Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial

Robert C Bailey, Stephen Moses, Corette B Parker, Kawango Agot, Ian Maclean, John N Krieger, Carolyn F M Williams, Richard T Campbell, Jeckoniah O Ndinya-Achola

Summary

Background **Male circumcision could provide substantial protection against acquisition of HIV-1 infection. Our aim was to determine whether male circumcision had a protective effect against HIV infection, and to assess safety and changes in sexual behaviour related to this intervention.**

Methods **We did a randomised controlled trial of 2784 men aged 18–24 years in Kisumu, Kenya. Men were randomly assigned to an intervention group (circumcision; n=1391) or a control group (delayed circumcision, 1393), and assessed by HIV testing, medical examinations, and behavioural interviews during follow-ups at 1, 3, 6, 12, 18, and 24 months. HIV seroincidence was estimated in an intention-to-treat analysis. This trial is registered with ClinicalTrials.gov, with the number NCT00059371.**

Findings **The trial was stopped early on December 12, 2006, after a third interim analysis reviewed by the data and safety monitoring board. The median length of follow-up was 24 months. Follow-up for HIV status was incomplete for 240 (8·6%) participants. 22 men in the intervention group and 47 in the control group had tested positive for HIV when the study was stopped. The 2-year HIV incidence was 2·1% (95% CI 1·2–3·0) in the circumcision group and 4·2% (3·0–5·4) in the control group (p=0·0065); the relative risk of HIV infection in circumcised men was 0·47 (0·28–0·78), which corresponds to a reduction in the risk of acquiring an HIV infection of 53% (22–72). Adjusting for non-adherence to treatment and excluding four men found to be seropositive at enrolment, the protective effect of circumcision was 60% (32–77). Adverse events related to the intervention (21 events in 1·5% of those circumcised) resolved quickly. No behavioural risk compensation after circumcision was observed.**

Interpretation **Male circumcision significantly reduces the risk of HIV acquisition in young men in Africa. Where appropriate, voluntary, safe, and affordable circumcision services should be integrated with other HIV preventive interventions and provided as expeditiously as possible.**

Lancet 2007; 369: 643–56

See **Editorial** page 615

See **Comment** page 617

See **Articles** page 657

See **Viewpoint** page 708

Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago, IL, USA (Prof R C Bailey PhD, Prof R T Campbell PhD); **Department of Medical Microbiology** (I Maclean PhD), **Community Health Sciences and Medicine** (Prof S Moses MD), **UNIM Project, Kisumu, Kenya and Department of Community Health Sciences** (K Agot PhD), **University of Manitoba, Winnipeg, Canada; RTI International, Research Triangle Park, NC, USA** (C B Parker DrPh); **Department of Urology, University of Washington School of Medicine, Seattle, WA, USA** (Prof J N Krieger MD); **Division of AIDS, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, USA** (C F M Williams PhD); **and Department of Medical Microbiology, University of Nairobi, Nairobi, Kenya** (Prof J O Ndinya-Achola MBchB)

Correspondence to:
Prof Robert C Bailey, Division of Epidemiology and Biostatistics, School of Public Health, University of Illinois at Chicago, 1603 West Taylor Street, Chicago, IL 60612, USA
rcbailey@uic.edu

Introduction

Although the availability of antiretroviral therapy for individuals infected with HIV is increasing worldwide, many more new infections are occurring for every additional person started on such treatment.[1] Prevention of new infections is the only realistic hope for stemming the HIV pandemic, yet currently available prevention measures have often been unsuccessful in restricting the spread of HIV, and there is little promise that an effective vaccine will be available within the next 15 years.[2] Effective new HIV preventive interventions are needed.

That male circumcision might reduce risk of HIV acquisition was first proposed in 1986.[3,4] Ecological studies have shown that, in regions where HIV transmission is predominantly heterosexual, the prevalence of HIV and of male circumcision are inversely correlated.[5–8] More than 30 cross-sectional studies have found the prevalence of HIV to be significantly higher in uncircumcised men than in those who are circumcised,[9] and 14 prospective studies all show a protective effect, ranging from 48% to 88%.[9–13] A systematic review and meta-analysis of studies from sub-Saharan Africa reported an adjusted relative risk of 0·42 (95% CI 0·34–0·54) in all circumcised men, with a stronger adjusted relative risk of 0·29 (0·20–0·41) in circumcised men who were at higher risk of acquiring HIV.[14] In a cohort study of Ugandan discordant couples in which the female was HIV infected and the male partner was initially HIV seronegative, 37 of 134 uncircumcised men versus none of 50 circumcised men became seropositive after about 2 years of follow-up.[15]

Biological studies suggest a plausible mechanism for this protection. The inner mucosal surface of the human foreskin, exposed upon erection, has nine times higher density of HIV target cells (Langerhans' cells, CD4+ T cells, and macrophages) than does cervical tissue.[16] The number of preputial target cells is increased in men with a history of recent sexually transmitted infections.[17] By contrast with the foreskin's inner surface, HIV target cells on the outer surface and the glans are protected by a layer of squamous epithelial cells.[16,18] In explant culture, several times more HIV-1 is taken up by Langerhans' cells and CD4+ T cells in foreskin than in cervical tissue; the virus does not infiltrate cells on the outer surface of the foreskin.[16] Other possible mechanisms by which the presence of the foreskin could lead to greater risk for HIV infection include poor hygiene,[19] greater incidence of ulcerative sexually transmitted infections,[20] and susceptibility of the foreskin to abrasions.[9]

Recently, a randomised controlled trial of male circumcision in 18–24-year-old men in Orange Farm,

South Africa, was stopped by the data and safety monitoring board when an interim analysis showed a 60% protective effect of circumcision in an intention-to-treat analysis, and a 76% protective effect in a per-protocol analysis that adjusted for crossovers. There were 20 HIV infections (incidence rate 0·85 per 100 person-years) in the circumcision group and 49 (2·1 per 100 person-years) in the uncircumcised group. Controlling for behavioural factors—eg, condom use, health-seeking behaviour, and sexual behaviour—the protective effect was much the same (61%).[21]

Upon announcement of the Orange Farm results in July, 2005,[22] the WHO and UN agencies issued a statement indicating that the evidence available up to that time for male circumcision having a protective effect against HIV infection was very promising, but that circumcision should not be promoted as a prevention strategy until results from this study, and a third trial in Rakai, Uganda, became available.[23] A Cochrane review had also cautioned against implementation of male circumcision as a preventive strategy in the absence of more data from clinical trials.[24]

Here we report the results of a randomised controlled trial of male circumcision in 18–24-year-old men in Kisumu, Kenya. Our aim was to determine the relative risk of HIV incidence in men randomly assigned to receive circumcision versus those who did not receive such treatment.

