Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial

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Summary

Background **Ecological and observational studies suggest that male circumcision reduces the risk of HIV acquisition in men. Our aim was to investigate the effect of male circumcision on HIV incidence in men.**

Methods **4996 uncircumcised, HIV-negative men aged 15–49 years who agreed to HIV testing and counselling were enrolled in this randomised trial in rural Rakai district, Uganda. Men were randomly assigned to receive immediate circumcision (n=2474) or circumcision delayed for 24 months (2522). HIV testing, physical examination, and interviews were repeated at 6, 12, and 24 month follow-up visits. The primary outcome was HIV incidence. Analyses were done on a modified intention-to-treat basis. This trial is registered with ClinicalTrials.gov, with the number NCT00425984.**

Findings **Baseline characteristics of the men in the intervention and control groups were much the same at enrolment. Retention rates were much the same in the two groups, with 90–92% of participants retained at all time points. In the modified intention-to-treat analysis, HIV incidence over 24 months was 0·66 cases per 100 person-years in the intervention group and 1·33 cases per 100 person-years in the control group (estimated efficacy of intervention 51%, 95% CI 16–72; p=0·006). The as-treated efficacy was 55% (95% CI 22–75; p=0·002); efficacy from the Kaplan-Meier time-to-HIV-detection as-treated analysis was 60% (30–77; p=0·003). HIV incidence was lower in the intervention group than it was in the control group in all sociodemographic, behavioural, and sexually transmitted disease symptom subgroups. Moderate or severe adverse events occurred in 84 (3·6%) circumcisions; all resolved with treatment. Behaviours were much the same in both groups during follow-up.**

Interpretation **Male circumcision reduced HIV incidence in men without behavioural disinhibition. Circumcision can be recommended for HIV prevention in men.**

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Introduction

A number of ecological and observational studies, mainly from sub-Saharan Africa, have suggested that male circumcision reduces the risk of HIV infection in men.[1–5] A meta-analysis of cross-sectional and prospective studies estimated that the adjusted summary rate ratio of male HIV acquisition associated with circumcision in general populations was 0·56 (95% CI 0·44–0·70); in high-risk populations the adjusted summary rate ratio was 0·29 (0·20–0·41).[1] However, observational findings do not consistently show protective associations in all studies, and to exclude the possibility of confounding due to differences in sexual risk behaviours and cultural or religious practices associated with circumcision is difficult. Thus, the potential efficacy of circumcision for HIV prevention can be determined only by randomised trials. One randomised trial done in South Africa was ended early after an interim analysis showed that circumcision reduced HIV incidence by 60% (32–76).[6] Two other randomised trials, one in Kisumu, Kenya and the other in Rakai, Uganda—the results of which we report here—were also stopped early on December 12, 2006, after interim analyses showed significant efficacy.

Methods

Patients

Our aim was to enrol 5000 HIV-negative, uncircumcised men aged 15–49 years who agreed to receive their HIV results through voluntary counselling and HIV testing provided by the study, and who consented to be randomly assigned to receive circumcision within about 2 weeks of enrolment (intervention group), or to have circumcision delayed for 24 months (control group). Screening and enrolment was done in a central study facility and in mobile facilities in the rural communities. Before screening, participants were informed of study procedures and risks through verbal presentations, written materials, and an information video. After providing written informed consent for screening, a venous blood sample was obtained for HIV testing, and participants were given a physical examination. Men who had contraindications for surgery (eg, anaemia, active genital infection, or other health risks) were treated, and if their medical condition resolved, they were re-screened and were enrolled into the trial if eligible. Those with anatomical abnormalities (eg, hypospadias) were excluded and referred to the urologist (SW) for management. Men who had medical indications for surgery (eg, severe phimosis) were excluded from the

trial and were offered circumcision as a service. Men who were HIV positive or declined to receive their HIV results were enrolled in a complementary trial that will be reported separately.

Eligible participants were asked to provide an additional written informed consent for enrolment. The consent forms described the risks and benefits of participation, randomisation, and other trial procedures, and provided information on HIV prevention (sexual abstinence, monogamous relationships with an uninfected partner, or consistent condom use). At enrolment, participants completed a detailed questionnaire administered by a trained interviewer on sociodemographic characteristics, sexual risk behaviours, genital hygiene, and health. Participants were asked to provide a urine sample for future testing of sexually transmitted infections. Two subpreputial and shaft swabs were also obtained for future testing for human papillomavirus infection and other sexually transmitted infections.

Procedures

Participants were randomly assigned to the intervention or control groups as follows. Treatment assignment was randomly generated in blocks of 20, stratified on community, with each community receiving four blocks of 20 assignment envelopes. Because enrolment occurred concurrently at more than one community site, this procedure ensured balance within sites. 20 assignments in opaque envelopes were placed in batches, and participants were asked to select one envelope from the box. After an assignment envelope was selected, it was replaced by the next envelope from the next batch designated for that community. This procedure could and did result in some temporary imbalance between study groups, with a maximum potential run of 20 instead of the standard ten same-group assignments, but it ensured that all participants had the opportunity to select one of 20 envelopes. An alternative procedure was considered in which participants would select from each block of 20 envelopes without replacement, which would ensure that every 20 assignments within a site was perfectly balanced. However, this method was rejected because it would progressively reduce a participant's options for envelope selection.

HIV status at screening was assessed by two enzyme immunoassays: Vironostika HIV-1 (Organon Teknika, Charlotte, NC, USA) and Welcozyme HIV 1+2 (Murex Diagnostics, Dartford, UK). Men with concordant negative results were enrolled into the trial. Discordant results were confirmed by western blot (Cambridge Biotech HIV-1 western blot, Caltype Biomedical Corp, Rockville, MD, USA); men who were negative by western blot were enrolled.

