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Male circumcision: Impact on human immunodeficiency virus and other sexually transmitted infections

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Abstract

High-quality data show that male circumcision reduces the risk of human immunodeficiency virus type 1 (HIV) infection by approximately 70% during heterosexual intercourse. Three major lines of evidence support this conclusion: biological data suggesting that this concept is plausible, data from observational studies supported by high-quality meta-analysis, and three randomized controlled trials involving more than 11,000 participants, also supported by high quality meta-analyses. The evidence from these biological studies, observational studies, randomized controlled clinical trials, meta-analyses, and cost-effectiveness studies is conclusive. Besides reducing risk of HIV infection, male circumcision also reduces the risk of a number of other sexually transmitted infections, including: high-risk human papillomavirus types, genital herpes, *Trichomonas vaginalis*, *Mycoplasma genitalium*, syphilis, chancroid and genital ulcer disease. These strong data reinforce policy statements promoting male circumcision as an important public health measure.

Keywords: Male circumcision, HIV infection, sexually transmitted infections, complications

Summary of recommendations

1. Voluntary medical male circumcision should be promoted because this proven strategy reduces HIV infection risk in heterosexual men by 70%.
2. Male circumcision should also be promoted based on strong data showing that circumcised men and their sexual partners are at substantially lower risk for multiple sexually transmitted infections.
3. Male circumcision should be advocated in most health care settings because the benefits of circumcision have been proven in developed and developing world settings.

1 Introduction

Male circumcision may be the oldest surgical procedure. It has certainly been one of the most controversial. This chapter considers the data suggesting that male circumcision has an important role as a public health measure by reducing the risk of heterosexually acquired human immunodeficiency virus type 1 (HIV) infection and the risk of several other sexually transmitted infections (STIs). First, we consider the strong data from Africa supporting implementation of male circumcision programs to limit HIV infection in high-risk populations. Then, we consider the role of male circumcision in reducing the risk of other STIs and the potential public health value of male circumcision in various settings.

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2 Methods and results

2.1 Male circumcision reduces HIV infection risk

Male circumcision represents one of the best-proven HIV prevention strategies. This strong data comes from biological evidence, observational studies supported by high-quality meta-analysis, and three randomized clinical trials [1], [2], [3] supported by high quality meta-analyses [4], [5], [6].

2.2 Biological evidence

Plausible mechanisms support the concept that there is increased risk of HIV and various other STIs among uncircumcised men. These biological mechanisms include:

1. an increased prevalence of inflammatory conditions, such as balanitis and balanoposthitis, as well as phimosis in uncircumcised men,
2. increased susceptibility of the mucosal surface of the prepuce to trauma and infection, and
3. the longer survival of pathogens in the warm, moist subpreputial space in uncircumcised men.

Targeted pyrosequencing studies found that circumcised men had a change in the overall penile microbiota (p=0.007) that included a decrease in putative anaerobic bacterial families (p=0.014) [7]. These observations suggest that the anoxic microenvironment of the subpreputial space may support pro-inflammatory anaerobes that can activate Langerhans cells to present HIV to CD4 cells in draining lymph nodes. The inner foreskin of uncircumcised men appears especially susceptible to HIV infection, possibly contributed by reduced 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 [8], [9], [10], [11] (Figure 1).
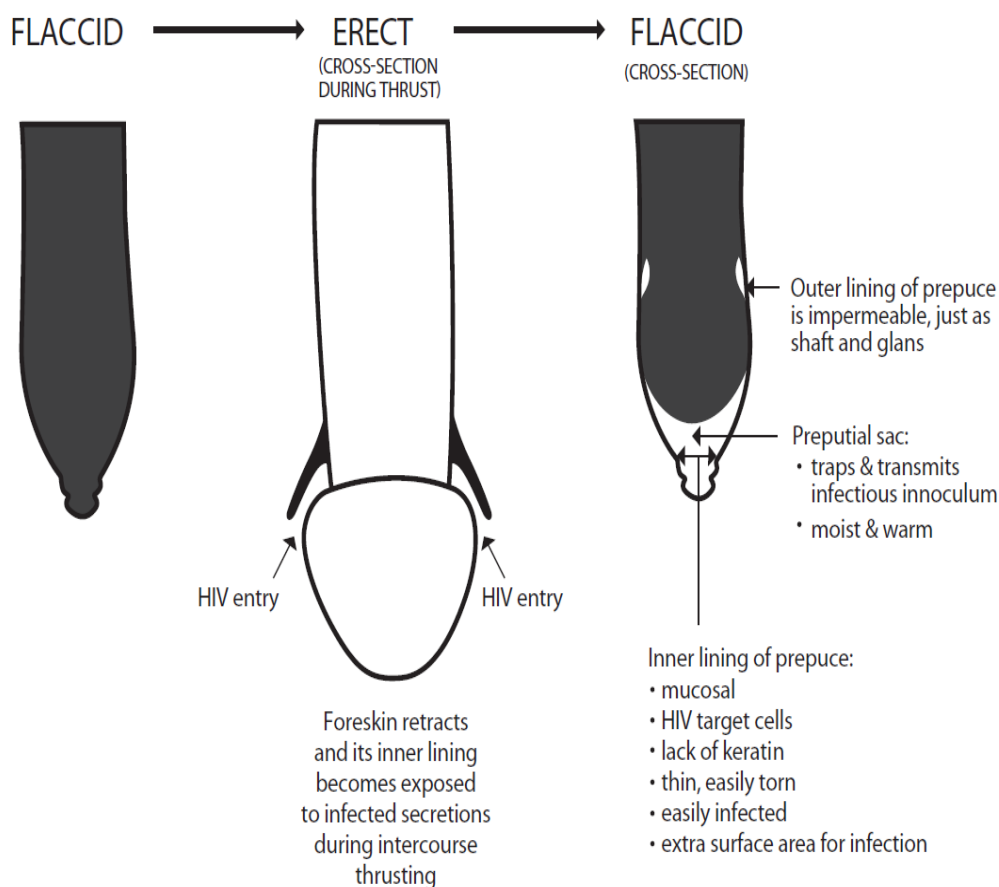
Figure 1: Foreskin-associated factors that have been proposed to explain the higher HIV infection observed in uncircumcised men. The diagram of an uncircumcised penis in the erect state (center) depicts a typical appearance of the foreskin during thrusting. It should be noted, however, that the length of the foreskin of different men varies across a wide range from very short to very long. Thus the extent to which the glans is bared during intercourse varies greatly between different uncircumcised individuals. The foreskin is pulled forward during the outward motion and backwards during the forward motion involved in the thrusting that takes place during intercourse. When inserted into the vagina of an infected woman the vulnerable inner lining becomes exposed to the infectious inoculum. Thrusting exacerbates exposure of the inner lining.