Methods

Participants

This trial was done in Kisumu district, Kenya. Kisumu is the capital city of Nyanza Province in western Kenya and has a population of about 500 000 residents.[25] Most residents self-identify as Luo, an ethnic group that does not traditionally practice circumcision. About 10% of Luo adult men in Kisumu are circumcised.[26] In 2003, HIV prevalence was about 25% in Luo women and 18% in Luo men.[27]

Participants were recruited via local newspapers, radio, fliers, and street shows by drama and musical groups. Recruitment began on Feb 4, 2002, and enrolment was completed on Sept 6, 2005. Public and private clinics were enlisted to refer patients with sexually transmitted infections, and peer outreach workers recruited participants from local youth organisations. Enrolled participants were each given up to three coupons valued at US$1·25 for every peer they recruited for initial screening. Potential participants were initially asked their residence, willingness to be tested for HIV, and proof of age. They were then seen privately by trained counsellors for HIV testing and counselling, verification of circumcision status, haemoglobin concentration, whether they were sexually active in the previous 12 months, and intention to remain in the area for at least 2 years. HIV-seropositive men were referred to a post-test counselling and support group established and supported by the project. Those individuals who were eligible were further informed about the trial, given a comprehensive consent form to read and study in any of three languages (English, Dholuo, and Kiswahili), and asked to return 2 days or more later. At the second screening visit, counsellors went through the consent form in detail. Participants who provided written informed consent had a medical examination, and a questionnaire was administered to assess sexual risk behaviours; blood was drawn and urine was collected for laboratory tests and repository; and urethral or penile swabs were taken if urethral discharge or genital ulcers were present. Participants with sexually transmitted infections or other treatable medical conditions were deferred until treated. Inclusion and exclusion criteria are listed in the panel. Participants were offered 300 Kenyan shillings (about $4) for each scheduled study visit to cover travel expenses and loss of income.

The research protocol was reviewed and approved by the Kenyatta National Hospital ethics and research committee, the University of Illinois institutional review board number three, the University of Manitoba biomedical research ethics board, the Research Triangle Institute institutional review board number one, and the University of Washington institutional review board. An advisory board of Kisumu community members from diverse backgrounds met about four times a year to advise the research team on conduct of the trial. The National Institute of Allergy and Infectious Diseases (NIAID) contracted WESTAT (Rockville, MD, USA) as the clinical site monitor for the trial. Monitoring visits occurred about three times per year. The NIAID vaccine and prevention data and safety monitoring board initially reviewed the protocol; periodically reviewed enrolment, data quality, adverse events, protocol deviations, and outcome measures; and gave advice based on results of interim analyses.

***Panel:* inclusion and exclusion criteria**

Inclusion criteria
Uncircumcised
HIV negative
Sexually active
Aged 18–24 years
Resident of Kisumu district
No plans to move for at least 2 years
Consent to participate
Haemoglobin 90 g/L or more

Exclusion criteria
Foreskin covers less than half the glans
Haemophiliac or other bleeding disorder
High prothrombin time index
Other medical condition contraindicating surgery
Absolute indication for circumcision

Procedures

Participants who met the study criteria were randomly assigned to either the intervention (circumcision) group or the control (delayed circumcision) group after being questioned to ensure their understanding of all study procedures and requirements for participation. Randomly permuted blocks of size 10 and 20 within age-groups of 18–20 years and 21–24 years were used to ensure approximately equal sample sizes in the two study groups within age strata. An opaque envelope system was used. The age stratum, the envelope number, and a randomisation identification number were printed on the outside of all envelopes. When a participant was ready for randomisation, the next envelope (based on envelope number) for the participant's age stratum was selected and the study coordinator wrote the participant's identification number on the outside of the envelope. The envelope was then opened by the participant and he read the assignment—circumcision or control—himself, in the presence of the study coordinator and one other staff member. The data coordinating centre routinely checked randomisation reports to validate compliance with the procedure. Men assigned to the circumcision group were scheduled for surgery the same day or shortly thereafter. Those assigned to the control group were asked to remain uncircumcised until the end of their 24 months of study participation, at which time they were offered circumcision at the study clinic.

All surgeries were done under local anaesthesia in the study clinic by study clinicians, using the standardised forceps-guided method described by Krieger and colleagues.[28] Participants were given verbal and written instructions on postoperative wound care, and were encouraged to come to the clinic or contact a study clinician at any time with medical problems. Postcircumcision visits were scheduled for 3, 8, and 30 days to check the wound, record any complications, and ask about sexual activity, level of pain, resumption of normal activities, and satisfaction with the procedure. Participants were counselled to refrain from sexual activity for at least 30 days after the procedure. Adverse events were assessed at every visit and classified as not related or possibly, probably, or definitely related to the surgical procedure. Severity was recorded as mild, moderate, or severe. All adverse events deemed to be possibly, probably, or definitely related to surgery were reviewed by more than one clinician. Regular case reviews were done with a local surgeon and the consultant urologist (JNK).

At each study visit—1, 3, 6, 12, 18 and 24 months after randomisation—all participants received HIV counselling and testing, underwent a genital examination to check circumcision status, and were asked questions about sexual activity. Follow-up was defined as incomplete with respect to HIV status if the participant had not been followed to seroconversion and a follow-up visit had been missed. Visits were deemed to be missed if 6 weeks late for the 1 month visit, 2 months late for the 3 month visit, or 5 months late for the 6, 12, 18, or 24 month visits.

At months 6, 12, 18, and 24, blood and urine were collected for diagnostic testing for sexually transmitted infections and repository, and an extensive questionnaire was administered to assess sexual function and behavioural factors associated with HIV infection. The nurse-counsellors who did the HIV testing and administered the questionnaire were blinded to study group, unless the participant divulged his circumcision status during counselling. All participants were provided free medical treatment throughout their 24 months of follow-up. Individually tailored risk reduction counselling occurred at every visit. Men who tested positive for a sexually transmitted infection were treated, received additional counselling, and were given a coupon for their sexual partner to receive free treatment at a neighbouring public clinic. Incident HIV-positive men were referred to the project's post-test counselling and support group and provided access to free HIV treatment and care. Condoms were provided free of charge to all men and their partners.