Men randomly assigned to the intervention group were asked to provide written consent for surgery on the day of the procedure, and were again provided with detailed information on the procedure, postoperative wound care, and the need to abstain from intercourse until complete wound healing had been certified by a clinical officer (equivalent to a physician's assistant). Participants were offered an information sheet to share with their wives or partners, explaining wound care, hygiene, and the need to abstain from intercourse until wound healing was complete. Surgery was provided within 2 weeks of enrolment to 2255 (91%) of the men in the intervention group; the median interval from enrolment to surgery was 2 days and the maximum delay was 149 days.

Circumcisions were done by trained and certified physicians in well-equipped operating theatres with careful attention to asepsis. All instruments, drapes, and other materials were autoclaved and sterility was assured by use of thermologues (Comply, 3M Healthcare, St Paul, MN, USA) and biological indicators (BT Sure, Barnsead/Thermolyne, Dubuque, IA, USA). Participants showered preoperatively to clean the genital area. The skin was prepared with povidone-iodine before administration of local anesthesia via a dorsal penile nerve block with a mixture of lidocaine and bupivacaine. Circumcision was done with the sleeve procedure, in which the foreskin was retracted and a distal incision made 0·5–1·0 cm proximal to the coronal sulcus, followed by a proximal incision on the unretracted prepuce at the corona. The superficial lamina of Bucks fascia was exposed and a sleeve of foreskin was freed from the underlying Bucks fascia and removed.[7] Bleeding was controlled with bipolar electrocautery and skin edges apposed with 4-0 absorbable sutures. Men were kept under observation for 30–60 minutes before discharge. Men who lived close to the surgical facility returned home, whereas those men who lived distant from the facility were offered free overnight accommodation in a study facility to ensure access to care should short-term complications arise.

Postoperative follow-up visits were scheduled at 24–48 hours, 5–9 days, and 4–6 weeks. The first visit was done at the surgical clinic site; subsequent visits occurred in mobile clinics in the communities. Care was available for participants at any time between scheduled visits. Follow-up was done by clinical officers who were trained by the urologist to diagnose and treat complications or to refer patients as needed. Potential adverse events related to surgery were predefined and graded as mild (requiring no treatment), moderate (requiring treatment), or severe complications (requiring surgical intervention [eg, wound exploration for active bleeding, repair of wound dehiscence], hospitalisation, or referral for specialised care). At each postoperative follow-up visit, participants were questioned about symptoms suggestive of complications, and the wound was inspected. Participants were asked about resumption of sexual intercourse, and those who had resumed such activity were asked about condom use.

All participants in both groups were followed up at 4–6 weeks, and at 6, 12, and 24 months post-enrolment. At each follow-up visit, participants answered questions on sexual risk behaviours (marital and non-marital

partners, condom use, alcohol consumption with sexual intercourse, and transactional sexual intercourse [ie, sexual intercourse in exchange for money or gifts]) and symptoms of sexually transmitted diseases (genital ulcer disease, urethral discharge, or dysuria) since their previous visit. Men were questioned about illnesses or hospitalisations to record all adverse events that occurred during trial participation. Additionally, men were examined to assess circumcision status and to diagnose any penile pathology. Samples of venous blood and urine and two penile swabs were collected, and repeat HIV counselling and testing and health education were provided. Free condoms were offered to all sexually active participants at all study visits, and were also available through community-based condom depots stocked by the Rakai programme.

The procedure for HIV testing at each follow-up visit was the same as at enrolment. All seroconversions or discordant enzyme immunoassay results were further assessed by western blot. For participants who had undergone seroconversion during follow-up, the previous serologically negative sample and in selected cases the first positive sample were tested by reverse transcriptase (RT) PCR (Amplicor HIV-1 Monitor version 1.5, Roche Molecular Systems, Branchburg, NJ, USA).

The Rakai Health Sciences Program has an HIV treatment programme that is funded by the Presidential Emergency Fund for AIDS Relief. Participants found to be HIV positive at trial screening and those who subsequently became infected with HIV during the trial were referred to the HIV treatment programme. All individuals enrolled into the HIV treatment programme were provided with prophylaxis with sulfamethoxazole-trimethoprim, insecticide-impregnated bednets, and water purification. Those who were eligible for antiretroviral therapy (CD4 cell count less than 250 cells per µL or WHO advanced stage III or stage IV disease) and who agreed to receive care were provided with antiretrovirals. None of the HIV-infected participants from the trial were eligible for antiretroviral therapy at the time of going to press.

The protocol was reviewed and approved by the Prevention Sciences Research Committee of the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID), in the US National Institutes of Health (NIH), and by the Rakai community advisory board. The study was approved by three institutional review boards: the Science and Ethics Committee of the Uganda Virus Research Institute (Entebbe, Uganda), the Committee for Human Research at Johns Hopkins University, Bloomberg School of Public Health (Baltimore, MD, USA), and the Western Institutional Review Board (Olympia, WA, USA). The trial was done in accordance with the Good Clinical Practices and International Clinical Harmonisation guidelines with clinical trial monitoring done by Westat Corporation under a Division of AIDS, NIAID, NIH contract. The NIH Vaccine and Prevention Data Safety Monitoring Board oversaw the trial. Participants were compensated for their time, travel costs, and absence from work. Men received US$5 at screening and enrolment, $5 at the time of surgery, and $5 on completion of postoperative follow-up. Control participants who were circumcised at completion of their 24 months of follow-up received identical compensation. The amount of compensation for routine follow-up visits at 6, 12, and 24 months was $3 per visit. The community advisory board and institutional review boards approved this compensation as appropriate.

