Published in final edited form as:

Br J Nurs. 2010 ; 19(10): 629–634.

Male circumcision, HIV and sexually transmitted infections: a review

Natasha Larke

Lecturer in Epidemiology and Medical Statistics, Medical Research Council Tropical Epidemiology Group, London School of Hygiene and Tropical Medicine, London

Abstract

Three randomized controlled trials in sub-Saharan Africa have shown that circumcision reduces the risk of acquiring HIV infection in men by approximately 60%. In this paper, we review the evidence that male circumcision protects against infection with HIV and other sexually transmitted infections (STIs) in men and their female partners. Data from the clinical trials indicate that circumcision may be protective against genital ulcer disease, *Herpes simplex* type 2, *Trichomonas vaginalis* and human papillomavirus infection in men. No evidence exists of a protective effect against *Chlamydia trachomatis* or *Neisseria gonorrhea*. There is weak evidence that circumcision has a direct protective effect on HIV infection in women, although there is likely to be an indirect benefit, since HIV prevalence is likely to be lower in circumcised male partners. Although there is little evidence from the trials of serious adverse events from the procedure and of behavioural risk compensation among circumcised men, essential operational research is being conducted to evaluate these key issues outside the trial setting as circumcision services are expanded. Following the publication of the clinical trial results in early 2007, the World Health Organization/UNAIDS has advised that promotion of male circumcision should be included as an additional HIV strategy for the prevention of heterosexually acquired HIV infection in men in areas of high HIV prevalence. As circumcision services are expanded in settings where resources are limited, non-physician providers including nurses will play an important role in the provision of services.

Keywords

Male circumcision; HIV/AIDS; Sexually transmitted infections; Sexual behaviour; Public health; Africa

Male circumcision is the surgical removal of foreskin of the penis. It is one of the most common surgeries worldwide – approximately 30–35% of men are circumcised globally (World Health Organization (WHO)/UNAIDS, 2008).

Circumcision is commonly practised for religious reasons and approximately 60% of circumcised men are Muslim. Almost all men in the Middle East, North Africa, Pakistan, Bangladesh and Indonesia are consequently circumcised. Circumcision is also common in West Africa, parts of Central and Eastern Africa, the USA, the Republic of Korea and the Philippines (WHO/UNAIDS, 2008), where it is generally practised for non-religious reasons or as a rite of passage to manhood.

The age at which circumcision is carried out is largely determined by religious or cultural factors. For example, Jewish boys are typically circumcised in a religious ceremony on the eighth day after birth (Ben Chaim et al, 2005; Amir et al, 2000), whereas boys in many Muslim countries are circumcised after one year of age (Yegane et al, 2006).

Biological evidence for the effect of male circumcision on HIV and sexually transmitted infections

The presence of a foreskin may increase a man's risk of acquiring HIV and other STIs in several ways. First, the inner mucosal surface of the foreskin is thinly keratinized (McCoombe and Short, 2006) and therefore more susceptible to abrasions, facilitating entry of infectious agents (Szabo and Short, 2000). Additionally a high concentration of Langerhans cells and CD4 cells – the target of HIV-1 virions – are found close to the epithelium of the foreskin (Donoval et al, 2006; McCoombe and Short, 2006; Patterson et al, 2002).

The warm, moist environment under the foreskin favours pathogen survival and replication. A recent study among 14 men in Uganda showed that, following circumcision, men had fewer pro-inflammatory anaerobic bacteria (Price et al, 2009). These bacteria may exacerbate existing infection and increase risk of genital ulcer disease (GUD) in uncircumcised men and of vaginal infections in female partners (Gray et al, 2009a; 2009b).

The size of the surface area of the foreskin is thought to be related to the risk of infection (Kigozi et al, 2009). Among men in the control arm of this Ugandan randomized controlled trial (RCT), the surface area of the foreskin in men was shown to be related to HIV acquisition; HIV incidence among men with the largest foreskin surface areas was twice that of men in the lowest quartile (adjusted rate ratio=2.37, 95% confidence interval (CI): 1.05–5.31).