Tissue explant studies found that efficient HIV transmission occurs following exposure of the inner, but not outer, foreskin to HIV-infected cells [12], [13]. Langerhans cells and T-cells within the inner foreskin epidermis are the first cells targeted by HIV, reflecting a dynamic process of immune cell relocation in the inner foreskin that is associated with secretion of specific chemokines to favor efficient HIV entry into the inner prepuce (Figure 2).
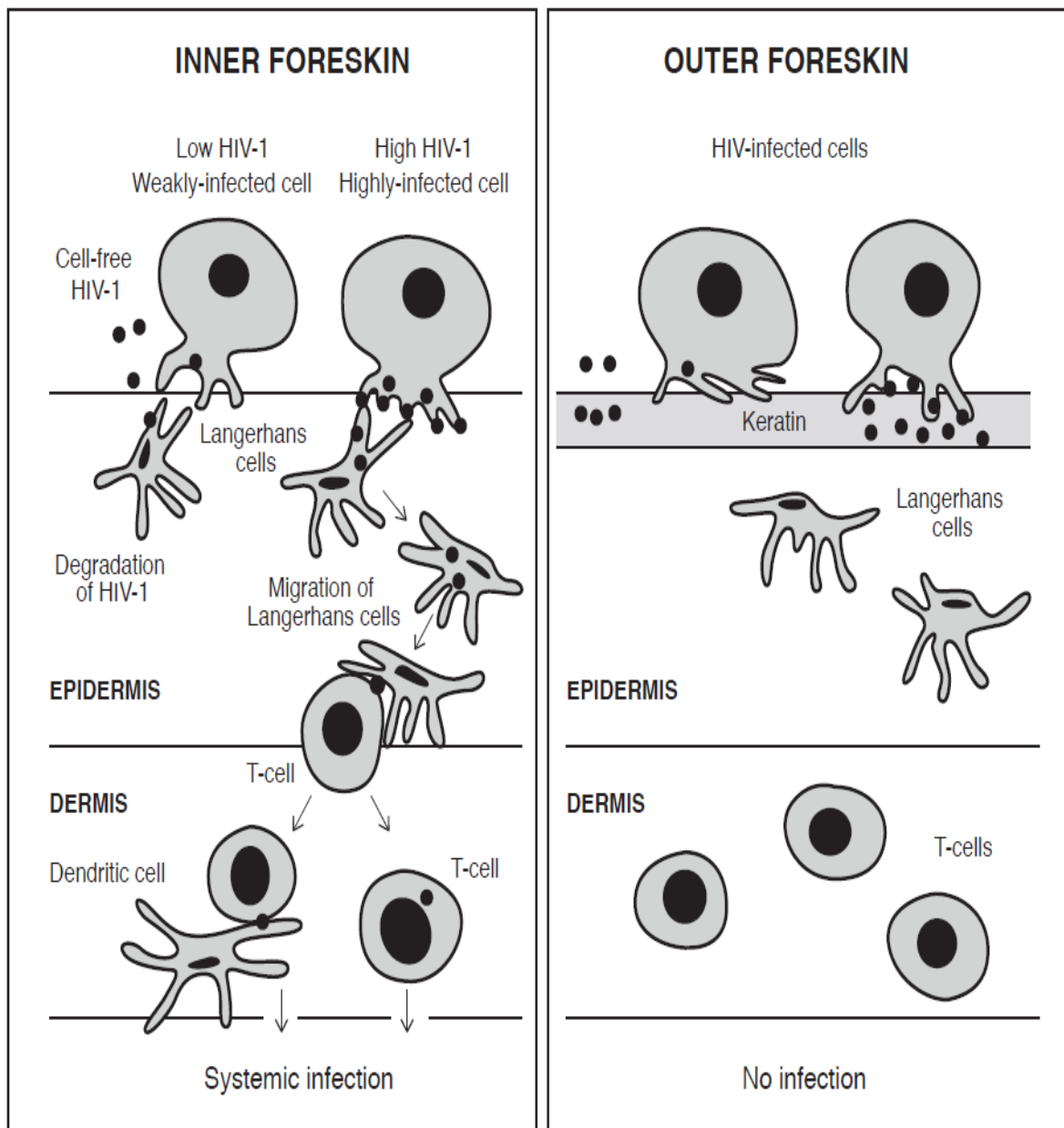
Figure 2: Current understanding of the foreskin-related mechanism of HIV-1 infection [13]. This involves formation of apical viral synapses between cells highly infected with HIV and dendrites of Langerhans cells. Local HIV budding and HIV capture ensues, resulting in cell-to-cell transfer of HIV (black dots) from infected cells to dendrites of Langerhans cells, a process that takes 1 hour. A reduction in CCL20/MIP-3-alpha secretion occurs as Langerhans cells migrate to the basal layers of the epidermis within 4 hours, where they transfer their HIV cargo to T-cells. At 4 hours T-cells are recruited from the dermis into the epidermis as a result of increased CCL5/RANTES secretion, so fuelling the formation of Langerhans cell-T-cell conjugates [12]. The T-cells can then also infect dendritic cells. In contrast, cell-free HIV particles or HIV in cells with a low viral load are taken up by Langerhans cells and degraded.

