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Male circumcision for HIV prevention: Current research and programmatic issues

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Abstract

Randomized controlled trials in sub-Saharan Africa have shown that adult male circumcision reduces the risk of HIV acquisition in men by about 60%. In this paper we review recent data on the association of male circumcision and HIV/STI in men and women. This includes a summary of data showing some evidence of an effect of male circumcision against genital ulcer disease, HSV-2 infection, HPV and *Trichomonas vaginalis*, but not *Chlamydia trachomatis* or *Neisseria gonorrhea* in men. Longitudinal studies among HIV discordant couples suggest that male circumcision may provide some direct long-term benefit to women, which may start after complete wound-healing. Circumcision may also protect against HIV acquisition in men who have sex with men and practice unprotected anal intercourse (either exclusively or predominantly), although this data is not consistent. To date, there is little evidence from the few studies available of either unsafe practices or reported increases in risky behaviour, or adverse changes in sexual satisfaction and function. As countries in southern and eastern Africa scale up services, operational research will likely be useful to iteratively improve programme delivery and impact, while identifying the best methods of integrating safe male circumcision services into HIV prevention strategies and strengthening health systems.

Keywords

HIV; male circumcision; prevention

Introduction

Three randomized controlled trials (RCTs) in sub-Saharan Africa have shown that adult male circumcision reduces the risk of HIV acquisition in men by about 60% [1-3]. In this paper we review recent data on biological mechanisms by which male circumcision may protect against infection, the impact of male circumcision on HIV infection in women and

men who have sex with men (MSM), and impact on other sexually transmitted infections (STIs), sexual behavior, satisfaction and function. We also discuss current topics of concern including the safety of the procedure, cost-effectiveness, potential population-level impact, roll-out of circumcision, and operational research on scale-up of circumcision.

Biological mechanisms for a protective effect of circumcision on HIV & STIs

There are several plausible biological mechanisms by which the foreskin may increase a man's risk of acquiring STIs, including microtears or abrasions in the inner mucosal surface of the foreskin which is retracted over the shaft during intercourse. Further, the environment under the foreskin is thought to favour pathogen survival and replication. Recent evidence for this comes from a Ugandan study, in which penile (coronal sulcus) swabs from 14 adult Ugandan men were taken approximately two weeks prior to circumcision, and again 12 months after circumcision [4]. Pyrosequencing techniques showed that circumcision was associated with significant decreases in anaerobic bacteria, including potential pathogens. The effect of circumcision on bacterial flora may partly explain the increased risk of genital ulcer disease (GUD) and HIV in uncircumcised men, and of vaginal infections in their female partners [5].

The superficial layers of the penis contain a high density of HIV-1 target cells including Langerhans/dendritic cells and CD4/CD8 T lymphocytes [6-8], and HIV may gain easier access to these through the thin foreskin [9]. A recent study of adult male foreskins found no difference in keratin thickness of the inner and outer foreskin [10], although samples came from men undergoing circumcision for medical indications, primarily phimosis, which may have affected the results. This may suggest that other mechanisms, as mentioned above, may be important. However, recent data from Uganda suggest that the surface area of the foreskin is related to risk of HIV acquisition [11]. In this study, the foreskins of men enrolled into the control arm of the RCT were measured, and analysed in relation to HIV incidence prior to circumcision. Men with the largest foreskin surface areas had twice the HIV incidence rate of those in the lowest quartile (adjusted rate ratio=2.37, 95%CI 1.05-5.31). Such an association is biologically plausible since larger foreskins imply a larger absolute number of HIV target cells. However, there was no increased risk in men with mid-sized foreskins compared with small foreskins, and there will have been scope for measurement error of foreskin area [11]. Unfortunately, it may be difficult to replicate these findings as few studies assess HIV incidence prior to male circumcision.

There is also some recent evidence that the foreskin may play a role in enhancing HIV transmission from an uncircumcised HIV-positive man to his partner. Foreskins of men enrolled in the Rakai RCT were analysed, and those of men with HIV and HSV-2 infections, and higher HIV viral load, were substantially more likely to have epithelial and stromal inflammation [12]. The authors suggest this may mean uncircumcised men are more likely to transmit HIV, especially when there is co-infection with HSV-2.