Male circumcision and HIV/STIs in men

Effect of circumcision on HIV infection

Early evidence of an association between male circumcision and HIV came from ecological studies that showed areas with high HIV prevalence in sub-Saharan Africa correlated with areas where circumcision was not traditionally performed (Moses et al, 1990; Halperin and Bailey, 1999; Drain et al, 2006).

Subsequently, several observational studies were conducted and a systematic review of 27 such studies showed that circumcised men were 60% less likely to have HIV infection than uncircumcised men (adjusted risk ratio=0.42; 95% CI: 0.34,0.54) (Weiss et al, 2000). In 2005, a further systematic review of 37 observational studies confirmed these findings (Siegfried et al, 2005).

However, observational studies are limited by biases, such as misclassification of circumcision and failure to adequately adjust for confounding factors. Indeed, the authors of the 2005 systematic review noted that the included studies were variable in quality and might not have been adjusted effectively for confounding.

Effect of circumcision on HIV infection: evidence from RCTs

To provide conclusive evidence of an effect of male circumcision on HIV infection, three RCTs were conducted in Uganda, Kenya and South Africa in 2000–06.

In total, 10 908 uncircumcised men were randomized to immediate circumcision (intervention arm) or circumcision at the end of the trial (control arm), and were followed up for up to 2 years so HIV incidence in the two arms could be compared. Trial characteristics are shown in Table 1 (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007b).

All three trials were stopped early because a strong and statistically significant effect of circumcision was observed: the incidence of HIV was reduced by around 60% in circumcised men in all three trials (Table 2), a finding consistent with that observed in the observational studies (Weiss et al, 2008; Siegfried et al, 2009).

Effect of circumcision on HIV infection among men who have sex with men

A recent review of the evidence for an effect of circumcision on HIV among men who have sex with men (MSM) highlighted weakness and inconsistencies in published evidence (Templeton et al, 2010). Any impact of circumcision among MSM is likely to benefit the insertive partner only, through similar mechanisms for penile-vaginal sex, since the circumcision status of a receptive partner is unlikely to affect their risk of infection.

One study in sub-Saharan Africa among MSM who primarily engage in insertive anal sex demonstrated an impact of circumcision on HIV infection (adjusted odds ratio=0.20; 95% CI: 0.10,0.20 (Lane et al, 2009).

In studies conducted among men practising both insertive and receptive anal intercourse, circumcision has been seen to have little effect on HIV infection (odds ratio=0.86; 95% CI: 0.65,1.13) (Millett et al, 2008).

Circumcision and ulcerative STIs

A meta-analysis of observational studies published prior to the RCTs suggested that circumcision reduces risk of GUD, including chancroid, syphilis and, to a lesser extent, genital herpes (Weiss et al, 2006).

Two RCTs have evaluated the effect of circumcision on GUD (Table 2). The risk of self-reported genital ulcer disease was significantly lower among circumcised men in the Kenyan trial (relative risk (RR)=0.53), and the Ugandan trials (RR=0.54; 95% CI: 0.46–0.66 respectively) (Bailey et al, 2007; Gray et al, 2009a). Only the Ugandan trial reported the impact on serological syphilis, and found no effect (adjusted hazard ratio 1.10, 95% CI: 0.75–1.65) (Tobian et al, 2009).

The effect of circumcision on *Herpes simplex* virus type 2 (HSV-2) is less clear than its effect on HIV. In the Ugandan and South African RCTs, the incidence of HSV-2 was approximately 30% lower among circumcised men (adjusted hazard ratio=0.72, 95% CI: 0.56–0.92 in Uganda and 0.68, 95% CI: 0.38–1.22 in South Africa) (Sobngwi-Tambekou et al, 2009a; Tobian et al, 2009), but no effect was observed in the Kenyan trial (RR=0.99, 95% CI: 0.67–1.46) (Bailey and Mehta, 2009).

A possible reason for this is that HSV-2 is shed from a wider area of the female genital tract than HIV and is more transmissible so may be less dependent on the foreskin as site of infection in men. Furthermore, the foreskin does not contain a high density of target cells for HSV-2, as it does for HIV. Considering the strong effect of circumcision on GUD, it is likely that circumcision protects against non-herpetic ulceration.