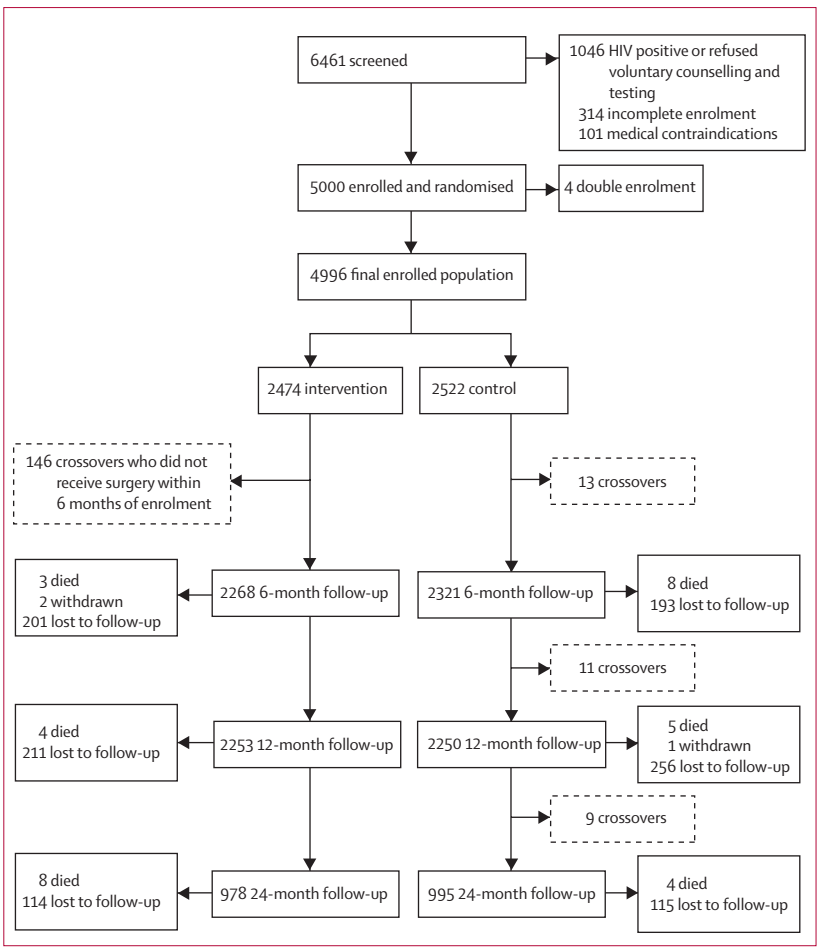

Figure 1: **Trial profile**

Statistical analysis

For incidence rate and Poisson regression calculations, HIV seroconversion was estimated assuming that

	Intervention group	Control group
6 months	2268/2469 (92%)	2321/2514 (92%)
12 months	2253/2464 (91%)	2250/2506 (90%)
24 months	978/1092 (90%)	995/1110 (90%)

Data are n/N (%). Percentages have been rounded.

Table 1: **Trial retention rates**

infection occurred at the mid-time point between the last negative and first positive serological tests, or at the time of the first positive RT-PCR for those participants seen during the period before HIV antibody seroconversion. For participants who were positive by PCR but who were negative for HIV antibody, the date of the positive PCR was used as the date of infection. In both groups, time from enrolment was accumulated up to the 24 month follow-up visit and HIV incidence was estimated per 100 person-years.

	Intervention group (n=2474)	Control group (n=2522)
Age (years)		
15–19	679 (27%)	719 (29%)
20–24	686 (28%)	686 (27%)
25–29	440 (18%)	473 (19%)
30–49	669 (27%)	643 (25%)
Marital status		
Never married	1161 (47%)	1222 (48%)
Currently married	1167 (47%)	1173 (47%)
Previously married	146 (6%)	127 (5%)
Religion		
Catholic	1649 (67%)	1730 (69%)
Protestant	667 (27%)	629 (25%)
Saved/Pentecostal/other	141 (6%)	146 (6%)
Muslim	17 (0·7%)	17 (0·7%)
Education		
No education	141 (6%)	147 (6%)
Primary	1631 (66%)	1669 (66%)
Secondary	603 (24%)	589 (23%)
Post-secondary	99 (4%)	116 (5%)
Number of sexual partners in the past year		
0	468 (19%)	494 (20%)
1	1152 (47%)	1168 (46%)
2	545 (22%)	586 (23%)
3+	309 (12%)	274 (11%)
Non-marital partners in the past year		
No	1220 (49%)	1238 (49%)
Yes	1254 (51%)	1284 (51%)
Condom use past year		
None	978 (40%)	941 (37%)
Inconsistent use	689 (28%)	732 (29%)
Consistent condom use	339 (14%)	355 (14%)
Alcohol use with sex in past 6 months	938 (38%)	966 (38%)
Transactional sexual intercourse*	38 (2%)	36 (1%)
Prior receipt of voluntary counselling and testing	648 (26%)	574 (23%)
Self-reported symptoms of sexually transmitted diseases in past year		
Genital ulcer disease	179 (7%)	176 (7%)
Urethral discharge	85 (3%)	94 (4%)
Dysuria	138 (6%)	162 (6%)

Data are n (%). Percentages have been rounded. *Sexual intercourse for money or gifts.