Circumcision and HIV/STIs in heterosexual men

Effect of male circumcision on HIV

Several observational studies on circumcision and HIV have been published recently, and most of these support the findings from the RCTs and previous observational epidemiological studies [1-3, 13]. For example in a recent prospective cohort study of plantation workers and adult dependents in rural Kericho, Kenya, circumcised men were at one-third the risk of HIV acquisition (adjusted hazard ratio (HR)=0.32, 95%CI 0.15-0.68) [14]. However, these data are difficult to interpret given the high correlation of ethnicity and circumcision status in this population (13% of 231 Luo men were circumcised compared with 94% of 1147 non-Luo men). Although numbers were small, there was no evidence of an association of circumcision with HIV incidence among the Luo (HR=1.09, 95%CI 0.12-4.91) or non-Luo men (HR=0.98, 95%CI 0.15-41.1) respectively. Another study, among international truck drivers in Azerbaijan also found that circumcised men were at substantially lower risk of HIV (adjusted OR=0.38, 95%CI 0.20-0.72) [15]. In contrast, a national population-based study of 3025 men in South Africa found no association of circumcision and prevalent HIV either overall, or among men who were circumcised before age 12 years (and hence before sexual debut) compared with uncircumcised men (adjusted OR=0.9, 95%CI 0.5-1.7) [16]. Similar data were seen in Kenya, Lesotho and Tanzania [17].

It is perhaps not surprising that observational studies, especially cross-sectional studies and surveys, find somewhat inconsistent results, given the limitations such as misclassification of circumcision status [18], lack of knowledge of relative timings of circumcision and HIV infection, and insufficient measurement and adjustment for confounding factors. Self-report of circumcision status is of limited reliability in some settings. Additionally, unhygienic circumcision practices where blades are used on several males, may increase risk of HIV transmission [19]. However, a recent Cochrane review of the circumcision RCTs concluded that there was little potential for significant biases affecting the trial results given the large sample sizes, the balance of possible confounding variables and the employment of acceptable statistical early stopping rules [20]. There are two conclusions to be drawn: first, observational studies and surveys may draw inaccurate conclusions and second, medical male circumcision does significantly reduce the risk of HIV acquisition.

Effect of male circumcision on ulcerative STI

It has been previously suggested that the protective effect of circumcision on HIV may be mediated through a protective effect of circumcision on GUD [21-22], and a meta-analysis of observational studies suggested that circumcision reduces risk of genital ulcer diseases (GUD), including chancroid, syphilis, and, to a lesser extent, genital herpes [23].

The most common single cause of GUD worldwide is HSV-2 infection, a driver of the HIV epidemic [24]. Data from the RCTs now enable us to further investigate the associations of circumcision, GUD and HSV-2 infection [25]. Two of the trials have reported the impact of circumcision on HSV-2 acquisition, with both finding some evidence of a protective effect (South Africa: adjusted RR=0.68, 95%CI 0.38-1.22; Uganda: adjusted RR=0.72, 95%CI 0.56-0.92 [26-27]), and modelling of the South African data suggests that circumcision

decreased the probability of per-sex-act female-male transmission probabilities of HSV-2 by almost 40% (RR=0.59, 95%CI 0.36-0.91). However, preliminary data from the Kenyan RCT found no association of circumcision on HSV-2 incidence (RR=0.99, 95%CI 0.67-1.46) [25], suggesting that the effect of circumcision on HSV-2 incidence is less clear than its effect on HIV. This may be because HSV-2 is shed from a wider area of the female genital tract than HIV is more transmissible (and hence less dependent on the foreskin as a portal of entry).

The risk of self-reported GUD was significantly lower amongst circumcised men in the Kenyan trial (RR=0.53), and among both HIV-positive and HIV-negative men in the Ugandan trials (RR=0.63, 95%CI 0.5-0.8 and 0.59, 95% CI 0.50-0.69 respectively) [28-30]. In general, the associations seen are weaker and less consistent than the findings for the association with HIV infection, perhaps not surprisingly due to the likely low sensitivity and specificity of self-reports of symptoms of GUD at booked visits.