Evidence suggests that the protective effect of circumcision on HIV may partly be mediated through a protective effect of circumcision on GUD. In the Ugandan trial, greater efficacy of circumcision on HIV was seen among men with genital ulcers during follow-up (RR=0.29; 95% CI: 0.03,1.29) than in men with no genital ulcers (RR=0.60; 95% CI: 0.33,1.08) (Gray et al, 2007b).

However, models indicate that a relatively small proportion of the impact of circumcision on HIV is mediated through GUD or other STIs. For example, models based on data from the

Kisumu (Bailey et al, 2007) trial estimate that about 10–20% of the HIV infections prevented by male circumcision were due to efficacy against STIs (Desai et al, 2006).

Circumcision and non-ulcerative STIs

The trials have also provided data on the association of circumcision with non-ulcerative STIs (Table 2). A meta-analysis of observational studies has suggested that circumcised men are half as likely to be infected with human papillomavirus (HPV) than uncircumcised men (odds ratio=0.52, 95% CI: 0.33,0.82) (Bosch et al, 2009).

Data from the South African and Ugandan trials have shown similar effects of circumcision: the prevalence of HPV isotypes high-risk for cervical cancer was 45% lower (95% CI: 10%, 54%) in circumcised men in the Ugandan trial and 42% lower (95% CI: 11%,48%) in circumcised men in the South African trial after adjustment for confounding (Bailey, 2007; Tobian et al, 2009). A lower risk of HPV prevalence among circumcised men could indicate that circumcision decreases either HPV incidence or increases clearance rates. Further work is needed to elucidate these findings and the implications for lower risks of cervical and penile cancers.

From trial data, circumcised men are less likely to be infected with *Trichomonas vaginalis* than uncircumcised men at final follow-up. In the South African trial, men randomized to circumcision were half as likely to have prevalent *Trichomonas vaginalis* infection 21 months after randomization (adjusted odds ratio=0.53, 95% CI: 0.28,1.02); an as-treated analysis provided stronger evidence of an intervention effect (adjusted odds ratio 0.47, 95% CI: 0.25,0.92) (Sobngwi-Tambekou et al, 2009b). A weaker effect was seen in the Kenyan trial (Mehta et al, 2009b).

There is relatively little evidence of circumcision having an effect on *Chlamydia trachomatis* infection in the trials (Mehta et al, 2009b; Sobngwi-Tambekou et al, 2009b) and no impact on *Neisseria gonorrhea* (Mehta et al, 2009b; Sobngwi-Tambekou et al, 2009b) (Table 2).

Male circumcision and HIV/STIs in women

Circumcision and HIV infection

A fourth RCT was conducted in Rakai, Uganda, to evaluate the impact of male circumcision on HIV acquisition in women (Wawer et al, 2009). In total, 922 HIV-infected men aged 15–49 years with high CD4 counts (> 350 cells/microlitres) were randomized to immediate or delayed circumcision and 163 uninfected female partners were enrolled and followed for up to 24 months. The trial was stopped early due to futility, as fewer female partners were enrolled than expected. A higher proportion of partners of circumcised men became HIV infected during the trial with a hazard ratio of 1.58 (95% CI: 0.68,3.66), although this is based on relatively few seroconversions.

Observational studies have provided varied results (Kapiga et al, 1998; Gray et al, 2000; Turner et al, 2007; Baeten et al, 2010). In one recent observational study, circumcision status was ascertained by a clinician and genetic linkage was used to identify transmission events that occurred within partnerships (Baeten et al, 2010). After adjustment for the male partner's HIV–1 viral load, the risk of HIV–1 transmission was lower in female partners of circumcised men than in partners of uncircumcised men (adjusted hazard ratio=0.64; 95% CI: 0.36–1.14).

One possible reason for the contrasting results between this observational study and the RCT is that males in the observational study were likely to have been circumcised in childhood or

adolescence, which would have allowed for complete wound healing and keratinization of the glans prior to exposure to HIV.