Table 2: **Enrolment characteristics, risk behaviours, and symptoms of sexually transmitted diseases by study group**

Exploratory analyses assessed the comparability of the two study groups at enrolment. HIV incidence during the trial was assessed by fixed covariates such as age, marital status, and education at enrolment, and by time-varying covariates such as sexual risk behaviours (eg, number of partners, non-marital relationships, condom use, and alcohol use), and symptoms of sexually transmitted diseases reported at follow-up visits. Men who were originally allocated to circumcision but who did not present for surgery within 6 months of enrolment were assessed as crossovers, as were individuals in the control group who opted to have circumcisions done outside the study.

We used a modified intention-to-treat approach for the primary efficacy analysis, which included all participants who were serologically or PCR negative at enrolment. Three participants who were PCR-positive but antibody negative at enrolment were deemed to have been infected before randomisation and were excluded from this modified intention-to-treat analysis. The primary modified intention-to-treat population included crossovers and participants who reported periods of sexual abstinence during the 24 months of follow-up. Incidence rate ratios (IRR) and 95% CI of HIV acquisition in the intervention versus the control group were estimated via exact methods, with Poisson multiple regression used for the adjusted analyses, including trend assessments. Because the trial was ended early, the Poisson analysis for the 0–24 month interval is weighted by the preponderance of person-time accrued during the first 12 months, and thus is a conservative estimate. Primary analyses adjusted for postulated potential confounders identified in previous studies in Rakai[8] and included baseline values of age, marital status, and sexual risk behaviours. Time varying covariates (eg, self-reported genital ulcer disease) could be in the causal pathway, so were not adjusted for during follow-up. We did an as-treated analysis that included control crossover participants who had received circumcision from outside sources, with person-time in the circumcised state ascribed to the beginning of the follow-up interval in which the surgery occurred. For crossovers in the intervention group who did not receive surgery, person-time was ascribed to the uncircumcised state from time of enrolment. Poisson multiple regression models were fit for the whole population and for strata of particular interest (eg, self-reported genital ulcer disease).

We did a Kaplan-Meier estimation based on analyses of time-to-detection of HIV infection at the visit at which positive serology or PCR was first identified. Due to the discrete nature of the timing of follow-up, data from visits were ascribed to the time of scheduled follow-up visits. An overall risk difference and risk ratios were calculated at the end of follow-up, with CI based on standard Greenwood formula variance estimates. The Kaplan-Meier risk ratios are not affected by the early trial closure, and this method was used in both other trials of male circumcision. Therefore, we present Kaplan-Meier risk ratios for comparative purposes.

To assess possible behavioural disinhibition, risk behaviours were tabulated by follow-up visit, and differences between study groups were assessed by χ^2 and Fisher exact tests. Symptoms of sexually transmitted diseases reported at each visit were cumulated over the 24 months of follow-up to estimate the prevalence of symptoms per 100 visits in intervention and control participants. Prevalence risk ratios (PRR) were estimated with log-binomial regression with a robust variance adjustment to account for within-person correlation. We also examined possible associations between reported symptoms of sexually transmitted diseases and incident HIV infection, by use of subgroup-specific models to determine whether any effects of circumcision on HIV incidence might be mediated by symptomatic sexually transmitted disease cofactors.

The frequencies of adverse events both related and unrelated to study participation were assessed in both study groups. Multiple adverse events diagnosed at a single visit were counted as separate events despite the fact that they could have been causally related (eg, wound dehiscence and infection), to provide an estimate of the maximum frequency of adverse events without making assumptions about causality.

The study had 80% power to detect a rate ratio of 0·5 for incident HIV in the intervention group relative to the control group, with a projected total person-time of 8993 person-years, assuming a 15% annual loss to follow-up and 10% crossover over 24 months. Formal statistical monitoring used the Lan-DeMets group sequential approach[9] with an O'Brien-Fleming type α spending function[10] to minimise the chance of inappropriate premature trial termination. Two interim analyses were done, the first with a data cutoff date of April 30, 2006, when about 43% of projected person-time had been accrued, and the second interim analysis with a data cutoff date of Oct 31, 2006, when about 72% of projected person-time had been accrued. The second interim analysis showed a significant difference in HIV incidence between the two study groups (nominal α=0·0215); as a result, NIAID terminated the trial for efficacy on Dec 12, 2006. The analyses presented here are based on all data accrued up to the time of trial closure in December, 2006, and encompass about 73% of total anticipated person-time. Results were deemed to be statistically significant at the α=0·05 level. All data were double entered. East was used for spending function calculations and Stata version 8 was used for analysis.

This trial is registered with ClinicalTrials.gov, with the number NCT00425984.

Role of the funding source

This trial was funded through a cooperative agreement with the Division of AIDS, NIAID/NIH. The study was done by the Rakai Health Sciences Program, a research collaboration between the Uganda Virus Research Institute, and researchers at Makerere University and Johns Hopkins University and Columbia University. FM, LHM, and MAC had full access to all the data until the trial closed. Thereafter, the principal investigator and co-investigators (RHG, GK, DS, MJW, FN, NKS, FWM, AND SJR) had access to all the data. Staff at the Division of AIDS maintained oversight of progress and reporting, and participated in study conduct and data interpretation as members of the study executive committee. Data analyses was done by the research teams at John Hopkins University and the Rakai Health Sciences Program. The corresponding author had final responsibility for preparing and submitting results for publication.