Synergy of male circumcision status, genital ulcer disease symptoms and HSV-2 infection on HIV incidence

In 1989, a cohort study of clients of sex workers in Nairobi found that uncircumcised men with GUD had almost twice the risk of HIV seroconversion as uncircumcised men without GUD (52.6% and 29.0% respectively over 3 months) [22]. Recent data from the Rakai RCT confirm this, and add HSV-2 infection status (Table 1) [30]. HIV incidence was highest among men who were uncircumcised, reported GUD symptoms, and had recently converted to HSV-2 (HIV incidence=9.88/100 pyr among men with all 3 of these). HSV-2 seronegative men were at lowest risk of HIV (<1/100 pyr) unless they were uncircumcised *and* reported GUD symptoms (incidence ~4/100 pyr). However, because of the low prevalence of GUD symptoms in the population (3.9%) a relatively small proportion of the effect of circumcision on HIV was due to symptomatic GUD (11.2%). Further, the low incidence of HSV-2 in this population meant that only 8.6% of HIV infections were estimated to be mediated through HSV-2 seroconversion, with wide confidence intervals (95%CI -1.2 to 77.7%). Finally, there was little effect of circumcision on HIV incidence among men who were HSV-2 positive at enrollment (adjusted RR=0.89, 95%CI 0.49-1.60) in the Rakai study suggesting that circumcision did not substantially reduce recurrences of genital herpes, and hence risk of HIV, in men with pre-existing HSV-2 infection. In contrast, circumcision did provide some protection against HIV infection among HSV-2 seroconvertors (adjusted RR=0.56, 95%CI 0.19-1.57).

In the South African trial, in which men were aged 18-24 years, HIV incidence was also highest among HSV-2 seroconvertors who were uncircumcised, but in contrast to the Ugandan data, there was a strong protective effect of circumcision regardless of HSV-2 status (negative, positive or seroconvertor) [26]. For example, the effect among those HSV-2 positive at baseline was 0.37 (95%CI 0.09-1.55) in the intention-to-treat analysis, similar to the effect in the Ugandan data when restricted to men aged 18-24 (adjusted RR=0.50, 95%CI 0.20-1.23). These results suggest that circumcision may have a stronger protective effect among younger men who have recently seroconverted to HSV-2 and are experiencing more frequent recurrences of genital herpes.

The data suggest that the protective effect of circumcision on HIV is largely direct, rather than through indirect protection against ulcerative GUD. However, circumcision does provide some protection against GUD and possibly HSV-2, and these factors are strongly associated with HIV incidence. The protective effect of circumcision on GUD among HSV-2 negative men suggests that circumcision protects against non-herpetic ulceration.

Male circumcision and HIV infection in women

Over time, expansion of male circumcision services will decrease HIV prevalence in men, and mathematical modelling confirms that women will benefit from expanded circumcision services through a lower risk of exposure to HIV infected men, especially in high HIV prevalence settings [31].

There is, however, relatively little evidence of a *direct* impact of male circumcision on risk of HIV infection in women. A RCT conducted in Rakai, Uganda randomised 922 HIV-infected men to either immediate or delayed circumcision [32]. Of these, 159 couples were enrolled and followed for at least one visit (mean follow-up time=1.3 years). The trial was stopped early due to the small number of female partners enrolled at the same time as the men, and evidence was inconclusive (hazard ratio=1.58, 95% CI:0.68-3.66) for HIV incidence in partners of circumcised versus non-circumcised men.

In the recently completed multicentre Partners in Prevention RCT of herpes suppressive therapy [33], 3408 HIV serodiscordant couples were recruited in 14 African sites. Among these, 1096 couples had a male HIV-positive partner and at least one follow-up visit of the female partner. Viral sequencing was used to determine whether incident HIV infections had occurred within the partnership. There was some evidence that the female partners of HIV-positive circumcised men were less likely to acquire HIV, although this was not statistically significant (adjusted RR=0.60, 95% CI 0.31-1.16). This finding is similar to that from the Rakai cohort study (adjusted hazard ratio=0.67, 95% CI 0.45-1.00) [34].