Although it is possible that no direct impact of circumcision on male-to-female transmission exists, there will be an indirect benefit to women since HIV prevalence is likely to fall in male partners as circumcision services are expanded. Mathematical modelling shows that 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 (UNAIDS/WHO/SACEMA Expert Group, 2009).

Circumcision and STI infection

Little evidence has been published on the effect of circumcision on STI transmission to female partners, with only the Uganda trial examining its effect on transmission of STIs from men to women. As with men, circumcision appears to provide some protection for women against GUD: the risk of prevalent GUD was 25% lower in female partners of circumcised men (RR=0.76; 95%CI: 0.60,0.97) (Gray et al, 2009b). Similarly, circumcision was observed to affect bacterial vaginosis and *Trichomonas vaginalis* prevalence among female partners of HIV-positive men (RR=0.80; 95% CI: 0.71, 0.89 and 0.43; 95% CI: 0.18,1.02 respectively) and of HIV-negative men (RR=0.80; 95% CI: 0.65,0.97 and RR=0.52; 95% CI: 0.05,0.98 respectively) (Gray et al, 2009b; Wawer et al, 2009).

While none of the RCTs examined the association between circumcision and HPV infection and cervical cancer in women, a number of observational studies have examined this relationship (Brinton et al, 1989; Kjaer et al, 1991; Castellsagué et al, 2002). In one study, having a circumcised partner led to a 30% decreased risk of cervical cancer in women (odds ratio=0.72; 95% CI: 0.49, 1.04) (Castellsagué et al, 2002).

Operational research

Following publication of the trial results in early 2007, an international consultation of researchers and stakeholders concluded that there was compelling evidence that male circumcision partially reduced the risk of HIV acquisition.

Consequently WHO/UNAIDS now advise that promotion of male circumcision should be included as an additional HIV strategy for the prevention of heterosexually acquired HIV infection in men in areas of high HIV prevalence (WHO/UNAIDS, 2007). Consequently, several countries in southern and eastern Africa are introducing or expanding safe male circumcision programmes.

Alongside the expansion of male circumcision services, operational research studies are being carried out to monitor and evaluate the optimal ways to roll out services. Key issues include the safety of adult male circumcision, the impact on sexual satisfaction and function, counselling packages to minimize risk compensation and methods of delivery.

Surgical safety

One of the major concerns about the expansion of circumcision services is the safety of the procedure, where common complications include bleeding, infection, pain and swelling.

In the RCTs, approximately 3–8% of surgeries were associated with an adverse event and most were mild (Auvert et al, 2005; Krieger et al, 2007; Kigozi et al, 2008a), although differences between these study may reflect differing definitions for adverse events. Complications are likely to be higher outside clinical trials, where the quality and quantity of training, supervision and resources vary.

A systematic review of complications among men in sub-Saharan Africa revealed a variable prevalence of complications among healthy men (0–24%), although most were minor (Muula et al, 2007). In some studies, there was a suggestion that the grade/training of personnel performing the surgery was associated with the frequency of complications, although this was not always statistically significant.

In one study among 562 adolescents from the Babukusu ethnic group in Kenya, 18% of men had a complication when the procedure was performed by a medical provider; complications were twice as frequent (35%) among procedures performed by a traditional surgeon within villages or household compounds (Bailey et al, 2008). Direct observation of 24 procedures revealed some permanent serious adverse events, including one life-threatening incident by a ‘medical’ practitioner who was later found to have no medical qualifications.

In the Ugandan trial, the frequency of complications was related to the number of procedures performed by the clinician, where complications resulted in 9% of surgeries for the first 20 performed, declining to 4% thereafter (Kigozi et al, 2008a). Considering the potential for a high prevalence of complications and severity of adverse events, WHO/UNAIDS have produced guidelines on provision of safe circumcision, to ensure the provision of safe and efficient circumcision services (WHO/UNAIDS/JHPIEGO, 2006; WHO, 2008a). Adolescent or adult circumcision is a more complex procedure than that performed in infants, requiring suturing. WHO/UNAIDS (2007) recommendations encourage countries to consider expanding services among infants as a longer-term HIV prevention strategy.