HIV serostatus and timing of seroconversion were determined as follows. If a participant was double positive or discordant on two rapid tests with the synthetic peptide test Determine HIV 1/2 (Abbott Diagnostic Division, Hoofddorp, Netherlands) and the recombinant antigen test Unigold Recombigen HIV Test (Trinity Biotech, Wicklow, Ireland) taken from the same fingerprick sample, then serum was drawn and sent to the International STD/HIV Collaborative Group laboratory at the University of Nairobi for double ELISA (Detect HIV 1/2, Adaltis Inc, Montreal, Canada, and Recombigen HIV 1/2, Trinity Biotech, Wicklow, Ireland). Results were available within 1 week. Participants were deemed to be confirmed positive if the ELISA tests were both positive. Two negative ELISA tests were considered negative; discordant ELISA tests were considered indeterminate and the participant was asked to return for additional testing 1–6 months later, depending on the visit. For purposes of determining serostatus for analysis of study data, blood specimens from all participants who tested positive on at least one rapid test and one ELISA test were sent to the Health Canada National HIV Reference Laboratory (Ottawa, Canada) for confirmatory testing by line immunoassay (INNO-LIA HIV 1/2, Immunogenetics NV, Ghent, Belgium). Specimens indeterminate by line immunoassay were tested by PCR at Health Canada or the Fred Hutchinson Cancer Research Center (Seattle, WA, USA), with the PCR result deemed to be definitive. Any participant confirmed as positive at a follow-up visit had his baseline specimen tested at the Health Canada laboratory to ascertain HIV serostatus at enrolment. Participants who had a confirmed positive test at the month 3 follow-up visit had their month 1 specimen tested by PCR. The HIV seroconversion visit was judged to be the first visit at which the participant had at least

one positive HIV rapid test and was confirmed as being HIV positive at the same or a subsequent visit according to the above procedure.

Statistical analysis

A target sample size of 2776 (1388 in each group) was set to detect a 50% difference in 2-year HIV seroincidence between the treatment groups, assuming a 15% non-informative loss-to-follow-up, 5% non-adherence to treatment assignment in either direction, 2·5 per 100 person-years annual HIV seroincidence in the control group, overall type I error rate of α=0·05 (two-sided), and 80% power. Two interim analyses and a final analysis were planned. Three interim analyses were done. The first used data accumulated through April 17, 2005, with about 37% of the potential follow-up experience accrued. This first analysis was assessed at α_1=0·000518 with the O'Brien and Fleming bound. The second analysis used data through May 13, 2006, with about 74% of the follow-up experience. The Lan and DeMets[29] spending function that preserves the O'Brien and Fleming bound while accounting more directly for the follow-up was used, and the bound for this second look at the data was α_2=0·0183. A third, unscheduled analysis was done at the request of the data and safety monitoring board using data through October 31, 2006, with about 87% of the follow-up experience accrued. By use of the same Lan and DeMets spending function, the stopping boundary for this third interim analysis was α_3=0·0269, and this boundary was crossed. On the recommendation of the data and safety monitoring board, the trial was stopped by the sponsor on December 12, 2006.

Data were recorded on paper forms and were then entered into a database at the study site via a customised data management system developed by the data coordinating at RTI International that included: data editing during data entry; tracking protocol visits and required forms; automated back-up and transmission processes; and system and database access security. Data were transmitted via the internet every night to the data coordinating centre. The coordinating centre did additional longitudinal data checks and posted queries on a study website for the clinic staff in Kisumu to review and to make corrections as appropriate. About 5% of study forms were re-keyed per month for quality assurance. The error rate at the item level was 0·3%.

The Kaplan-Meier[30] method was used to estimate the HIV event distribution over time by treatment, accounting for staggered enrolment and incomplete, discrete follow-up. The time of HIV-positive status was credited to the follow-up visit when HIV was first detected. HIV-negative participants were censored in the analysis at the last regular follow-up visit completed where HIV status was ascertained. Estimates of 2-year HIV seroincidences and corresponding standard errors obtained by Greenwood's formula[31] were used to test for differences between the treatments on the primary outcome (HIV seroconversion). The primary analysis was by intention-to-treat; participants were included in the analysis in the group to which they were randomly assigned and all participants with follow-up for HIV status were included in the analysis.

A secondary analysis, that used the same statistical approach described above, excluded participants subsequently confirmed as HIV positive by PCR at baseline, and one further analysis excluded those confirmed positive at either baseline or at 1 month. Furthermore, an as-treated analysis was done with a time-dependent covariate in a Cox regression model[32,33] for circumcision status at each follow-up visit to take into account those individuals who did not adhere to their randomisation assignment; in this analysis, a time-dependent variable for the circumcision status of each participant at each follow-up visit was constructed and included as a single time-dependent predictor variable in a Cox regression model with all participants. Thus, irrespective of treatment assignment, participants were accounted in this analysis as they were treated with respect to circumcision. Cox regression models with fixed covariates were used to consider various baseline adjustments to the treatment effect. Age-group and variables that seemed to be slightly imbalanced were used—ie, ethnic group, occupation, infection with herpes simplex virus type 2, and infection with *Chlamydia trachomatis*. These variables were considered independently for association with HIV incidence, then singly, as adjustments to the treatment effect. Finally, the set of variables was included in a model as an adjustment to the treatment effect.

All hazard or risk ratios were estimated with the parameter estimates from Cox regression. An exact method for computing the likelihood was specified to handle ties.

Behavioural outcomes were assessed in longitudinal analyses with the generalised estimating equations extension of generalised linear models proposed by Liang and Zeger.[34] Outcomes are binary, and for each specific outcome, the logit was modelled as a linear function of treatment, visit (month 0, 6, 12, 18, and 24) and the interaction of treatment and visit. The baseline response was included in the longitudinal stream. Visit was treated as a categorical variable and follow-up visits were compared with baseline. The interaction terms tested differences between treatment groups in change from baseline. Testing included an overall test of difference by treatment in the changes from baseline (four degrees of freedom test: month 6, 12, 18, and 24), and a test for difference by treatment in the specific change from baseline to month 24 (one degree of freedom test). No adjustment was made for multiple tests. The p values reported are those associated with Wald statistics, with empirical standard errors. The working correlation between measurements at any two follow-up times was specified as constant.

In addition to the methods used for the primary outcome and the behavioural outcome measures, the significance of

