cells presumably increases risk of infection (Fig. 2). In contrast, in circumcised men, the penile shaft is thought to be covered with a thickly keratinized epithelium, providing some protection from infection [31••]. A study of distribution of HIV-1 target cells among foreskins of 39 men circumcised in Kisumu, Kenya during the RCT [30••] found that Langerhans cells were more likely to be found near the surface of the epithelium than other cells, again potentially increasing risk of HIV-1 infection in uncircumcised men. Perhaps the most direct evidence of the susceptibility of the foreskin to HIV-1 infection comes from Patterson *et al.* [34] who infected foreskin biopsies *ex vivo* with HIV-1 in explant culture, and found that infectivity of the inner mucosal surface was several times greater than that of cervical tissue, which is a known site of HIV-1 acquisition in women.

Male circumcision, genital hygiene and HIV infection

The role of genital hygiene in the association between male circumcision and HIV infection is unclear [35,36]. One recent study of 386 uncircumcised men attending an STD clinic in Durban, South Africa, defined subpreputial penile wetness as a marker of poor penile hygiene, and

Figure 2 Flaccid uncircumcised penis (top) and erect uncircumcised penis with the foreskin retracted showing likely sites of HIV-1 entry (bottom)



found a significant association between this and HIV infection (OR = 2.38, CI 1.43–3.97). Subpreputial penile wetness itself was associated with lower socio-economic status, more lifetime sexual partners, and not washing after sex [37•]. Another cross-sectional study, of 150 male partners of women with lower genital tract symptoms from a family planning clinic and an STD clinic in Nairobi, Kenya, also found that increased postcoital washing was associated with lower HIV infection. Male circumcision was significantly associated with lower risk of HIV in this study (OR = 0.12, CI 0.02–0.91) [38•] in addition to being associated with superior genital hygiene.

Male circumcision and ulcerative sexually transmitted infection

The impact of male circumcision on HIV will also be affected by any impact on other STIs, which are themselves co-factors for HIV transmission. The first systematic review and meta-analysis of the association of male circumcision with ulcerative STDs (syphilis, chancroid and genital herpes) was recently published [16••]. Twenty-six articles met the inclusion criteria for the review. Most syphilis studies reported a substantially reduced risk among circumcised men (summary RR = 0.67, 95% CI 0.54–0.83), although there was significant between-study heterogeneity ($P = 0.01$). There was also strong evidence of a reduced risk of chancroid in circumcised men but, in contrast, only weak evidence of an association with HSV2 infection (summary RR = 0.88, 95% CI 0.77–1.01). The results suggest that potential male circumcision interventions to reduce HIV in high-risk populations may provide additional benefit by protecting against some other STIs.

These data are supported by recently published data from the 2001 Botswana AIDS Impact Survey [39]. In this large nationally representative study, 17% of men reported being circumcised, and were significantly less likely to report recent urethral discharge or genital ulcer (adjusted OR = 0.61, CI 0.57–0.66). The size of this study enables precise estimates of effect, but conclusions about the impact of circumcision on STDs are limited because of the reliance on self-reported STDs and the joint outcome of urethral discharge and genital ulcer, rather than analyses of these separately.

Male circumcision and *Chlamydia trachomatis*

Chlamydia trachomatis is the most common bacterial STD, with an estimated 89 million new cases of genital chlamydial infection annually [40]. Recent evidence for a protective effect of male circumcision with *C. trachomatis* infection in women comes from a large, multicentre case–control study of invasive cervical cancer [41•]. The study was located in five sites (Colombia, Spain, Brazil, Thailand and the Philippines) and participants were 1029 female controls with a stable male partner. Circumcision is the cultural norm in the Philippines (prevalence of 92.5% in this study) but uncommon in the study populations from the other countries. Overall, *C. trachomatis* seroprevalence was significantly lower in women with a circumcised partner (adjusted OR = 0.18, CI 0.05–0.58). Unfortunately, there was little power to analyse within countries, due to the low prevalence of circumcision in Brazil, Colombia and Spain (five or fewer women had circumcised partners, and none of these were *C. trachomatis* seropositive). A limitation of this study was the low participation rate (serology available for only 29% of eligible women) which may limit generalizability of the study. In addition, studies of female infection and male circumcision are usually limited by lack of specific information about partners at the time of infection. In this study, however, results were similar when restricted to women who reported only one lifetime partner (OR = 0.21, CI 0.06–0.72).