Sexual behaviour after circumcision

Another major concern about the expansion of circumcision services is that increases in unsafe sex may occur if men believe they are completely protected from HIV infection following circumcision.

While few differences were observed in sexual behaviour between the intervention and control arm in the three RCTs (Auvert et al, 2005; Bailey et al, 2007; Gray et al, 2007b), different patterns of sexual behaviour may be expected during the scale-up of circumcision.

In these trials men were not aware of the protective effect of circumcision on HIV infection and were provided with high quality behavioural counselling. Such counselling may not be feasible outside the trial setting, in the overstretched health services that will provide circumcision services in the scale-up.

In the Ugandan RCT, there was some evidence that recently circumcised HIV-positive men who resumed sexual activity early might be more likely to transmit HIV to female partners in the first 6 months after surgery than those who waited until complete wound healing, but these 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 6/63 seroconversions (9.5%) among those who resumed sex after this time ($p=0.06$) (Wawer et al, 2009). In a pooled analysis from all three RCTs, there was a suggestion that early sex may increase the risk of HIV acquisition in men, although this analysis was underpowered (odds ratio=2.99; 95% CI: 0.32,13.6) (Mehta et al, 2009a).

Further observational studies are needed to monitor levels of risk compensation and early resumption of sex, and research is being conducted within the trial sites. One study in Nyanza, Kenya, is following newly circumcised and uncircumcised men for 24 months, to monitor behaviour, perceptions of HIV risk and sexual function and satisfaction (Bailey,

2009). Another study in the same site is assessing community-level perceptions of circumcision and HIV risk up to 5 years after initiation of the scale-up. Further studies are also needed to evaluate methods to limit behaviour change in resource-poor settings.

The impact of circumcision on sexual function and satisfaction has yet to be rigorously evaluated. In the trial settings, very high levels of satisfaction (>98%) were reported in both arms of the trial in Uganda; in Kenya, reported sexual dysfunction decreased during the trial and were similar in the two arms (Kigozi et al, 2008b; Krieger et al, 2008). Studies outside trial settings are commonly prone to bias, since men are often circumcised for medical reasons that affect sexual function.

Circumcision is likely to represent a cost-effective strategy. The estimated cost per adult male circumcision in Africa is between \$30 and \$60 (Martin et al, 2007), although neonatal circumcision costs about one third of this. In the Gauteng Province, South Africa, HIV prevalence is 25.6%, and circumcision is not commonly practised: assuming all men were circumcised, models suggest it is likely to cost US\$181 per HIV infection averted (Kahn et al, 2006). In Rakai, Uganda, where HIV incidence is lower, assuming that 75% of males are circumcised, it is estimated to cost US\$2 631 per HIV infection averted (Gray et al, 2007c).

Scale-up of circumcision services for HIV prevention

Countries with high HIV prevalence and generalized heterosexual epidemics have been identified as a priority for expanding circumcision services and include Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe (WHO/UNAIDS, 2009; de Bruyn et al, 2010). Progress in the scale-up of service provision has been slower than anticipated but experience in running and expanding services is growing. Situation analyses, policy and strategy development to guide scale-up, and initial training of safe circumcision providers have been carried out in all countries.

Botswana, Kenya and Swaziland have begun to implement quality assurance programmes; South Africa, Swaziland, Zambia and Zimbabwe have set up some impressive service delivery pilot programmes. Country ownership and leadership are critical to programme scale-up. As such, the most rapid progress has been in countries such as Kenya and Botswana, where the ministries of health have taken leadership for programme scale-up.

The role of nursing in the scale-up of circumcision services

As circumcision services are scaled up, additional health workers will be required. Expanding the range of medical services provided by non-physician providers including nurses (so-called task shifting), could be an effective way to improve access to healthcare services in resource-limited settings (WHO, 2008b).