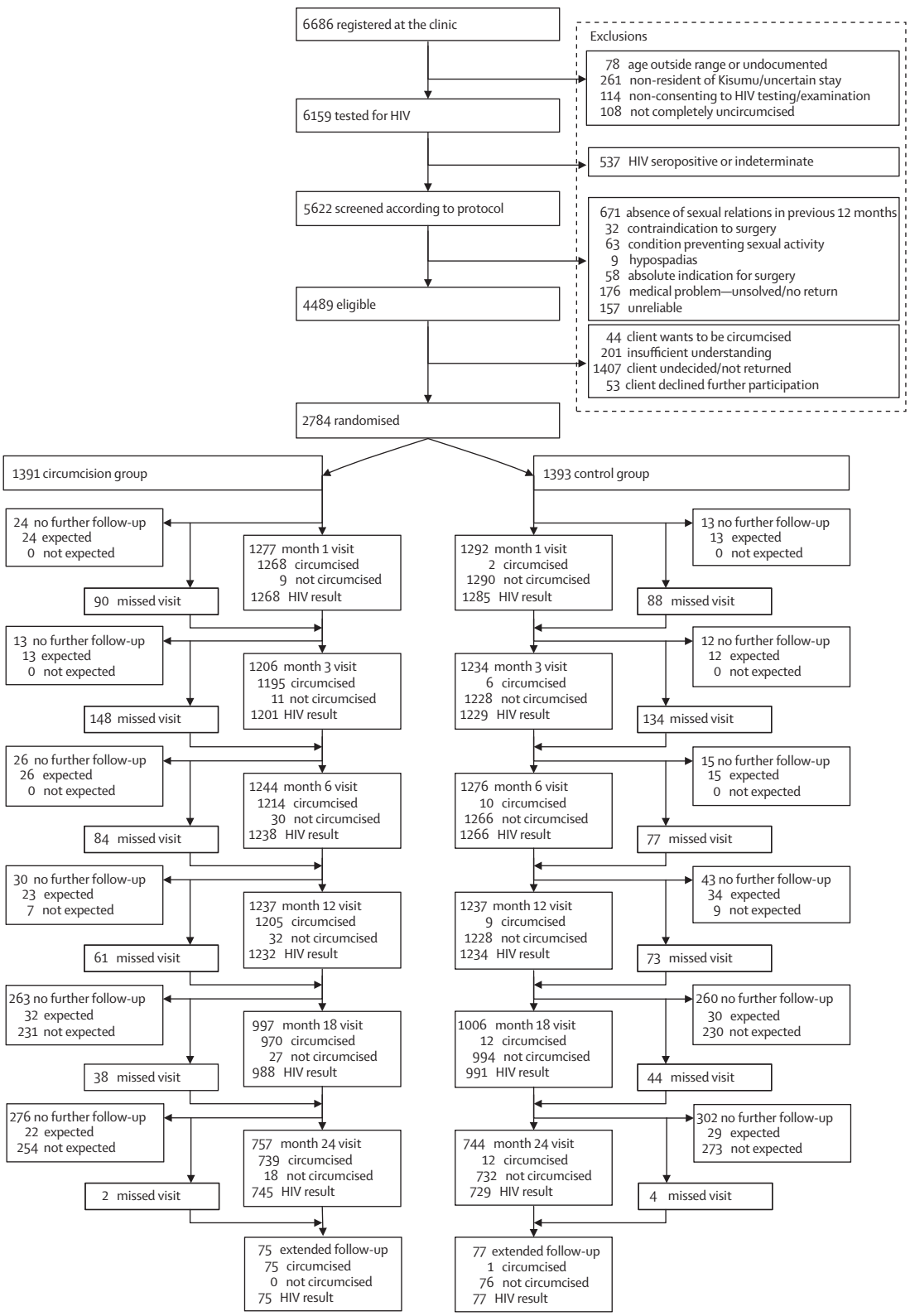


Figure 1: **Trial profile**
Because the exclusion categories were not mutually exclusive, exclusions might add up to more than the total number of individuals excluded. For each follow-up visit, participants with no further follow-up were classified as "expected" if they were eligible for that study visit but passed the window period and did not return for a subsequent visit. Those classified as "not expected" are those whose participation was truncated due to closure of the database on Oct 31, 2006. From March, 2006, participants who remained on study were invited to participate in an extended follow-up, beginning with 30 month visits in August, 2006. Numbers with extended follow-up visits are shown. Data from these visits could contribute outcome information (eg, negative status for HIV) accountable to previous visits for which no HIV test was available.

differences between groups was assessed with Fisher exact tests or χ^2 tests for proportions, Wilcoxon-Mann-Whitney tests for continuous and ordinal distributions, and log-rank tests for time-to-event distributions. All analyses are based on data available through Oct 31, 2006. All p values reported are two-sided. Analyses were done with SAS versions 8.2 and 9.1.

This trial is registered with ClinicalTrials.gov, with the number NCT00059371.

Role of the funding source

This trial was funded through a cooperative agreement with the Division of AIDS, NIAID/NIH and a grant from the Canadian Institutes for Health Research. The NIAID prevention and science review committee required minor revisions to the protocol. Only C B Parker had full access to all the data until the trial closed. Thereafter, the principal investigator and all co-investigators 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. RC Bailey had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 6686 men initially came to the study clinic; 6159 (92%) met preliminary criteria. Of these, 478 (8%) were HIV seropositive, 59 (1%) were of indeterminate HIV status, and 5622 (91%) were seronegative. Of the seronegative individuals, 1133 (20%) were excluded for other reasons. Thus 4489 individuals were eligible for randomisation. Of these, 1407 were undecided or did not return for randomisation, 53 declined further participation, 201 were considered to have insufficient understanding of the protocol, and 44 wanted to be assigned to the circumcision group only. Thus, 2784 men were randomised: 1391 to the treatment (circumcision) group and 1393 to the control group.

The median age of the 2784 randomised participants was 20·0 years (IQR 19–22); of these individuals, 2739 (98%) identified themselves as Luo (table 1). Two-thirds (n=1837) had greater than a primary education and 1793 (64%) were unemployed. Most men identified themselves as unskilled workers, farm labourers, or fishermen (n=1653, 59%); 632 (23%) were students. Only about 7% reported being married or living with a partner. The treatment groups were much the same at baseline in terms of demographic characteristics, physical characteristics, prevalence of sexually transmitted infections, and reported sexual history with women. Six men reported having sexual intercourse with another man, five of whom were in the circumcision group. All six of these men also reported having sexual intercourse with women. 37 participants did not return for any subsequent visits after assessment at baseline (24 in the circumcision group and 13 in the control group) and contributed no information to the primary outcome analysis.

The median timing for the month 1 post-randomisation visit was 31 days (IQR 30–32); it was 92 days (91–93) for month 3, 184 days (182–189) for month 6, 365 days (365–371) for month 12, 549 days (547–560) for month 18, and 732 days (730–741) for month 24. There were no differences in the timing of the follow-up visits by group. The median length of follow-up was 24 months (18–24). 16 men withdrew themselves from the study before their month 24 visit: 15 (1%) in the circumcision group and one (0·1%) in the control group. The reasons given for withdrawal were: unable to come for visits (n=4), unhappy with waiting time at the clinic (5), randomised to circumcision (2), and no reason expressed (5). Withdrawals occurred between 0–1 months (n=3), 1–3 months (3), 3–6 months (3), 6–12 months (2), 12–18 months (4), and 18–24 months (1). Four men died of causes unrelated to participation in the study (two in each group), and three men (two in the circumcised group and one in the control group) were uncooperative and withdrawn by the study team. Of the 1738 participants randomised at least 24 months plus 2 weeks earlier, 1501 (86%) had completed 24 months follow-up at the time of analysis. For earlier study visits the number of follow-ups and percentages among participants reaching the time lapse since randomisation were: 2569 (92%) for month 1, 2440 (88%) for month 3, 2520 (91%) for month 6, 2474 (89%) for month 12, and 2003 (87%) for month 18. Overall, follow-up for HIV status was incomplete for 240 (8·6%) participants: 126 (9·1%) in the circumcision group and 114 (8·2%) in the control group. There were no significant differences in the event distribution with time for the missed visits. The 240 participants with incomplete information on HIV status were more likely to have some secondary education or above than the 2544 participants with complete information (76% *vs* 65%, p=0·0006). Otherwise the two groups were much the same.