2.3 Observational studies

The concept that circumcision might protect against HIV infection was first suggested in 1986 [14]. In the late 1980s epidemiological support was provided by ecological studies comparing male circumcision prevalence and HIV prevalence in sub-Saharan Africa [15] and later across 118 developing countries [16]. Additional evidence came from well-done systematic reviews of the observational study data comparing prevalence of HIV infection in circumcised and uncircumcised men from the same populations [5], [17]. One review considered 27 sub-Saharan African studies [5], while the other was a global review of 37 studies [17]. Circumcised men had substantially lower risk of HIV infection. A well-done meta-analysis of the 15 studies that adjusted for potential confounders found that the reduction in risk of HIV infection in men was both large and highly significant statistically (adjusted risk ratio (RR) 0.42, 95% confidence interval (CI) 0.34–0.54) [5]. Later studies also found large HIV risk reductions among circumcised men [18]. Overall, analysis of the observational study data suggests that circumcised men have an approximately 58% reduction in risk of HIV infection during heterosexual intercourse with an infected female partner.

2.4 Randomized controlled clinical trials

While provocative and statistically significant, observational studies cannot prove causality (i.e., that male circumcision represents the critical factor causing decreased risk of heterosexually-acquired HIV infection among men in circumcised populations) [19]. Large clinical trials were needed. Three randomized, prospective clinical trials were conducted among consenting healthy men in South Africa [1], Kenya [2] and Uganda [3]. The trials started in 2002–2003 and all three trials were stopped early following recommendations by independent Data and Safety Monitoring Boards because interim analyses found highly significant decreases in HIV infection among men in the intervention (circumcised) arm of each trial.

The three trials enrolled a total of 11,054 uncircumcised men aged ≥18 years. Participants were randomly assigned (1:1) to circumcision or control arms, then followed for up to 2 years (Table 1). In each study, men assigned to the circumcision and control arms were well matched for demographic and behavioral factors. Retention rates were high (86–92%; Table 1). Subsequent meta-analysis of the trial results using a random-effects model following the QUORUM statement recommendations found no evidence of heterogeneity among the trials [18]. Combining the data from all three trials, the overall rate ratio (RR) was 0.42 (CI 0.31–0.57), representing a 58% protective effect (CI 43–69%), identical to the protection found in the observational studies (58%; 95% CI 46–66%). It should be noted that the clinical trials each used standard "intention-to-treat" analyses. These analyses classify participants based on the treatment assigned (either circumcision or not circumcised), rather than whether they were actually circumcised if they were assigned to circumcision, or if they were circumcised outside of the study, if assigned to the non-circumcised group.