	Intervention group	Control group	Incidence rate ratio (95% CI)	p value
0–6 months follow-up interval				
Number of participants	2263	2319		
Incident events	14	19		
Person-years	1172·1	1206·7		
Incidence per 100 person-years	1·19	1·58	0·76 (0·35–1·60)	0·439
6–12 months follow-up interval				
Number of participants	2235	2229		
Incident events	5	14		
Person-years	1190·7	1176·3		
Incidence per 100 person-years	0·42	1·19	0·35 (0·10–1·04)	0·0389
12–24 months follow-up interval				
Number of participants	964	980		
Incident events	3	12		
Person-years	989·7	1008·7		
Incidence per 100 person-years	0·30	1·19	0·25 (0·05–0·94)	0·0233
Total 0–24 months follow-up				
Cumulative number of participants	2387	2430		
Cumulative incident events	22	45		
Cumulative person-years	3352·4	3391·8		
Cumulative incidence per 100 person-years	0·66	1·33	0·49 (0·28–0·84)	0·0057

Table 3: **HIV incidence by study group and follow-up interval, and cumulative HIV incidence over 2 years**

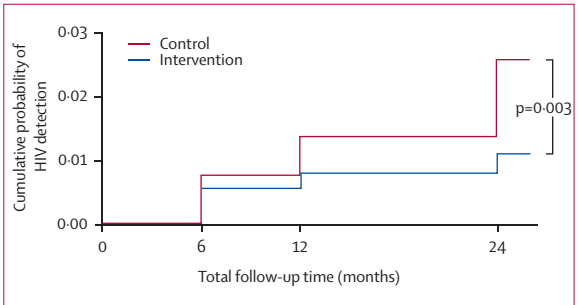

Figure 2: **Kaplan-Meier cumulative probabilities of HIV detection by study group**
Actual visits grouped by the three scheduled visits at 6 months, 12 months, and 24 months after enrolment. The cumulative probabilities of HIV infection were 1·1% in the intervention group and 2·6% in the control group over 24 months.

Results

Figure 1 shows the trial profile. 5000 eligible men were initially enrolled. However, during follow-up we discovered that four men (two in each study group) had re-enrolled under assumed names. For these individuals, the first enrolment record was retained in the dataset for the primary intent-to-treat analysis and the second enrolment was deleted, leaving 4996 enrolled participants. 146 (6%) participants in the intervention group did not come for surgery within 6 months of randomisation and

	Intervention group		Control group		Incidence rate ratio (95% CI)
	HIV incidence/ person-years	HIV incidence (cases per 100 person-years)	HIV incidence/ person-years	HIV incidence (cases per 100 person-years)	
Characteristics at enrolment					
Age (years)					
15–19	4/928·5	0·43	6/963·7	0·63	0·69 (0·14–2·92)
20–24	9/931·1	0·97	18/932·1	1·93	0·50 (0·20–1·17)
25–29	6/589·1	1·02	12/627·5	1·91	0·53 (0·16–1·53)
30–49	3/903·8	0·33	9/868·5	1·04	0·32 (0·06–1·28)
Marital status					
Never married	8/1575·5	0·51	18/1636·4	1·10	0·46 (0·17–1·12)
Currently married	10/1588·3	0·63	19/1582·4	1·20	0·52 (0·22–1·19)
Previously married	4/188·6	2·12	8/172·9	4·63	0·46 (0·10–1·71)
Education					
No education/primary	15/2385·3	0·63	32/2397·1	1·33	0·47 (0·24–0·90)
Secondary education	8/835·3	0·72	11/832	1·32	0·54 (0·16–1·60)
Post-secondary education	1/131·8	0·76	2/161·6	1·24	0·61 (0·01–11·78)
Behaviour and symptoms of sexually transmitted infections during follow-up					
Number of sexual partners					
0	3/590·3	0·51	3/661·8	0·45	1·12 (0·15–8·37)
1	14/1766·8	0·79	25/1720·3	1·45	0·55 (0·26–1·09)
2+	5/905·3	0·55	17/930·4	1·83	0·30 (0·09–0·85)
Type of relationship					
No non-marital relationships	15/2215·0	0·68	24/2251·9	1·07	0·64 (0·31–1·26)
Non-marital sexual partners	7/1047·5	0·67	21/1060·5	1·98	0·34 (0·12–0·82)
Condom use					
No condom use*	9/1233·1	0·73	14/1295·6	1·08	0·68 (0·29–1·56)
Inconsistent condom use*	7/939·4	0·75	21/885·7	2·37	0·31 (0·11–0·77)
Consistent condom use*	3/499·7	0·60	7/469·4	1·49	0·40 (0·07–1·76)
Alcohol use					
No alcohol use with sexual intercourse*	4/1315·7	0·30	14/1182·9	1·18	0·26 (0·06–0·82)
Alcohol use with sexual intercourse*	15/1356·5	1·11	28/1467·7	1·91	0·58 (0·29–1·12)
Transactional sexual intercourse					
No*	19/2633·9	0·72	41/2615·9	1·57	0·46 (0·25–0·81)
Yes*	0/37·7		1/34·7	2·88	0·00 (0·00–35·9)
Genital ulceration					
No genital ulcers	20/3153·1	0·63	33/3122·6	1·06	0·60 (0·33–1·08)
Genital ulcers	2/109·9	1·82	12/189·8	6·32	0·29 (0·03–1·29)
Urethral discharge					
No discharge	20/3198·3	0·63	39/3241·4	1·20	0·52 (0·28–0·91)
Urethral discharge	2/64·7	3·09	6/71·0	8·45	0·37 (0·04–2·05)
Dysuria					
No dysuria	20/3151·5	0·63	40/3203·0	1·25	0·51 (0·28–0·89)
Dysuria	2/111·5	1·79	5/109·4	4·57	0·39 (0·04–2·40)

*Among those sexually active in the follow-up interval.