Public health issues of increased uptake of male circumcision for HIV prevention

The data reviewed in this article raise challenges for public health. Following publication of the Orange Farm results, demand for male circumcision has reportedly increased in some countries with high HIV incidence, such as Swaziland and Zambia [42]. If the two ongoing RCTs confirm the South African findings, countries may

decide to include male circumcision as an additional preventive measure within comprehensive HIV prevention packages. There are, however, many concerns around the implementation of male circumcision for HIV prevention [43•], and WHO/UNAIDS have not endorsed the procedure. The UN Work Plan on Male Circumcision [44] is addressing these concerns by focusing on improving the safety of current male circumcision practices and assisting countries to obtain the data necessary for informed decision-making regarding the role of male circumcision in HIV-prevention programming.

If circumcision is performed under poor hygienic conditions by inadequately trained practitioners, side effects can be serious, including infection, bleeding and permanent injury. Complications are also more likely with adult circumcision than with neonatal circumcision. Even under the strict guidelines of the South African trial, adverse events (mainly pain, swelling and bleeding) during surgery or in the month following surgery were reported for 3.8% of men (60/1568), although follow-up of patients for an average of 18 months indicated very few adverse events (<1%) [7••]. The rate of adverse events among adult men circumcised in the Kenyan RCT was 1.8%, mostly wound disruption, infection and bleeding. None were rated as severe, and the complication rate fell dramatically as clinicians performed more procedures [45]. A surgical manual and guidance on training, regulatory, licensing and ethical issues (including counselling on sexual behaviour) have been developed, along with a rapid assessment toolkit to determine circumcision prevalence, side effects and acceptability [46].

A major concern of increased uptake of male circumcision to reduce HIV risk is that, because circumcision will not provide complete protection, there may be risk compensation (i.e. increases in risky behaviour sparked by perceived decreases in risk) [47]. In the South African trial, circumcised men reported more risky behaviour, specifically a higher reported number of sexual acts [7••]. Preliminary, blinded, data from the Kenyan RCT show little change in reported behaviour overall during the trial, suggesting little evidence of risk compensation [48]. Behaviour change following circumcision within trials may differ from that in the 'real world', however, where less intensive counselling may be given to men undergoing circumcision. Reassuringly, there is little evidence for this to date. One cohort study in Siaya and Bondo districts in Kenya examined risk compensation among 324 recently circumcised men and 324 uncircumcised men. Men were followed for 12 months, with no evidence that circumcised men engaged in riskier sexual behaviour, such as more sex with casual partners, than the uncircumcised men [49].

Another concern is the cultural acceptability of introduction of male circumcision in previously noncircumcising communities. A review of the 13 acceptability studies to date, all from sub-Saharan Africa [50], showed that, across nine countries, 29–81% of uncircumcised men were willing to become circumcised, 50–79% of women favored circumcision for their partners, and 50–90% of men and women were willing to circumcise their sons. The lowest level of acceptability by uncircumcised men (29%) was from a study in eastern Uganda in 1997, before male circumcision was widely perceived as possibly being associated with STIs and HIV [50]. Otherwise, more than half of men in the regions studied were willing to become circumcised. These studies found consistently that the main barriers to acceptability were cost, fear of pain, and safety concerns, with improved hygiene and other health benefits the main facilitators.

Conclusion

The compelling findings of the South African trial, together with the predicted dramatic impact of male circumcision on HIV rates in sub-Saharan Africa, have elevated male circumcision to the top of the list of potential new methods of HIV prevention. There is now reported increased demand for the procedure in some countries most affected by HIV, despite the fact that it is not being recommended by international agencies. If the ongoing trials show a similar impact, then safe adult male circumcision (not neonatal circumcision) is likely to be added to the current package of proven HIV prevention measures in settings with high HIV incidence. Concerns about the safety and logistics of increased uptake of male circumcision are starting to be addressed within the UN Work Plan on Male Circumcision and HIV, and will need to be expanded and continued at local country level. In addition, provision of circumcision services to young men in areas of high HIV incidence could provide a much-needed opportunity to provide education and counselling to this hard-to-reach population.

Acknowledgements

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References and recommended reading

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

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 107–108).

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