Table 1: Summary of the three randomized controlled trials of male circumcision on HIV infection in sub-Saharan Africa (modified from Weiss et al. [18]); Note: CI = confidence interval

	South Africa [1]	**Kenya [2]**	**Uganda [3]**
Participants	3,274	2,784	4,996
Age range (years)	18–24	18–24	15–49
Setting	Peri-urban	Urban	Rural
Circumcision method	Forceps-guided by local general practitioners; Monopolar cautery	Forceps-guided by study clinicians; No cautery	Sleeve method by study clinicians; Bipolar cautery

	South Africa [1]	Kenya [2]	Uganda [3]
Visit schedule (months)	3, 12 and 21	1, 3, 6, 12, 18 and 24	6, 12 and 24
Retention rate	92% at 21 months	86% at 24 months	90% at 24 months
Person-years of follow-up	4,693	4,428	6,744
HIV infections (circumcision: control)	20:49	22:47	22:45
Risk ratio (95% CI) Significance		0.47 (0.28–0.78) P=0.0065	0.499 (0.16–0.72) P=0.006
Summary risk ratio for all three trials (95% CI)		0.42 (0.31–0.57)	

In clinical terms the true protection provided by male circumcision may be better estimated by an "as-treated" analysis that assigns outcomes according to the actual circumcision status of participants. Some participants did not adhere to the arm they were randomly assigned to. Meta-analysis of the "as-treated" outcomes from the three trials shows even stronger protection against HIV infection in the circumcision group (summary RR 0.35; 95% CI 0.24–0.54) [18]. Thus, the three randomized controlled trials involving more than 11,000 men found that male circumcision was associated with 58% reduction in HIV infection risk in the "intent-to-treat" analysis and 65% reduction in HIV infection risk in the "as-treated" analysis. These findings closely mirror the observational study findings [20], [21].

2.5 Extended follow-up of participants in the clinical trials

As summarized above, the randomized clinical trials found substantial (approximately 65%) reduction in HIV infection risk among the circumcised men after 21–24 months of follow-up. These strong data led to stoppage of the clinical trials, so that circumcision could be offered to participants in the control (non-circumcision) arm of the studies. Longer-term follow-up data are, nevertheless, available for two of the trials.

Long-term follow-up from participants in the trial in Kisumu, Kenya was used to estimate the 72-month efficacy of male circumcision against HIV infection [22]. A Cox proportional hazards regression model incorporating stabilized inverse probability of treatment and censoring was used to estimate the efficacy of male circumcision on HIV risk. After 72 months, the cumulative HIV incidence was 7.2% (95% CI 6.0–8.7) for the participants overall: 4.8% among circumcised men and 11.0% among uncircumcised men. The crude hazard ratio of HIV seroconversion for circumcised vs. uncircumcised men was 0.38 (95% CI: 0.26–0.55). In weight-adjusted Cox regression, the hazard ratio was 0.42 (95% CI: 0.26–0.66). Thus, the efficacy of male circumcision to prevent HIV infection was sustained at 58% at 72 months, similar to overall findings of the three trials.

These findings are consistent with long-term follow-up of participants in the Rakai, Uganda clinical trial. Surveillance was continued for up to 4.8 years [23]. An "as treated" analysis used Cox regression models adjusted for socio-demographic and time-dependent sexual behaviors. HIV incidence was 0.50/100 person-years for circumcised men and 1.93/100 person-years for uncircumcised men [23]. In control arm participants, post-trial HIV incidence was 0.54/100 person-years in circumcised and 1.71/100 person-years in uncircumcised men [adjusted effectiveness 67% (95% CI 38–83%)]. There

was no significant difference in socio-demographic characteristics or sexual behaviors between controls accepting male circumcision and those remaining uncircumcised. These findings confirm the high effectiveness of male circumcision for HIV prevention for almost 5 years following closure of the clinical trial.

In contrast to other HIV-prevention strategies, male circumcision is a 1-time procedure that confers life-long partial protection against heterosexual HIV infection of men. Based largely on the clinical trial data the World Health Organization in 2007 recommended expansion of male circumcision services in priority countries in sub-Saharan Africa, and medical male circumcision has been promoted by national policies in multiple countries [24]. Success has been variable, depending on the setting.

2.6 Cost-effectiveness of male circumcision

Detailed analyses of the African trials indicate that male circumcision is likely to be very cost-effective, and highly likely to provide cost-savings [25]. The South African study data were modeled to estimate that 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 (cost savings of US$ 2,631 per circumcision). Data from the Kenyan trial were used to estimate that the cost was $ 200 per HIV infection averted [18]. Costs were higher in Uganda, where 39 circumcisions were estimated to prevent one HIV infection over 10 years, with a cost of US$ 2,631 per HIV infection averted over 10 years [26]. Since the benefits of circumcision are life-long, and economies of scale should decrease costs, male circumcision is likely to prove very cost-effective in high-risk African settings.