Table 4: **Cumulative HIV incidence over 24 months by sociodemographic characteristics at enrolment, and behavioural characteristics and symptoms of sexually transmitted infections during follow-up**

	Intervention group		Control group		Prevalence risk ratio (95% CI)*	p value
	Episodes/number of visits	Rate (%)	Episodes/number of visits	Rate (%)		
Genital ulcer disease	168/5494	3·1%	322/5564	5·8%	0·53 (0·43–0·64)	<0·0001
Genital discharge	99/5494	1·8%	120/5564	2·2%	0·84 (0·63–1·11)	0·21
Dysuria	176/5494	3·2%	184/5564	3·3%	0·97 (0·77–1·21)	0·78

*Based on robust variance estimates adjusting for multiple observations on the same individuals

Table 5: **Prevalence of self-reported symptoms of sexually transmitted infections per visit, cumulatively over 24 months follow-up**

were classified as crossovers. Among the controls, 33 men were circumcised from other sources, a crossover rate of 1·3%. There were 15 deaths among participants in the intervention group over 3352·4 person-years and 17 deaths in the control group over 3391·8 person-years (4·5 deaths per 1000 person-years *vs* 5·0 deaths per 1000 person-years, p=0·8). None of the deaths were related to trial participation.

Trial retention rates are shown in table 1. All 1 year follow-up visits had been completed at time of trial termination, and retention rates at 12 months were equivalent in both groups. By December 12, 2006, the date of trial termination, 44% of men in both groups had reached their 24 month follow-up time point; retention rates for these men were much the same in both groups.

The baseline characteristics of the enrolled participants are shown in table 2. The two arms were much the same in terms of sociodemographic characteristics (age, marital status, religion, and education) and in sexual risk behaviours (number or partners, condom use, alcohol consumption with sex, and sex for money or gifts). At enrolment, previous receipt of voluntary counselling and testing was slightly higher in the intervention group than in the control group. The two groups reported similar rates of symptoms of sexually transmitted infections.

Table 3 shows HIV incidence by study arm and follow-up visit intervals, together with cumulative incidence over 2 years. The intention-to-treat analysis showed a progressive decrease in incidence in the intervention group over the entire follow-up period (p for trend 0·014). Incidence fell in the control group between the time of first follow-up and the time of second follow-up, and remained stable thereafter; however, the trend was not significant (p=0·6). The IRR of HIV acquisition associated with circumcision also fell over time; this increase in efficacy was of borderline significance (p=0·054 for the time-by-study arm interaction). The 24 month cumulative HIV incidence was 0·66 cases per 100 person-years in the intervention group, compared with 1·33 cases per 100 person-years in the control group. The unadjusted IRR was 0·49 (95% CI 0·28–0·84; p=0·0057). After adjustment for age, marital status, and sexual risk behaviours at enrolment, the IRR was 0·49 (0·29–0·81; p=0·003). Figure 2 shows the Kaplan-Meier survival curves for time-to-detection of HIV infection for the modified intention-to-treat analysis. The difference between the cumulative probabilities of HIV detection was significant (p=0·003) and the risk ratio was 0·43 (0·24–0·75). The as-treated Poisson analysis, which assigned person-time according to the actual circumcision status of participants, showed an incidence of 0·61 cases per 100 person-years in the intervention group (20 events in 3268·1 person-years), and 1·35 cases per 100 person-years in the control group (47 events in 3481·6 person-years) with an IRR of 0·45 (95% CI 0·25–0·78; p=0·0022). The as-treated Kaplan-Meier risk ratio was 0·40 (0·23–0·70, p=0·003).

Table 4 shows cumulative HIV incidence over 24 months by sociodemographic characteristics at enrolment, and by self-reported sexual risk behaviours and symptoms of sexually transmitted infections during follow-up. The rates of HIV acquisition were lower among circumcised men in all strata of characteristics, risk behaviours and symptoms of sexually transmitted infections examined, with the exception of those men who reported no sexual activity within the follow-up interval of seroconversion. HIV incidence was highest in the 25–29 year age-group, but in all age-groups, incidence was lower in the intervention than in the control group. Similarly, HIV incidence was lower in circumcised than in uncircumcised men in all categories of marital status and education. Among sexually active men, circumcision reduced HIV acquisition irrespective of the number of partners, non-marital relationships, condom use, consumption of alcohol before sexual intercourse, and transactional sexual intercourse. Men reporting symptoms of sexually transmitted diseases during a follow-up interval had higher rates of HIV acquisition than did asymptomatic participants, but the protective effects of circumcision were observed irrespective of the presence of such symptoms. However, circumcision was not protective against HIV acquisition in the few men who reported no sexual activity in a given follow-up interval. There were six incident cases (three in each group) during periods of reported abstinence. None of these six participants reported receipt of injections or transfusions during the follow-up interval of HIV seroconversion; these participants probably under-reported their sexual activity.

The prevalence rates of self-reported symptoms of sexually transmitted diseases reported at each follow-up visit, cumulated over 24 months, are shown in table 5. Over all study visits, the prevalence of self-reported genital ulcers during the preceding interval was lower in the