A systematic review estimated an overall 20% reduction in HIV incidence in female partners of circumcised, versus non-circumcised men [35]. However, this was largely based on observational studies, which are susceptible to biases, including misreporting of the male partners' circumcision status at time of infection. A definitive answer of any direct benefit of male circumcision on male-female HIV transmission would come from an RCT of circumcision among heterosexual HIV-positive men in discordant relationships, with viral sequencing for confirmation of source of infection, but such a trial is likely to be unfeasible for logistical reasons [35].

Of concern, the Ugandan RCT suggested a potential *increased* risk to female partners of HIV-positive circumcised men if sexual intercourse resumes before complete wound healing [32]. An increased risk during the healing period is biologically plausible, and highlights the need for careful pre- and post-circumcision counselling on the need for abstinence until full wound healing, followed by consistent condom use. Counselling is likely to be most effective if female partners are included where possible, and messages include full measures to protect female partners including condom provision, HIV counselling and testing, and risk reduction counselling. At a population-level, mathematical modelling shows that any

transient increased risk will have little population-level adverse impact due to the relative brevity of this healing period [31], but it would be useful to include rigorous monitoring and evaluation of expansion of male circumcision services to ensure that there are no adverse consequences for female partners of men who become circumcised.

Male circumcision and non-ulcerative STI in men and women

Table 2 summarises evidence from the RCTs on the effect of circumcision on non-ulcerative STIs. The strongest effect of circumcision was observed on *Trichomonas vaginalis* prevalence in the South African trial, where circumcised men were less likely to be infected at the final follow-up visit compared to uncircumcised men (adjusted odds ratio 0.53, 95%CI 0.28-1.02) [36] and a weaker effect on *Trichomonas vaginalis* incidence was seen in the Kenyan trial [37]. A reduced risk of *Trichomonas vaginalis* in wives of circumcised men was seen in the Ugandan trials of both HIV positive and negative men, along with a reduced risk of bacterial vaginosis in wives of HIV negative, but not positive, circumcised men [5, 32]. There is relatively little evidence of an effect of circumcision on *Chlamydia trachomatis*, and no evidence for an effect on *Neisseria gonorrhea* among men in the trials [36-37].

Finally, a strong effect of circumcision was also observed on the prevalence of human papillomavirus (HPV) at the final follow-up visit in both the Ugandan and South African trials [27, 38]. In both trials the prevalence of high-risk HPV (HR-HPV) isotypes was approximately 30-35% lower in the circumcised arm compared to control arm. The consistent findings of these trial results confirm a meta-analysis of observational studies which found that circumcised men were at significantly lower risk of HPV (OR=0.52, 95%CI 0.33-0.82) [39]. There are however, debates about possible detection bias [40] if samples are taken from sites which tend to have higher prevalence of HPV in HPV-infected circumcised, than HPV-infected uncircumcised men [41-43], such as the glans/corona (sampled in the Ugandan trial) or possibly the urethra (sampled in the South African trial). More generally, a lower risk of HPV prevalence among circumcised men could indicate that circumcision decreases either HPV incidence, or increases clearance rates. The few studies which have looked at this suggest that the impact of circumcision on HPV prevalence is more likely due to an impact on clearance than incidence [44-46]. Further work is needed to elucidate these findings, and the implications for lower risks of cervical and penile cancers.

Male circumcision and HIV infection in men who have sex with men

There is a growing body of literature on the impact of circumcision among MSM, as discussed in a recent comprehensive review [47]. One might expect little effect of circumcision on HIV transmission among MSM overall, as most infections occur through unprotected receptive penile-anal intercourse [48], and circumcision status of the receptive partner would not be expected to modify this risk. However, it is biologically plausible that circumcision provides partial protection against HIV and other STIs acquired through *insertive* penile-anal intercourse, through similar mechanisms as for penile-vaginal intercourse. Based on this, several recent studies have focused on the effect of circumcision among men who primarily engage in insertive anal sex [49-53]. These include the first study

from sub-Saharan Africa on circumcision and HIV risk among MSM [51], in which 378 men were recruited through respondent-driven sampling in Soweto, South Africa. In this population, 28% of MSM reported unprotected insertive anal intercourse in the past 6 months, and 85% reported ever having insertive anal intercourse. HIV prevalence was substantially lower among circumcised men than uncircumcised men (5.8% vs 17.3%; adjusted OR=0.2, 95% CI 0.1-0.2). However, in this sample the majority of men (84%) also had sex with women, so it is difficult to quantify any effect of circumcision on HIV transmission between men. Similar effects have been seen in Australia and Latin America [49-50] but not in the United States [52-54] among MSM who report to be exclusively or predominantly insertive.