Few controls (n=16, 1%) were non-adherent to treatment assignment and became circumcised during the study. Of participants randomised to circumcision, 886 (64%) had their procedures on the day of randomisation, 1116 (80%) within 1 day, 1231 (88%) within 3 days, and 1322 (95%) within 6 weeks. In total, 1334 (96%) of the participants randomised to circumcision were circumcised. There were no differences at baseline between the 69 men who did not adhere to circumcision treatment within 6 weeks of randomisation and the 1322 who did, except that 10% (7) of those who did not receive circumcision were married and living with their wife versus just 5% (64) of those who did.

During the study, seroconversion occurred in 22 participants in the circumcision group and 47 of those in the control group. The 2-year HIV incidence was 2·1% (95% CI 1·2–3·0) in the circumcision group and 4·2% (3·0–5·4) in the control group (p=0·0065); combined, it was 3·1% (2·4–3·9). Figure 2 shows the Kaplan-Meier estimates of the cumulative incidence of HIV for the 24 months of follow-up; incidence for

	Circumcision group	Control group	Overall
Demographic characteristics			
Age (years)	20 (19–22; 18–28; 1391)	20 (19–22; 17–24; 1393)	20 (19–22; 17–28; 2784)
Ethnic group			
Luo	1361 (98%)	1378 (99%)	2739 (98%)
Other	30 (2%)	15 (1%)	45 (2%)
Education level			
Less than secondary	468 (34%)	479 (34%)	947 (34%)
Any secondary or above	923 (66%)	914 (66%)	1837 (66%)
Employment status			
Employed and receiving a salary	128 (9%)	134 (10%)	262 (9%)
Self-employed	374 (27%)	355 (25%)	729 (26%)
Unemployed	889 (64%)	904 (65%)	1793 (64%)
Occupation			
Professional/managerial	25 (2%)	39 (3%)	64 (2%)
Skilled worker	141 (10%)	113 (8%)	254 (9%)
Semi-skilled worker	95 (7%)	86 (6%)	181 (7%)
Unskilled worker	698 (50%)	758 (54%)	1456 (52%)
Farm labourer/fisherman	107 (8%)	90 (6%)	197 (7%)
Student	325 (23%)	307 (22%)	632 (23%)
Marital status			
Not married (no live-in partner)	1296 (93%)	1291 (93%)	2587 (93%)
Not married (with live-in partner)	9 (0·6%)	11 (0·8%)	20 (0·7%)
Married (not living with wife)	11 (0·8%)	19 (1%)	30 (1%)
Married (living with wife)	71 (5%)	65 (5%)	136 (5%)
Physical and laboratory findings			
Weight (kg)	63 (59–68; 42–91; 1391)	62 (58–67; 40–100; 1392)	63 (59–67; 40–100; 2783)
Haemoglobin (g/L)	154 (143–163; 90–199; 1386)	153 (142–164; 83–201; 1391)	153 (142–163; 83–201; 2777)
Herpes simplex virus 2			
Positive	405 (29%)	363 (26%)	768 (28%)
Negative	980 (71%)	1029 (74%)	2009 (72%)
Syphilis			
Positive	19 (1%)	9 (0·6%)	28 (1%)
Negative	1369 (99%)	1379 (99·4%)	2748 (99%)
Trichomonas vaginalis			
Positive	27 (2%)	31 (2%)	58 (2%)
Negative	1351 (98%)	1350 (98%)	2701 (98%)
Neisseria gonorrhoeae			
Positive	32 (2%)	25 (2%)	57 (2%)
Negative	1342 (98%)	1355 (98%)	2697 (98%)
Chlamydia trachomatis			
Positive	73 (5%)	55 (4%)	128 (5%)
Negative	1300 (95%)	1325 (96%)	2625 (95%)
Haemophilus duereyi			
Positive	0 (0%)	0 (0%)	0 (0%)
Negative	21 (100%)	8 (100%)	29 (100%)
Sexual history with women			
Age at first sexual encounter (years)	16 (14–17; 5–23; 1346)	16 (14–17; 6–24; 1354)	16 (14–17; 5–24; 2700)
Sexual intercourse with any partner in previous 6 months			
Yes	1196 (86%)	1195 (86%)	2391 (86%)
No	192 (14%)	194 (14%)	386 (14%)

(Continues on next page)

(Continued from previous page)

Number of partners in previous 6 months			
0	192 (14%)	194 (14%)	386 (14%)
1	611 (44%)	616 (44%)	1227 (44%)
2+	585 (42%)	579 (42%)	1164 (42%)
Number of partners over lifetime	4 (3–7; 1–120; 1290)	4 (3–7; 1–390; 1303)	4 (3–7; 1–390; 2593)
Gave gifts or money to a woman for sexual intercourse in previous 6 months			
Yes	194 (16%)	210 (18%)	404 (17%)
No	1002 (84%)	985 (82%)	1987 (83%)
Drank alcohol at last time of having sexual intercourse			
Yes	142 (10%)	150 (11%)	292 (11%)
No	1248 (90%)	1239 (89%)	2487 (89%)
Used a condom at last time of having vaginal sexual intercourse			
Yes	686 (49%)	653 (47%)	1339 (48%)
No	704 (51%)	736 (53%)	1440 (52%)
Used a condom with sexual intercourse in previous 6 months			
Always	265 (22%)	254 (21%)	519 (22%)
Inconsistent	620 (52%)	632 (53%)	1252 (52%)
Never	308 (26%)	307 (26%)	615 (26%)
Last occurrence of sexual intercourse was with regular partner			
Yes	842 (80%)	826 (78%)	1668 (79%)
No	211 (20%)	227 (22%)	438 (21%)
Trouble achieving/maintaining erection in previous 6 months (participants with partner in previous 6 months)			
Yes	80 (7%)	89 (7%)	169 (7%)
No	1111 (93%)	1104 (93%)	2215 (93%)
Sexual history with men			
Ever had sexual relations with a boy or man			
Yes	5 (0·4%)	1 (0·1%)	6 (0·2%)
No	1385 (99·6%)	1388 (99·9%)	2773 (99·8%)
Injection history			
Received an injection for any reason in previous 6 months			
Yes	391 (28%)	360 (26%)	751 (27%)
No	998 (72%)	1029 (74%)	2027 (73%)

Sample sizes vary slightly from the number of randomised participants due to different data sources. Data are median (IQR; range; n) for ordinal data, or n (%) for categorical data.