Modeling exercises using updated, country-specific, data from priority countries in Eastern and Southern Africa show that the cost ranges from US$ 65.85 to US$ 95.15 per circumcision performed [27]. Scaling up adult voluntary medical male circumcision services to reach and maintain 80% coverage would avert 3.36 million new HIV infections through 2025. This scale-up would cost a total US$ 2 billion between 2011 and 2025. However, scale-up would result in net savings of US$ 16.51 billion due to reduced HIV treatment and care costs.

2.7 Implementation of voluntary medical circumcision programs in sub-Saharan Africa

The protective effect of male circumcision against heterosexually acquired HIV infection in men was confirmed by the three well-designed randomized clinical trials in sub-Saharan Africa outlined above [1], [2], [3]. The consistency of the findings was supported by a Cochrane committee meta-analysis [6]. These findings led the World Health Organization and UNAIDS to endorse male circumcision as an additional important intervention to help reduce HIV prevalence in epidemic settings [28]. Voluntary medical male circumcision programs were then rolled out with support from the World Bank, the US President's Fund for AIDS Relief (PEPFAR), the Bill & Melinda Gates Foundation and other bodies.

The voluntary medical male circumcision programs have been proven to be highly effective in reducing HIV infections and saving lives. Two recent meta-analyses have shown that the level of protection is approx. 70%. One, by Lei et al. included 4 RCTs and 11 prospective cohort studies (pooled adjusted risk ratio 0.30; 95% CI 0.24–0.38; P<0.00001) [29]. A not statistically significant reduction in HIV infection risk was seen in women (pooled adjusted RR 0.68; 95% CI 0.40–1.15; P=0.15). The other meta-analysis, by Sharma et al. reported a significant 72% risk reduction for heterosexual (RR 0.28; 95% CI 0.14–0.59) and homosexual (RR 0.80; 95% CI 0.69–0.92) males [30].

As of September 2017, there have been more than 15.2 million voluntary medical male circumcisions in eastern and southern African countries, the majority being for adolescents (males 10–19 years of age) [31]. Targeting adolescents as a special priority appears appropriate for public health programs because adolescents represent 34–55% of the target population [32]. Further, in many settings uptake of

circumcision services among adolescents is culturally and socially more acceptable than among adults. There are, moreover, fewer barriers regarding sexual abstinence during healing or female partner pressures. Circumcision before the age of sexual debut has maximum long-term impact on reducing HIV risk at the individual level and consequently reduces the risk of transmission within the population.

2.8 Complications of male circumcision

Another important issue is to compare the potential benefits of male circumcision with potential risks.

Some of the best data were obtained prospectively during the randomized clinical trials. However, it is difficult to directly compare adverse event rates in the three trials. The trials employed different visit schedules and different adverse event definitions and criteria. In the Kisumu, Kenya trial, adverse events possibly, probably or definitely related to circumcision occurred after 23 of 1,334 circumcisions (1.7%) [33], [34]. The adverse events were all classified as mild or moderate in severity and resolved quickly. There were no severe adverse events. In the Orange Farm, South Africa trial, adverse events were recorded for 54 (3.6%) of circumcisions of 1,495 HIV-negative men [1]. In the Rakai, Uganda trial, surgery-related adverse events occurred after 178 (7.6%) of 2,328 circumcisions [3]. This may reflect differences in management. The risk of moderate adverse events related to surgery was 3% in the Uganda trial, including 5 adverse events categorized as severe (0.2%). All of these complications were managed successfully. Thus, the incidence of adverse events for medical circumcision in the trials was considered acceptably low.

Limited data on adverse events are available from public health programs. A study from South Africa monitored events prospectively [35]. After 602 circumcisions, adverse event rates were: 0.2% intra-operatively, and 0.7, 0.3 and 0.6% at 2-, 7- and 21-day visits, respectively. The frequency of severe events was 0.4, 0.3 and 0.6% at 2-, 7- and 21-day visits, respectively. Swelling and wound infections were the most common adverse events with a mean duration of 7 days.

In Malawi, a group problem-solving approach was used to evaluate adverse events in a male circumcision program and to improve outcomes [36]. Baseline audits of 3,000 charts identified 257 procedure-related adverse events (8.6%), including 6 (0.2%) classified as mild, 218 (7.3%) moderate, and 33 (1.1%) severe. After implementation of a quality improvement plan, a repeat audit of 2,540 cases identified 115 procedure-related adverse events (4.5%), including 67 (2.6%) classified as mild, 28 (1.1%) moderate, and 20 (0.8%) severe. Reports of moderate-plus-severe (program-reportable) events decreased by 75% (from 8.4% to 1.9%, p<0.001). These data suggest that public health programs promoting male circumcision may achieve rates of adverse events comparable to rates observed in the clinical trials.