Most studies have looked at whether circumcision protects against HIV or other STI in MSM regardless of insertive/receptive practice, and a systematic review and meta-analysis of 14 observational studies found little association of circumcision with HIV infection (OR=0.86, 95% CI 0.65-1.13) [55]. However, there was substantial heterogeneity of effect between these studies. A subgroup analysis restricted to studies conducted before widespread availability of highly-active antiretroviral therapy (HAART) found a significant association (OR=0.47, 95% CI 0.32-0.69; based on 3 studies). This may be a chance finding, or may be explained by increases in sexual risk behaviors of MSM after HAART, or a limited additional benefit of circumcision given lower viral loads of men on HAART. A meta-analysis of the association of circumcision with STIs other than HIV found little effect (OR=1.02, 95% CI 0.83-1.26, based on 7 studies).

Despite a lack of strong evidence for an effect of circumcision among MSM, a cost-effectiveness study of various circumcision strategies for HIV prevention among MSM in Australia found that circumcision could be cost-effective, assuming a 60% efficacy among insertive men and that 33% of men were insertive only, 57% insertive and receptive, and 10% receptive only [56]. However, results were very context-specific and sensitive to assumptions including a very high uptake of circumcision. The results of studies of the willingness of MSM to be circumcised vary. A 2008 study among MSM in 3 UK cities found that only 10% of uncircumcised men would be willing to participate in a research study on circumcision and HIV (McDaid, personal communication), and a similar question asked in China found that 17% of uncircumcised were 'absolutely' willing to participate in a trial [57]. In a US study 53% of uncircumcised MSM would be willing to be circumcised if it were proven to reduce HIV among MSM [58] (a different question to the UK and Chinese studies).

Current operational research issues of male circumcision for HIV prevention

Following the recommendations published by WHO/UNAIDS in 2007 [59], several countries in southern and eastern Africa began introducing or expanding safe male circumcision programs. Operational research studies have been designed to monitor key programmatic issues including the safety of the procedure, the effectiveness of counseling to minimize risk compensation (i.e. increased unprotected sex among circumcised men who perceive they have an 'invisible condom'), impact on sexual function and satisfaction, and

methods to match supply and demand of circumcision. In addition, a website has been created which acts as global resource centre of circumcision for HIV prevention and contains information on research, training and implementation of circumcision [60].

Safety of male circumcision

Common complications of male circumcision include bleeding, wound infection, and swelling. Circumcision is a more complex procedure in adolescents and adults than in infants, requiring suturing. In the trials, complications were observed in 2-7% of HIV-negative men [3, 61-62], and in 6-8% of HIV positive men [3, 62]. The majority of these were mild. In the Rakai and Kenyan trials, safety increased with number of surgeries performed by the physician. However, there is potential for a higher risk of complications outside of trial settings characterized by training, supervision and adequate resources [62]. A systematic review of circumcision complications amongst men in Anglophone Africa showed that prevalence of complications varied widely (from 0-24%). Most of these were minor, but these risks are still cause for concern [63]. A further review showed that circumcision was safest in neonates, and that the procedure can be associated with serious complications, especially when conducted by untrained providers, with inadequate equipment, or in unhygienic conditions [64]. For example, a study among 562 adolescents from the Babukusu ethnic group in western Kenya found that 18% of men had a complication when the procedure was performed by an untrained medical provider without adequate equipment, and 35% had complications when the procedure was performed traditionally [29]

To help ensure the provision of safe and efficient adult male circumcision services, national clinical protocols and quality assurance standards have been, or are being, developed; WHO/UNAIDS have produced guidelines on provision of safe circumcision [65-66]. As neonatal or infant circumcision is a simpler and safer procedure than adult circumcision, WHO/UNAIDS recommendations encourage countries to consider expanding services amongst infants as a longer-term HIV prevention strategy.