Table 1: **Baseline characteristics**

intervals of follow-up are provided in table 2. The risk ratio (RR) of HIV acquisition in the circumcision group compared with the control group was 0·47 (95% CI 0·28–0·78), which corresponds to a reduction in the risk of acquiring an HIV infection in the circumcision group of 53% (22–72). The Kaplan-Meier estimates of the incidence of HIV at 12 months were 1·0% (0·5–1·6) for the circumcision group and 2·3% (1·5–3·1) for the control group (p=0·0103).

Upon further testing by PCR, three participants (two in the circumcision group and one in the control group) originally judged to be HIV positive at month 1 were found to be positive at baseline. Furthermore, one participant in the circumcision group originally deemed to be HIV positive at month 6 was confirmed as being positive at baseline. Excluding these four participants from the analysis, the 2-year HIV incidence in the circumcision group was 1·9% (95% CI 1·0–2·7) versus 4·1% (2·9–5·3) in the control group (p=0·0031); which corresponds to an RR of 0·41 (0·24–0·70), or a reduction in the risk of HIV seroconversion among circumcised men of 59% (30–76).

Excluding the participants who were confirmed HIV positive at baseline, before PCR confirmatory testing,

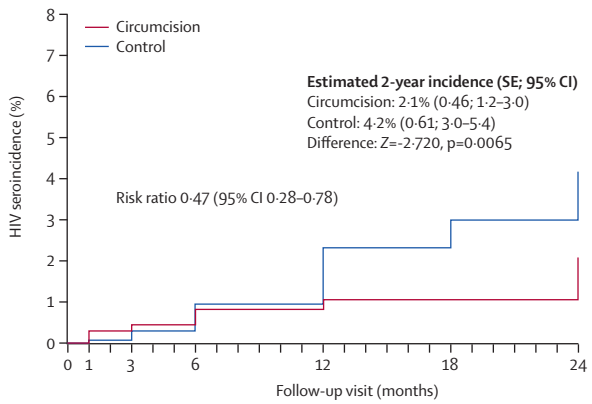
there were two HIV seroconversions in the circumcision group in the first month after randomisation and another two between months 1 and 3. Subsequent PCR testing indicated that all four were actually HIV positive at month 1; no individuals in the control group were seropositive by PCR at month 1. There were three confirmed seroconversions in the control group between month 1 and month 3, and none in the circumcision group. Thus, there were seven early seroconverters (month 1 or month 3): four in the circumcision group and three in the control group. Three of the four in the circumcision group reported no sexual activity in the month after circumcision. We cannot exclude the possibility that any of these individuals were actually HIV positive at baseline, and that their infection was not detected. Two of the three early seroconverters in the control group also denied sexual activity in the period before seroconversion. An analysis excluding the four individuals confirmed as being seropositive at baseline and the four additional early seroconverters positive at month 1 estimated 2-year HIV incidences to be 1·6% (95% CI 0·8–2·4) for the circumcision group and 4·1% (2·9–5·3) for the control group (p=0·0007). The RR was 0·32 (0·18–0·58), which corresponds to a 68% (42–82) protective effect of circumcision against HIV infection.

The as-treated analysis—which adjusted for individuals who did not adhere to the randomisation assignment—estimated the RR of circumcision to be 0·45 (95% CI 0·27–0·76). Excluding the four participants who were confirmed as being HIV positive at baseline, the RR of circumcision was 0·40 (0·23–0·68), which is equivalent to a 60% (32–77) protective effect of circumcision against HIV acquisition.

Treatment results within age strata (ages 18–20 and 21–24 years) were consistent with the overall results and there were no significant differences between the age-groups in the 2-year HIV incidence (p=0·51). For the participants who enrolled when they were 18–20 years of age, the 2-year HIV incidences were 2·5% (95% CI 1·0–3·9) in the circumcision group and 4·3% (2·6–6·1) in the control group (p=0·12). For the 21–24-year-old group, the rates were 1·7% (0·6–2·8) in the circumcision group and 4·0% (2·4–5·7) in the control groups (p=0·02). The study was not powered to detect treatment differences within the two age-groups.

After adjustment for baseline variables for which there seemed to be differences between the two study groups at baseline, only infection with herpes simplex virus 2 at baseline was found to be associated with HIV incidence (RR 1·91, 95% CI 1·18–3·08). The treatment effect remained strong with all adjustments that were considered, and the adjusted RR varied between 0·44 and 0·47.

Not all circumcised men adhered to the 30-day period of post-circumcision abstinence. 60 participants (4·5%) in the circumcision group reported having had sexual intercourse before 30 days post-circumcision, including one of the early seroconverters (month 1) noted above, and another whose HIV infection was detected at the month 6 visit. Both of these participants had adhered to treatment.



Circumcision (n=1391)						
Number at risk	1367	1351	1323	1287	1029	764
Number HIV positive	4	2	5	3	0	8 (22 total)
Control (n=1393)						
Number at risk	1380	1368	1350	1302	1035	740
Number HIV positive	1	3	9	18	7	9 (47 total)

Figure 2: **Cumulative HIV seroincidence across follow-up visits by treatment**
Time to HIV-positive status is taken as the first visit when a positive HIV test result is noted. Time is credited as the follow-up visit month. Participants without HIV-positive status are censored at the last regular follow-up visit completed where HIV testing was done, credited specifically as months 1, 3, 6, 12, 18, and 24.

	Circumcision group	Control group	Total
0–6 months*	0·8% (0·3–1·3)	1·0% (0·4–1·5)	0·9% (0·5–1·2)
6–12 months†	0·2% (0·1–0·7)	1·4% (0·8–2·2)	0·8% (0·5–1·3)
12–18 months†	0·0% (0·0–0·5)	0·7% (0·3–1·5)	0·3% (0·1–0·7)
18–24 months†	1·0% (0·5–2·1)	1·2% (0·6–2·4)	1·1% (0·7–1·8)
0–24 months*	2·1% (1·2–3·0)	4·2% (3·0–5·4)	3·1% (2·4–3·9)

Data are % (95% CI). *Based on Kaplan-Meier methods. †Based on the number of new incidents of HIV infection detected for the interval divided by the number of participants at risk during the interval.