	Intervention group	Control group	p value
6 months follow-up (reference period 6 months since enrolment)			
Total number seen	2268 (100%)	2321 (100%)	
Number of sexual partners			0·1
0	467 (21%)	534 (23%)	
1	1263 (56%)	1223 (53%)	
2	407 (18%)	435 (19%)	
3+	131 (6%)	129 (6%)	
Non-marital partners*	697 (39%)	704 (39%)	0·8
Consistent condom use*	334 (19%)	295 (17%)	0·11
Inconsistent use*	662 (37%)	557 (31%)	0·0004
No condom use*	805 (45%)	935 (52%)	<0·0001
Alcohol use with sexual intercourse*	889 (49%)	981 (55%)	0·001
Transactional sexual intercourse*	29 (2%)	29 (2%)	1·0
12 months follow-up (reference period 6 months)			
Total number seen	2253 (100%)	2250 (100%)	
Number of sexual partners			0·4
0	437 (19%)	477 (21%)	
1	1249 (56%)	1201 (53%)	
2	463 (21%)	458 (20%)	
3+	103 (5%)	114 (5%)	
Non-marital partners*	699 (39%)	692 (39%)	0·9
Consistent condom use*	333 (18%)	323 (18%)	0·9
Inconsistent use*	533 (29%)	536 (30%)	0·6
No condom use*	949 (52%)	914 (52%)	0·7
Alcohol use with sexual intercourse*	962 (53%)	996 (56%)	0·06
Transactional sexual intercourse*	21 (1%)	17 (1%)	0·6
24 months follow up (reference period 12 months)			
Total number seen	978 (100%)	995 (100%)	
Number of sexual partners			0·8
0	131 (13%)	145 (15%)	
1	499 (51%)	498 (50%)	
2	247 (25%)	244 (25%)	
3+	100 (10%)	108 (11%)	
Non-marital partners*	335 (40%)	350 (41%)	0·7
Consistent condom use*	158 (19%)	160 (19%)	1·0
Inconsistent use*	332 (39%)	331 (39%)	0·9
No condom use*	356 (42%)	359 (42%)	0·9
Alcohol use with sexual intercourse*	429 (51%)	481 (57%)	0·02
Transactional sexual intercourse*	11 (1%)	12 (1%)	0·8

Date are n (%). *Among those who reported sexual activity in the follow-up interval.

Table 6: **Sexual risk behaviours by study group and follow-up visit**

intervention group than in the control group (3·1% *vs* 5·8%; PRR 0·53, 95% CI 0·43–0·64; p<0·0001). However, circumcision had little effect on the prevalence of urethral discharge or dysuria.

To assess possible behavioural disinhibition, sexual risk behaviours were assessed at each follow-up visit (table 6). During the first 6 month follow-up interval, sexual activity was reported by 1801 (79%) participants in the intervention group, compared with 1787 (77%) of those in the control group (p=0·049). Consistent condom use during this interval was slightly higher in the intervention group than it was in the control group (table 6; p=0·11). Similarly, inconsistent condom use was higher in the intervention group than it was in the control group (table 6; p=0·0004). At the 12 and 24 months follow-up visits, the number of sexual partners, non-marital relationships, and condom use were much the same in the two groups. However, participants in the control group reported slightly higher rates of alcohol use with sexual intercourse in all follow-up intervals than did those in the intervention group; this was significant at the 6 month (p=0·001) and 24 month (p=0·02) visits (table 6). Transactional sexual intercourse was infrequent and did not differ between study groups. There is, therefore, no consistent or substantial evidence of behavioural disinhibition after circumcision in the study population.

Adverse events unrelated to trial participation were frequent. 1391 adverse events were reported in the intervention group, compared with 1320 in the control group (56% *vs* 52%; p=0·083). Of these adverse events, 1213 (87%) in the intervention group were unrelated to the trial; all adverse events in the control group were unrelated to the trial. Almost half of the unrelated adverse events were mild grade 1 events (46% [n=558] of those in the intervention group and 50% [n=660] of those in the control group). The rate of all adverse events related to surgery in the intervention group was about 8% (178 events in 2328 surgeries); most of these events were mild (94 of 178 events). The rate of moderate adverse events related to surgery was about 3% (79 events in 2328 surgeries), and there were five severe adverse events, with a rate of 0·2 events per 100 surgeries. The severe adverse events included one wound infection, two haematomas that required re-exploration and ligation of active bleeding vessels, one wound disruption due to external cause, and one case of severe postoperative herpetic ulceration not involving the surgical wound requiring hospitalisation in the programme's facility. All moderate and severe adverse events were successfully managed and resolved.

Discussion

This large, randomised trial of adult male circumcision in a rural Ugandan population shows that such a surgical intervention reduces the risk of the acquisition of HIV in men. We noted a significant reduction in HIV incidence among circumcised men compared with uncircumcised control participants. The efficacy of circumcision for prevention of incident HIV was 51% in the Poisson intention-to-treat analysis; adjustment for enrolment characteristics, behaviours, and symptoms of sexually transmitted infections did not affect this estimate. In the as-treated Poisson analysis, efficacy was 55% and the Kaplan-Meier estimate of efficacy was 60%. These findings are compatible with observational data,[1–5] as well as data from a randomised trial in South Africa (60% intention-to-treat efficacy and 76% as-treated efficacy in a semi-urban population aged 18–24 years),[6] and a trial in Kenya (53% intention-to-treat efficacy

and 60% as-treated efficacy in an urban population, aged 18–24 years),[11] suggesting similar efficacy in widely divergent populations. Thus, circumcision must now be deemed to be a proven intervention for reducing the risk of heterosexually acquired HIV infection in adult men.

HIV incidence in the intervention group fell significantly over time, whereas it remained fairly constant in the control group, and the protective efficacy of circumcision increased progressively during later follow-up intervals (eg, 75% efficacy during the 12–24 month follow-up interval, table 3). The Kaplan-Meier curves for time to detection of HIV infection did not diverge until the twelfth month of follow-up, meaning that the difference in HIV acquisition began during the 6–12 month follow-up interval (figure 2). The HIV incidence in the control group (1·3 cases per 100 person-years), is identical to that seen in uncircumcised men in the Rakai population at the time the trial was done.[12] Also, 45% of HIV-negative uncircumcised men in the Rakai cohort volunteered to enroll in the trial, which suggests that the trial results are probably generalisable to the Rakai population as a whole. At the time of trial closure, 80% of eligible control participants who had completed 24 months follow-up agreed to be circumcised, suggesting high acceptability.