Sexual behaviour following male circumcision

There are concerns that post-circumcision risk compensation, i.e. increases in unsafe sexual practices, may occur if men and their partners perceive that circumcision provides complete protection from HIV infection. The trials found few differences in reported sexual behaviour by circumcision status [1-3]. Further, a recent pooled analysis of the three trials found that most newly circumcised men (over 95% in Kisumu and Rakai; 78% in South Africa) delayed sexual intercourse until after wound healing [67]. However, this may not reflect patterns of behaviour change during scale-up of circumcision for several reasons. Firstly, men enrolled in the trials did not have compelling evidence that circumcision reduced the risk of HIV. Furthermore, they received repeated behavioural counselling that may be difficult to replicate outside a trial setting in already over-stretched health services. Results from one study conducted outside a trial setting but prior to the trials results are promising. Among 648 men from Western Kenya, those who elected to be circumcised reported similar risky sexual behavior following the procedure compared to men who remained

uncircumcised [68]. It is reassuring that mathematical modelling suggests that if risk compensation is confined to newly or already circumcised men and their partners, there will be little impact on the population-level protective effect of circumcision [69]. However, the beneficial effect of circumcision could be reduced if risk behaviours increase across the entire population, including uncircumcised men and their partners [31]. Ongoing work is being conducted in the trial sites to monitor reported behavior during scale-up, including two studies in Nyanza region, one of which is following newly circumcised and uncircumcised men for 24 months, to monitor behavior, perceptions of HIV risk and sexual function and satisfaction, and the other is assessing community-level perceptions of circumcision and HIV risk up to 5 years after initiation of scale-up [70]. Similar studies might be useful, including work to evaluate optimal counseling strategies among men requesting circumcision, but also among men already circumcised, uncircumcised men, and their partners, and to assess the effectiveness of social change communication strategies aimed at reinforcing safer sex norms as male circumcision services are scaled up.

Sexual satisfaction and function

To our knowledge, there has not been a systematic review of the evidence of any impact of circumcision on sexual function. Observational studies of the effect of circumcision on sexual satisfaction and function tend to be small and subject to biases as adult men are often circumcised for medical reasons that affect sexual function. Data from the trials suggest no discernable impact of circumcision on sexual satisfaction and function. In the Ugandan trial, very high levels of satisfaction (>98%) were reported in both arms of the trial [71], and there was similarly no evidence that circumcision affected sexual satisfaction of the female partners [72]. Similarly, in Kenya, there was no difference in reported sexual function between circumcised and uncircumcised men, although circumcised men reported increased penile sensitivity and enhanced ease of reaching orgasm [73].

Cost-effectiveness of male circumcision for HIV prevention

As a one-off procedure requiring no ongoing user-adherence, male circumcision is likely to be a cost-effective HIV prevention strategy [69, 74]. The estimated cost per adult male circumcision is between \$30 and \$60, depending on the setting [75], with neonatal circumcision costing about a third of this. Models estimate a cost per HIV infection averted of between \$100 and \$400 in high HIV prevalence settings over a 20 year period [31]. Comparative modeling of the cost per HIV infection averted assuming 80% adult and newborn males were circumcised by 2015 showed a cost per HIV infection averted of \$US500 or less in six countries (Kenya, Lesotho, South Africa, Swaziland, Zambia and Zimbabwe). Given the costs of treatment, circumcising sexually active adult men is actually cost-saving, with potential net cost-savings of US \$20.2 billion between 2009 and 2025 [76]. In addition, circumcision provides protection against urinary tract infections in children [77] and other sexually transmitted infections in adults, so cost-savings are likely to be greater.

Scale-up of male circumcision services for HIV prevention

Thirteen Southern and Eastern African countries (Botswana, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia and

Zimbabwe) with high HIV prevalence, low levels of male circumcision and generalized heterosexual epidemics are WHO/UNAIDS priority countries for male circumcision scale-up and are moving forward at varying speeds to develop national programmes [78]. The progress of implementation of circumcision in these countries has recently been reviewed [79].