In particular, nurses are likely to play an essential role in the provision of presurgical assessments, treatment and counselling (WHO, 2008b). Furthermore, in some countries – including Namibia (WHO/UNAIDS, 2009) and Swaziland (WHO, 2009) – task shifting of surgical tasks to nurses is being explored as a way to increase the number of circumcision service providers.

In Ghana, while the majority of procedures are performed by traditional circumcision providers, called Wanzams, there are also medical providers of circumcision, including experienced theatre nurses and experienced nurse anesthetists who perform the procedure in hospital (WHO, 2006). As with any cadre of medical personnel, successful task shifting of services to nurses will require careful training and supervision.

Conclusions

Male circumcision is the only intervention to have proven efficacy against HIV infection in multiple RCTs. However, this protection is only partial (approximately 60%) and access to safe circumcision services accompanied by comprehensive behavioural counselling is needed. Further operational research in southern and eastern Africa is critical to identify the best method of integrating safe circumcision services into health systems, as well as the development of counselling materials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key POINTS

- Circumcision reduces the risk of acquiring HIV infection by men by approximately 60%.
- Female partners of circumcised men may benefit indirectly, since HIV is likely to be lower in circumcised men.
- The World Health Organization and UNAIDS recommend promoting male circumcision as an additional, important strategy for the prevention of heterosexually acquired HIV infection in men in areas of high HIV prevalence.
- Circumcision services need to be safe and accompanied by comprehensive behavioural counselling.
- Observational studies are needed to monitor levels of risk compensation and early resumption of sex after surgery.
- As circumcision services are expanded in areas where resources are limited, non-physician practitioners including nurses may provide services, such as presurgical assessment and counselling, and even surgery itself. Such task-shifting will require training and supervision.

Table 1

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

Trial setting	South Africa (Auvert et al, 2005) Semi-urban	Uganda (Gray et al, 2007b) Rural	Kenya (Bailey et al, 2007) Urban
Background HIV incidence	~3-5/100 person years	~1.5/100 person years	~2.5/100 person years
Age range	18-24	15-49	18-24
Surgeons	General MDs	Medical officer	Medical officer
Surgical method	Forceps guided	Sleeve	Forceps guided
Number of men	3520	5000	2800

Table 2

Impact of male circumcision on HIV and other sexually transmitted infections among men in randomized controlled trials

Infection	Outcome measure	Trial	Reference	RR ^a	95%CI
HIV	Incidence	South Africa	(Auvert et al, 2005)	0.40	0.24,0.68
	Incidence	Kenya	(Bailey et al, 2007)	0.47	0.28,0.78
	Incidence	Uganda	(Gray et al, 2007a)	0.49	0.28,0.84
Ulcerative STIs					
Herpes simplex virus type 2	Incidence	South Africa	(Sobngwi-Tambekou et al, 2009a)	0.68	0.38,1.22
	Incidence	Uganda	(Tobian et al, 2009)	0.72	0.565,0.92
Syphilis	Prevalence	Uganda	(Tobian et al, 2009)	1.10	0.75,1.65
Genital ulcer disease	Incidence	Kenya	(Bailey, 2007)	0.53	
	Prevalence	Uganda	(Gray et al, 2009a)	0.54	0.44,0.66
Non-ulcerative STIs					
High-risk human papilloma virus	Prevalence	South Africa	(Auvert et al, 2009)	0.68	0.52,0.89
	Prevalence	Uganda	(Tobian et al, 2009)	0.65	0.46,0.90
<i>Neisseria gonorrhoea</i>	Prevalence	South Africa		0.94	0.69,1.29
	Incidence	Kenya	(Mehta et al, 2009b)	0.95	0.68,1.34
<i>Chlamydia trachomatis</i>	Prevalence	South Africa	(Sobngwi-Tambekou et al, 2009b)	0.56	0.32,1.00
	Incidence	Kenya		0.87	0.65,1.16
<i>Trichomonas vaginalis</i>	Prevalence	South Africa	(Sobngwi-Tambekou et al, 2009b)	0.53	0.28,1.02
	Incidence	Kenya	(Mehta et al, 2009b)	0.77	0.44,1.36

^aBest estimate relative risk; adjusted where available and crude otherwise