2.9 Circumcision and sexual function

The potential for male sexual dysfunction after circumcision has been considered in a number of studies and detailed reviews [37], [38], [39], [40], [41], [42]. Two prospective studies evaluated sexual function and pleasure among participants in the randomized controlled trials of circumcision to reduce HIV prevalence [37], [40]. Participants in the Kisumu trial underwent detailed evaluations at 1, 3, 6, 12, 18, and 24 months after circumcision [37]. Changes in sexual function over time were not associated with circumcision status. Compared to before they were circumcised, 64% of circumcised men reported their penis was, "much more sensitive" and 55% rated their ease of reaching orgasm as, "much more" at month 24.

Similar results were reported among participants in the Rakai trial [40]. In this study participants were followed up at 6, 12 and 24 months, when information on sexual desire, satisfaction and erectile dysfunction was collected. Again, there was no difference in sexual function between the study arms. Thus, adult male circumcision was not associated with sexual dysfunction in either study. Similarly, male circumcision had no adverse effect on sexual function in a clinical trial carried out in the Dominican Republic [43].

Findings in these prospective studies fit with other patient reports and physiological observations as well as a systematic review of the histological correlates relevant to penile sensitivity and sexual pleasure [39], [44]. The detailed review by Cox et al. found that, "any sexual effect of circumcised men may depend solely on exposure of the glans and not on the absence of the prepuce" [39].

2.10 Potential for "behavioral disinhibition"

An increase in high-risk sex practices (known as "risk compensation" or "behavioral disinhibition") after circumcision could in theory partly offset the protective effect of male circumcision. All three trials considered the potential for behavioral disinhibition. The Ugandan trial found no difference in sexual behaviors by circumcision status [3]. The South African trial showed a significantly increased mean number of sex acts between 4 and 21 months among the circumcised men, but no increase in the number of sexual partners or change in condom use [1]. The Kenyan trial found a decrease in reported risk-taking behaviors during the 24 month study in both circumcised and uncircumcised men [2]. Combined analysis of data from the three trials found that most men delayed intercourse after circumcision and that early sexual activity after circumcision was not associated with increased risk of HIV infection, although the statistical power was limited [45]. Despite these reassuring observations, circumcised men should be strongly advised to delay intercourse in order to limit the potential for an increase in HIV infection risk until wound healing is complete [45], [46].

2.11 Male circumcision reduces the risk of other sexually transmitted infections (STIs)

Below we summarize the quality evidence addressing whether or not male circumcision protects against specific STIs.

2.11.1 Oncogenic human papillomaviruses (HPV)

A recent meta-analysis of 30 studies concluded that, "Male circumcision was strongly associated with reduced odds of genital HPV prevalence" (OR 0.68; 95% CI 0.56–0.82) [47]. That meta-analysis treated all types of studies equally. Recent reviews and risk-benefit analyses [48], [49] found that average risk reduction was 40% in 6 RCTs and 53–65% in 2 earlier meta-analyses. In a large multinational study published in the *New England Journal of Medicine* penile HPV was detected in 19.6% of uncircumcised and 5.5% of circumcised men [50]. After adjustment for age at first intercourse, lifetime number of sexual partners, and other potential confounders, circumcised men were less likely than uncircumcised men to be infected with HPV (OR 0.37; 95% CI 0.16–0.85) [50]. A randomized clinical trial in 2012 found incidence of flat penile lesions (mostly caused by high-risk HPV types) was 98% lower among circumcised men and that men with high HPV16/18/31 (high-risk HPV) viral load (OR = 5.2; 95% CI = 1.1–24.4) had higher odds of flat penile lesions [51]. Male circumcision does protect against infection by the (low-risk) HPV genotypes responsible for genital warts, because these genotypes infect the shaft and genital area generally, whereas high-risk genotypes mostly infect the foreskin and underlying glans. A randomized clinical trial found, moreover, that circumcised men had a shorter duration of infection of the glans/coronal sulcus [52], but duration of infection did not vary by circumcision status in the penile shaft, scrotum, or all genital sites combined. Thus, clearance is greatest in precisely the area of the penis exposed by male circumcision. A US study found that male circumcision was significantly associated with an increased likelihood of clearance of any HPV infection (HR 2.7; 95% CI, 1.3–5.7) and of clearance of oncogenic (high-risk) HPV infection (HR 3.2; 95% CI, 1.4–7.4]), but not with an increased likelihood of clearance of non oncogenic (low-risk) HPV infection [53]. Another 2017 meta-analysis, by Zhu et al., conceded that, "sampling sites also played an important role in the final results," and that, "selection bias in our metaanalysis" (i.e., not taking into account penile sites used for sampling) affected the conclusions [47]. Use of a single combined sample for the penis and scrotum was explained as the reason for a negative result in one study [54].

In summary, male circumcision reduces penile infection risk and also increases clearance of high-risk HPV genotypes.