Table 2: **Incidence rates for intervals of follow-up**

All but one of the 1334 men who were circumcised returned for their 3-day postsurgical visit, and all but six returned after 8 days. All those employed had resumed working by the 3-day visit. Among all men circumcised, 1287 (96%) reported having returned to normal activities by the 3-day visit, and all but one person had returned to normal activities by the 8-day visit. At the 3-day visit, 643 (48%) reported no pain, 690 (52%) reported very mild pain, and none reported mild to severe pain. By the 8-day visit, 1179 (89%) reported no pain, and 148 (11%) reported very mild pain. Of the 1334 men circumcised, 1281 (96%) had a 30-day postsurgical wound examination. The wound was judged to be completely healed in all but 16 (1%) individuals. All had returned to normal general activities. All wounds were completely healed by the month 3 visit. 1274 (99·5%) individuals were "very satisfied" and six (0·5%) were "somewhat satisfied" with their circumcision; one

	Number of occurrences	Severity	Related to surgery?
Bleeding	5	2 mild, 3 moderate	Definitely
Infection	5	2 mild, 3 moderate	Definitely
Disruption	4	Mild	Definitely
Delayed healing	3	Mild	Definitely
Swelling	2	1 mild, 1 moderate	Definitely
Anaesthetic-related event	1	Moderate	Definitely
Wound at base of penis	1	Moderate	Probably
Pubic abscess	1	Moderate	Possibly
Folliculitis	1	Mild	Possibly
Erectile dysfunction	1	Moderate	Possibly

Table 3: **Adverse events recorded by severity and relatedness to the surgery**

person was "somewhat dissatisfied", and none were "very dissatisfied". The somewhat dissatisfied participant reported weak erections at his month 1 visit, but this complaint resolved at subsequent visits and he was sexually active.

Table 3 summarises the 24 adverse events recorded as possibly, probably, or definitely related to circumcision that occurred in 23 (1·7%, 95% CI 1·1–2·6) of the 1334 participants. Postoperative bleeding (n=5) and infections (5) were the most common adverse events; wound disruptions (4), delayed healing (3), and swelling at the incision site (2) were also recorded more than once. There was an anaesthetic-related event when a participant had a generalised convulsion, possibly triggered by excessive use of local anaesthetic combined with hypoglycaemia, since the patient had not eaten for 36 hours before the surgery. Thereafter, our surgical protocol was modified to restrict the amount of local anaesthetic used. 21 adverse events among 20 participants (1·5%, 95% CI 0·9–2·3) were probably or definitely related to surgery. All were mild or moderate in severity. None was judged to be severe, and, except for the case of erectile dysfunction, all adverse events resolved with treatment within hours or days. We note that erectile dysfunction was reported post-randomisation in both study groups, with an incidence of 1·5% in the circumcision group and 1·0% in the control group (p=0·24).

10 154 unrelated adverse events were recorded among 1979 (71%) participants. The most frequent unrelated adverse events were upper respiratory tract infections (3189 events, 1184 participants, 43%), malaria (2271 events, 1076 participants, 39%), skin or mucous membrane infections (1011 events, 682 participants, 24%), and gastroenteritis (456 events, 327 participants, 12%). Study groups did not differ with respect to these common illnesses. There were 32 severe adverse events and four deaths, all unrelated to participation in the study. Severe adverse events were those that resulted in hospitalisation and consisted mostly of trauma due to traffic or work-related accidents, and to severe malaria and tuberculosis. There were 17 severe adverse events in 16 participants in the circumcision group and 15 severe adverse events in 14 participants in the control group. Deaths were due to traffic injuries (n=2), shooting by police (1), and beating by thugs (1), with two deaths in the circumcision group and two in the control group. Men in the control group had higher frequencies of abdominal or gastrointestinal conditions (p=0·047) and, as expected, of balanitis, phimosis, or paraphimosis (p<0·0001) than did those in the circumcision group.

	Circumcision group	Control group	p value*
Unprotected sexual intercourse with any partner in previous 6 months (p=0·1666†)			
Baseline	867/1385 (63%)	872/1387 (63%)	
Month 6	623/1231 (51%)	623/1262 (49%)	
Month 12	631/1227 (51%)	585/1228 (48%)	
Month 18	505/985 (51%)	495/988 (50%)	
Month 24	381/741 (51%)	331/727 (46%)	0·0349
Last time had sexual relations with a casual partner (p=0·8044†)			
Baseline	211/1053 (20%)	227/1053 (22%)	
Month 6	180/929 (19%)	192/955 (20%)	
Month 12	199/1014 (20%)	204/1007 (20%)	
Month 18	198/985 (20%)	196/988 (20%)	
Month 24	140/741 (19%)	125/729 (17%)	0·2174
Sexual abstinence in previous 6 months (p=0·4287†)			
Baseline	192/1388 (14%)	194/1389 (14%)	
Month 6	191/1232 (16%)	216/1263 (17%)	
Month 12	188/1227 (15%)	203/1229 (17%)	
Month 18	155/985 (16%)	166/988 (17%)	
Month 24	104/741 (14%)	132/728 (18%)	0·0825
Consistent condom use in previous 6 months (p=0·1143†)			
Baseline	265/1193 (22%)	254/1193 (21%)	
Month 6	370/1040 (36%)	378/1046 (36%)	
Month 12	358/1039 (34%)	398/1025 (39%)	
Month 18	296/830 (36%)	304/822 (37%)	
Month 24	231/637 (36%)	246/595 (41%)	0·0326
Two or more partners in previous 6 months (p=0·0383†)			
Baseline	585/1388 (42%)	579/1389 (42%)	
Month 6	409/1232 (33%)	443/1263 (35%)	
Month 12	360/1227 (29%)	408/1229 (33%)	
Month 18	294/985 (30%)	300/988 (30%)	
Month 24	225/741 (30%)	199/728 (27%)	0·2044

Data are n/N (%). *Test for difference between the treatment groups in change from baseline to month 24. †Global test for any differences between the treatment groups in changes from baseline to follow-up visits.

Table 4: **Sexual history with women reported at baseline and follow-up visits**

Five behavioural variables were selected a priori for detailed analysis of changes in HIV risk behaviour by treatment group (table 4). From baseline to month 6, circumcised and uncircumcised participants both reported safer sexual behaviours in absolute terms, with a lower proportion of men reporting unprotected sexual intercourse with any partner, sexual intercourse

with a casual partner at the last time of such relations, and having two or more sexual partners in the previous 6 months. Similarly, the proportion of men practising sexual abstinence and using a condom consistently during the previous 6 months rose from baseline to month 6. These gains were sustained for the duration of the 24 months of follow-up, with the exception of sexual abstinence in the circumcision group, which returned to baseline level at month 24.

There was little difference between circumcised and uncircumcised men in change in sexual behaviour measures across the follow-up visits, with the exception of two or more partners in the previous 6 months (p=0·0383). There was a linear decrease across visits in the proportion of men in the control group reporting two or more partners in the previous 6 months, whereas the proportion reporting the same behaviour in the circumcision group fell from month 0 to month 6 and remained fairly stable thereafter. Focusing on change specifically from baseline to month 24, differences between the study groups were found for unprotected sexual intercourse (p=0·0349) and consistent condom use (p=0·0326), with individuals in the control group practising the safer sexual behaviours (table 4). Notably greater proportions of circumcised men reported riskier behaviours on all of the other three behavioural variables at month 24, although the differences were small and not significant.