Key elements considered critical to male circumcision programme scale-up include: leadership and partnerships; situation analysis; advocacy; enabling policy and regulatory environment; costing and impact analyses, strategy and operational plans for national implementation; quality assurance and improvement; human resource development; commodity security; social change communication, and monitoring and evaluation. By the end of 2009, all thirteen countries had conducted situation analyses, were developing policies and strategies to guide scale up, and had conducted some initial training of providers on safe male circumcision. Botswana, Kenya, and Swaziland had begun to implement quality assurance programmes. Progress in the scale up of service provision has been slower than anticipated but experience is growing. For example, although by the end of October 2009 Kenya had completed over 40,000 circumcisions in the first year of scale-up [60], a further acceleration of pace occurred with the launch of a Rapid Results Initiative that saw over 36,000 circumcisions performed in 30 days (Zebedee Mwandu, personal communication). Other countries, including South Africa, Swaziland, Zambia and Zimbabwe, have set up some service delivery pilot programmes but these have not yet been scaled up nationally.

The most rapid progress has been in countries such as Kenya and Botswana where the Ministry of Health has taken leadership for programme scale-up and politicians have ‘championed’ the cause. These results suggest that country ownership and leadership make scale-up of programmes more likely to succeed.

Conclusions

Male circumcision is the only intervention to have proven efficacy against HIV infection in adults in multiple randomized controlled trials. This protection is only partial (approximately 60%) and therefore safe male circumcision services should also include services that promote and provide male condoms, STI management and safer sex counselling. These services should be integrated within existing HIV prevention programmes including strategies to strengthen community support for safer sex norms. As countries in southern and eastern Africa scale up services, operational research will be essential to iteratively improve programme delivery and impact while identifying the best methods of integrating safe male circumcision services into comprehensive HIV prevention strategies while strengthening health systems.

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Table 1
Effects of HSV2, circumcision status and GUD symptoms on HIV incidence in the Ugandan trial [30]

Rank	Status	HIV incidence per 100 pyr (95% CI)
1.	HSV2 seroconverter, uncircumcised, GUD symptoms	9.88 (2.7-25.3)
2.	HSV2 seroconverter, circumcised, GUD symptoms	6.45 (0.2-35.9)
3.	HSV2 seropositive, uncircumcised, GUD symptoms	4.25 (1.4-9.9)
		4.10 (0.8-11.9)
	HSV2 seropositive, circumcised, GUD symptoms	3.94 (1.1-10.1)
	HSV2 negative, uncircumcised, GUD symptoms	
4.	HSV2 seroconverter, uncircumcised, no GUD	3.13 (1.4-6.2)
5.	HSV2 seroconverter, circumcised, no GUD	1.95 (0.5-5.0)
6.	HSV2 seropositive, uncircumcised, no GUD	1.45 (0.9-2.3)
	HSV2 seropositive, circumcised, no GUD	1.37 (0.8-2.2)
7.	HSV2 seronegative, uncircumcised, no GUD	0.64 (0.4-1.0)
8.	HSV2 seronegative, circumcised, no GUD	0.26 (0.1-0.5)
	HSV2 seronegative, circumcised, GUD	0 (0-6.3)

Table 2
Impact of male circumcision on non-ulcerative STIs in the African RCTs

STI	Population	Trial	Ref	Outcome measure	RR	95%CI
Trichomonas vaginalis	HIV negative men	S Africa	[36]	Prevalence	0.53	0.28-1.02
		Kenya	[37]	Incidence	0.77	0.44-1.36
	HIV negative wives of HIV negative men	Uganda	[5]	Prevalence	0.52	0.05-0.98
	Wives of HIV positive men	Uganda	[32]	Prevalence	0.43	0.18-1.02
Bacterial vaginosis (BV)	HIV negative wives of HIV negative men	Uganda	[5]	Prevalence	0.80	0.71-0.89
Severe BV			[5]		0.31	0.18-0.54
BV	Wives of HIV positive men	Uganda	[32]	Prevalence	0.80	0.65-0.97
Chlamydia trachomatis	HIV negative men	S Africa	[36]	Prevalence	0.56	0.32-1.00
		Kenya	[37]	Incidence	0.87	0.65-1.16
N. Gonorrhoea	HIV negative men	S Africa	[36]	Prevalence	0.94	0.69-1.29
		Kenya	[37]	Incidence	0.95	0.68-1.34
High risk HPV	HIV negative men	S Africa	[38]	Prevalence	0.68	0.52-0.89
		Uganda	[27]		0.65	0.46-0.90