2.11.2 Genital herpes virus type 2 (HSV-2)

Data from the randomized clinical trials in sub-Saharan Africa found significant decreases of 45%, 30%, and 28% in HSV-2 infection rates after male circumcision [55], [56], [57], [58]. The 2006 meta-analysis by Weiss et al. that predated the randomized clinical trials also found that HSV-2 risk was 15% (OR 0.74–0.98) lower in circumcised men, after adjustment for confounding factors [21].

2.11.3 Other STIs in males

Randomized clinical trials and other studies found approximately 50% lower syphilis, chancroid, genital ulcer disease, *Trichomonas vaginalis* and *Mycoplasma genitalium* rates among circumcised men [48]. Genital ulcers of uncircumcised men contain a higher prevalence of anaerobic bacteria. RCT data showed that MC reduces total bacterial load and microbiota biodiversity [59]. The 2006 meta-analysis by Weiss et al. found that syphilis rates were 33% lower in circumcised men [21]. Although a randomized clinical trial by Tobian et al. did not find a reduction in syphilis, this may have resulted from lack of power due to the small number of syphilis infections identified on follow-up testing [60]. Another large study found 42% lower syphilis risk in circumcised men [61], acknowledged by Tobian as showing that male circumcision *does* reduce syphilis risk [70].

2.11.4 Protection against STIs in women

Findings on the impact of male circumcision on STI risk in women are mixed. For HPV, one might expect that by lowering high-risk HPV infection risk in men, male circumcision would also reduce infection risk in women, and thus cervical dysplasia, which can progress to cervical cancer. In a large multinational study, "to minimize confounding as a result of the women's having had male partners other than the current partner, [they] restricted the analysis to 1,420 men whose female partner reported having had only one sexual partner" [50]. They then rated the "sexual-behavior risk index" of the men. Men were considered high-risk if they reported ≥6 sexual partners and first intercourse prior to 17 years of age. Men were considered low-risk if they reported ≤5 sexual partners and first sexual intercourse > age 17 years. The remaining men were considered intermediate risk. Monogamous women whose male partners had either a high or an intermediate sexual-behavior risk index (n=374 and 511 women, respectively) were less likely to have had a cervical cancer diagnosis if the male partner was circumcised (OR 0.18 [95% CI 0.04–0.89] and 0.50 [95% CI 0.27–0.94], respectively). A RCT found the prevalence and incidence of high-risk HPV after 2 years were, respectively, 28% and 23% lower among women with circumcised male partners than women with uncircumcised partners [63].

Current HPV vaccines are prophylactic not therapeutic. The vaccines are primarily administered to girls in early high school, and are directed at only the two or four (depending on the product) most common genotypes of over 14, high-risk HPV genotypes. These genotypes are found in approximately 70% of cervical cancers. A recent systematic review of real-world experience with HPV vaccination [64] reveals the suboptimal effectiveness of HPV vaccination (see Figure 3C of that publication). In Australia, one of the earliest countries to vaccinate girls, there was an 86% (not 100%) decrease in *vaccine genotypes* (HPVs 6, 11, 16 and 18) [64]. As with other public health interventions, a package of multiple preventive measures is likely to have a greater impact than vaccination alone.

A study in Pittsburgh found that HSV-2 infection risk was twice as high in women who had ever had intercourse with an uncircumcised man (OR 2.2; 95% CI 1.4–3.6; n=1,207). Similarly, a randomized clinical trial found 2-fold higher HSV-2 infection risk over 12 months in 783 wives of uncircumcised men [65]. But one trial found no significant decrease in HSV-2 acquisition by the female partners of circumcised men.

As for other STIs, a randomized clinical trial found women with circumcised male partners had 22% lower genital ulcer disease, 40% lower overall bacterial vaginosis, 61% lower severe bacterial vaginosis, and 48% lower *Trichomonas vaginalis*, but no difference in dysuria or vaginal discharge [65]. A large prospective cohort study of 2,946 HIV-negative couples found syphilis was 75% lower among female partners of circumcised men [61].

A large multinational study found that *Chlamydia trachomatis* seropositivity was 5.6-fold higher in women with an uncircumcised partner [66]. This finding also applied to women who had only had one sexual partner. Prevalence of *C. pneumoniae*, which is not transmitted sexually, did not differ. The authors suggest that infected cervicovaginal secretions may be trapped under the prepuce for longer in uncircumcised men, increasing risk of penile urethral infection and transmission to the vagina during sexual intercourse [66]. A prospective study in Uganda, Zimbabwe and Thailand found no difference in chlamydial, gonococcal or trichomonal infections in women as a function of the circumcision status of their sexual partners.

A systematic review by researchers from the US Centers for Disease Control and Prevention and Johns Hopkins University identified 9 randomized clinical trials and 48 observational studies [67]. Key findings were that male circumcision reduced acquisition of STIs and cervical cancer in women. The data were strongest for HSV2, chlamydia and syphilis, medium consistency for any HPV type and low-risk HPV types, intermediate consistency for any STI, candidiasis, dysuria, genital warts, gonorrhoea, high-risk HPV viral load and *Mycoplasma genitalium*, with discrepant values for bacterial vaginosis, HIV, high-risk HPV, non-specific genital ulcers, trichomoniasis and vaginal discharge rendering these low-consistency (See also the editorial on this study [68]). Clearly, reduced population prevalence of STIs in men will translate into lower risk of STI exposure in women.