We did not find evidence that men in the intervention group adopted higher sexual risk behaviours than did those in the control group (table 6). This could have been due to the intensive health education provided during the trial to minimise risk compensation. These findings differ from those from the South African trial, which reported an increase in the mean number of sexual contacts in men in the intervention group.[6] Future circumcision programmes must emphasise that circumcision provides only part protection, and that there is a critical need to practise safer sex after circumcision (eg, partner limitation and consistent condom use).

Circumcision also reduced the rate of self-reported symptoms of genital ulcer disease with a cumulative efficacy of 48% over all follow-up visits (table 5), which is comparable with the protective effects of circumcision on genital ulcer disease in observational studies.[13] At this time, we cannot determine whether the procedure reduced the incidence of ulcerative infections due to syphilis, herpes simplex virus 2, and *Haemophilus ducreyi*, or whether removal of the prepuce reduced the severity, duration, or recurrence of ulceration, leading to lower recognition of symptoms. Since genital ulcer disease is a risk factor for the acquisition of HIV,[14–16] and symptomatic genital ulcer disease was associated with higher rates of HIV acquisition in this trial (table 4), it is plausible that the protective effect of circumcision on HIV could be mediated in part by the protective effects of the procedure on self-reported genital ulcer disease. By contrast, there was no effect of circumcision on symptoms of discharge or dysuria (table 5), which is consistent with data from observational studies that indicate a lack of an effect of circumcision on gonorrhoea or chlamydia prevalence.[3,17] The finding is biologically plausible since it suggests that circumcision could be protective against cutaneously acquired infections harboured in the moist subpreputial space, but the procedure does not seem to be protective against urethral infections, which presumably are unaffected by the removal of the foreskin.

That circumcision reduces the risk of male HIV infection is biologically plausible. The foreskin is rich in HIV target cells (Langerhans' and dendritic cells, CD4+ T cells, and macrophages),[18–21] and the inner preputial mucosa is unkeratinised, making it vulnerable to HIV infection.[20,22] The foreskin is retracted over the shaft during intercourse, which exposes the inner mucosa to vaginal and cervical fluids.[22] Also, breaches in the mucosa can occur due to microtears during intercourse, especially at the frenulum,[22] and uncircumcised men are more susceptible to genital ulcer disease, which could increase HIV entry.[13,22]

The 24 month transmission risks were 2·6% in the control group and 1·11% in the intervention group, giving a risk difference of 1·49%. Thus, assuming completion of 24 months of follow-up, we estimate that about 67 circumcisions are needed to prevent one HIV infection in the 2-year postoperative interval. However, this estimate does not include possible reductions in secondary transmissions to women or the probable long-term effectiveness of circumcision in men. Mathematical models have been used to estimate the number of surgeries required per HIV infection averted in both men and women over varying periods of time. In Rakai, a stochastic simulation model suggested that, with a circumcision efficacy of 50% and an HIV incidence of 1·3 per 100 person-years in uncircumcised men, the number of surgeries per HIV infection averted over 10 years was about 35, assuming all uncircumcised men accept the procedure.[12] In South Africa, with a circumcision efficacy of 60% and HIV incidence among uncircumcised men of 3·8 per 100 person-years, the number of surgeries per infection averted over 20 years is much lower.[23] Thus, the number of surgeries needed to prevent one HIV infection will vary depending on background HIV incidence, the level of acceptance, and the duration of projected protection. Policymakers will have to determine whether adult male circumcision is likely to be an appropriate and cost-effective intervention in specific settings. In the longer term, neonatal circumcision or circumcision of younger boys will provide a simpler, safer, and cheaper option, although the HIV benefits will be delayed until these boys reach sexual maturity.

Adult male circumcision is not without risk. In this trial the rate of moderate and severe adverse events related to surgery was almost 4%, which is comparable with rates in the South African and Kenyan trials.[6,9] One should note that there were cases in which appropriate follow-up management was required to prevent more serious sequelae. Furthermore, substantially higher complication rates have been reported when surgery is done in rural clinics or by traditional circumcisers.[24] The scale-up of

circumcision services will require careful attention to training of personnel, provision of facilities, equipment and supplies, postoperative care to minimise and manage complications, and monitoring of the quality of services and surgical outcomes.

The use of surgery for disease prevention is an unusual public-health intervention. One precedent is the mass sterilisation camps in India during the 1970s, which were poorly implemented and resulted in serious surgical complications, deaths, and ultimately the collapse of the programmes.[25,26] Thus, future provision of circumcision for HIV prevention must maintain the highest achievable levels of safety to be acceptable and sustainable.

The consistency of epidemiological evidence from three randomised trials and multiple observational studies presents a compelling case for the promotion of male circumcision for HIV prevention in populations where circumcision is infrequently practiced and where HIV transmission is mainly due to heterosexual intercourse. Such practice is especially relevant in east and southern Africa, where circumcision rates are low in many populations and the HIV epidemic is most severe. However, trials that are stopped early could overestimate efficacy when compared with subsequent studies[27] and to undertake long-term post-circumcision trial surveillance is essential to determine the effectiveness of circumcision in populations with varying HIV prevalence, and to assess the durability of any observed benefits. Furthermore, to assess whether perceptions of circumcision efficacy lead to an exaggerated belief in the protective effects of the procedure, thus engendering increases in HIV risk behaviours, will be important.

Contributors

All authors took part in the design, implementation, and analysis of this study and saw and approved the final version.

Conflict of interest statement

We declare that we have no conflict of interest.

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