2.11.5 Male circumcision provides protection against STIs in men who have sex with men (MSM)

Male circumcision does not protect MSM against HIV infection during *receptive* anal intercourse. The majority of MSM engage in this form of intercourse. A meta-analysis [69] and other studies [70] indicate that male circumcision is protective for MSM who predominantly adopt an *insertive* role during anal intercourse. Circumcision also provided 57% protection against oncogenic HPV [71]and incident syphilis (HR 0.35; 95% CI 0.15–0.85), particularly in the one-third of MSM who engaged predominantly in insertive anal intercourse (HR 0.10; 95% CI 0.01–0.81) [72]. An explanation for association with incident but not prevalent syphilis in an Australian study is that men who initiated MSM sexual activity during the late 80s and 90s when syphilis prevalence was low would have been at very low risk of acquiring syphilis irrespective of their circumcision status, but only since 2001 has syphilis re-emerged in Australian MSM [72].

2.11.6 Condoms

The level of protection provided by condoms provide against HIV infection is 80%, and this only applies if condoms are used consistently and correctly [73], [74]. A Cochrane systematic review and meta-analysis of randomized clinical trials of condom use (2 of these being in the US, one in England and 4 in Africa) found, "little clinical evidence of effectiveness" and no "favorable results" for HIV prevention [75]. This study did find that condoms were 42% effective against syphilis infection [75].

Unlike condoms, male circumcision is a one-off procedure that does not require future voluntary compliance each time a man has intercourse. In this respect, male circumcision can thus be compared with vaccination. However, the only vaccines currently in widespread use (in early high school females and increasingly in males) for STI prevention are those that protect against certain HPV genotypes. Because male circumcision and condom use each provide a reasonable degree of protection against STIs, both measures should be advocated [76].

2.12 Contrary claims and analyses

In an extensive article, Van Howe adopted meta-regression analyses to support his view that male circumcision does not protect against STIs [77]. A detailed critique exposed serious flaws in Van Howe's analyses, as well as misrepresentation of data [78]. Critiques of Van Howe's previous meta-analyses of male circumcision in relation to sexually transmitted urethritis and HPV have also been published [79], [80]. Meta-analyses and meta-regression analyses by Van Howe, and articles by others disputing the protection provided by male circumcision against HIV infection in heterosexual men, have also been exposed as seriously flawed [15], [76], [81], [82], [83], [84], [85], [86], [87], [88], [89], [90], [91], [92], [93], [94].

2.13 Is male circumcision an important public health consideration in developed countries?

Much of the data and analyses outlined above come from the developing world, especially Africa, because we concentrated on summarizing the highest quality data. This raises the question, "How relevant are these studies to other clinical and public health settings?"

Studies from the US [61], [95], [96], Europe [44], [97] and Australia [98] suggest that male circumcision offers similar benefits in other clinical settings. Comprehensive reviews of the available data led the US Centers for Disease Control and Prevention [99], the American Academy of Pediatrics [100] and the American Urological Association [101] to develop policy statements strongly supporting male circumcision, especially neonatal male circumcision, as a public health measure.

3 Further research

The strong epidemiological, clinical trial and basic science data outlined above constitute compelling evidence for the medical and public health benefits of male circumcision for males and their sexual partners. There remain some important priorities for future research in the following areas:

1. Developing methods to improve education of medical professionals and the general public on the long-term benefits of voluntary male medical circumcision.
2. Further definition of the magnitude and mechanisms underlying the reduction of STI risk for circumcised males and their sexual partners.
3. Improving implementation of medical male circumcision as a public health measure.

4 Conclusions

Male circumcision may be the oldest, and certainly the most common surgical procedure. The positive findings in the three randomized controlled trials show that circumcision reduces a man's risk of HIV infection by approximately two-thirds. Circumcision also reduces the risk of other important sexually transmitted infections, including oncogenic HPV, genital HSV, trichomoniasis, genital mycoplasma, syphilis and chancroid, as well as genital ulcer disease. Since high-risk types of HPV are found in half of penile cancers and virtually all cervical cancer cases, male circumcision has an important role in prevention of urogenital cancers. In addition to other health benefits, male circumcision provides a much-needed addition to the limited HIV prevention armamentarium. The evidence from biological studies, observational studies, randomized controlled clinical trials, meta-analyses and cost-effectiveness studies is conclusive. The challenges to implementation of safe male circumcision services in resource-limited settings are now being faced and met in multiple developing country settings. Data and analyses also support policy statements that male circumcision offers important public health benefits in developed country settings of Europe, North America and the Asia-Pacific region.

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