Discussion

Our results confirm that male circumcision substantially reduces the risk of acquiring an HIV infection. Circumcision provided a 53% (95% CI 22–72) protective effect against HIV acquisition compared with the control group and a 60% (32–77) protective effect after adjustments for non-adherence and for those individuals who were found to be HIV positive at baseline. These findings are much the same as those from the Orange Farm trial in South Africa (60% [32–76] protection against HIV infection, with a larger reduction of 76% [56–86] found in a per-protocol analysis that adjusted for crossovers)[21] and to the recently announced 51% protective effect found in Rakai, Uganda.[35] All three trials testing the efficacy of male circumcision against HIV acquisition in African men were stopped by their data and safety monitoring boards before their designed completion because of significant reductions in HIV incidence in the circumcision groups, making it unethical to continue following control group participants without offering them circumcision. Finding a causal relation between HIV infection and male circumcision is consistent with the reductions in HIV prevalence found in meta-analyses of observational studies[14,24] and with investigations of the immunohistochemistry of foreskin tissue.[16–18] Such consistency of clinical, observational, and biological data has not been reported for any other intervention that addresses reduction of HIV incidence in adults.

There was a difference of 7% (53% *vs* 60%) in the estimated protective effect of circumcision against HIV infection between the intention-to-treat analysis and the as-treated analysis, which accounted for men who did not adhere to treatment and those confirmed seropositive at baseline. Although the conclusions from the two analyses are the same, the two measures of effect size should be considered in the context of an increased effect of male circumcision on HIV prevalence at the population level. For planning purposes, the 60% protective effect probably represents the more accurate estimate of the treatment effect, since it compares truly circumcised HIV-negative men to truly uncircumcised HIV-negative men post-randomisation. Recent simulation models based on the assumption of a 60% protective effect of circumcision estimate that as many as 2 million new HIV infections and 300 000 deaths could be averted over the next 10 years in sub-Saharan Africa, assuming 100% uptake of male circumcision. Over the next 20 years, these numbers could amount to 3·7 million and 2·7 million, respectively.[36] Other models, also based on a 60% protective effect, estimate that HIV prevalence could be reduced by half to two-thirds (depending upon the level of uptake of male circumcision) in currently high prevalence areas, including Nyanza Province, Kenya, where this study was done (unpublished data). Furthermore, based on 2005 conditions in Gauteng Province, South Africa, male circumcision would be highly cost-effective, saving about $2·4 million over 20 years per 1000 circumcisions.[37]

This study showed that medical circumcision can be provided safely to adult men in a developing country setting. Adverse event rates were comparable with rates documented for neonatal circumcision in developed countries.[38–40] Currently, rates of complications in clinical settings in Africa are poorly documented, but could vary between 2% to as high as 17·5%.[41–43] The 1·5% rate of adverse events in our study was lower than the 3·6% rate in Orange Farm.[21] Both studies used much the same forceps-guided method.[28] The difference in rates could be a result of multiple factors: all procedures in Kisumu were done at our study clinic by our own, highly trained and experienced practitioners; we had regular surgical case conferences to review outcomes; participants were given clear written postoperative instructions; and participants had scheduled clinic visits 3, 8, and 30 days after the procedure. The Orange Farm trial contracted experienced local private practitioners to do the operations in their own offices, and patients were seen only if they came back with a complication. The Orange Farm trial might more closely resemble what the situation is likely to be under non-study conditions. Our results indicate that extensive training, proper instrumentation, clear postoperative instructions, and continuing quality assurance and control are helpful to assure optimum outcomes.[28,44] These lessons will be important for implementation of wide-scale medical male circumcision interventions.

If circumcised men believe that they are protected from HIV infection, there is a possibility that they will compensate for their perceived risk reduction by engaging in higher risk behaviours. A moderate level of risk compensation could mitigate any benefit of circumcision in preventing HIV infections. Some observational studies have found that circumcised men engage in higher risk behaviours than uncircumcised men,[45,46] and the Orange Farm trial found that circumcised men had slightly higher levels of risk, as measured by five behavioural factors.[21] However, a prospective cohort study in Siaya and Bondo districts, near the site of our trial, found no increase in risky sexual acts by men after circumcision compared with uncircumcised controls.[47] Our study documented a reduction in risk behaviours in both circumcised and uncircumcised participants from baseline to follow-up, indicating that the initial behavioural counselling and voluntary HIV testing offered to the participants were effective. During follow-up visits as a whole, there were no significant differences between circumcised and uncircumcised men in change of the measured sexual behaviours, except in the proportion of men having two or more sexual partners, which showed a progressive decline in the control group; in the circumcision group, the proportion remained stable after month 6. Circumcised men exhibited slightly riskier behaviour on all five assessed measures at month 24 and this was significant for two of the measures—unprotected sexual intercourse with any partner in the previous 6 months and consistent condom use—at that time point. However, the differences between the two groups are attributable to increases in safer sexual practices in the control group rather than to riskier behaviour patterns in the circumcision group, indicating that risk compensation[48] (ie, behavioural disinhibition) did not occur during the 24 months of this study. The reasons men in the control group might have decreased their HIV risk behaviours more than those in the circumcision group are speculative, but could be due to changes in the Kisumu community, differential counselling by study staff, or a perception that being uncircumcised puts one at greater risk. Whether the differences in risk behaviours persist after 24 months remains to be seen. We will continue to follow the cohort to observe behavioural changes as well as HIV seroconversion rates for as long as 5 years after randomisation.

All men in the circumcision group were counselled to refrain from masturbation and sexual activity for at least 30 days after surgery. However, 60 of 1334 (4%) failed to abstain by their own report. Of these 60 men, two seroconverted during their study participation—one at month 6 and the other at month 1. The month 1 seroconverter could have become infected with HIV through sexual activity before his surgical wound had fully healed. There were three other circumcised participants who denied being sexually active in the first month after surgery, but who seroconverted after 1 month. These findings reinforce the importance of developing effective counselling techniques to promote abstinence from sexual activity for at least the first month after circumcision.

There were several limitations to this study. Medical workers could not be blinded to treatment. However, non-medical staff who did HIV tests, administered questionnaires, and counselled participants about risk reduction were blinded to treatment, although some participants divulged their circumcision status during counselling. Questions directly relevant to circumcision status were asked by medical staff only. Measurement of behavioural risk compensation relied on self-report, which could result in under or over-reporting; however, there is no a priori expectation for the direction in which this might occur, nor any suggestion that this should differ between treatment groups. Some participants did not report for all scheduled study visits. HIV test results were incomplete for 9% of the participants; however, there were no baseline differences between those with complete follow-up for HIV status and those without. With such a low frequency of missed visits and an annual HIV seroincidence of 1·6%, any undetected HIV infections would have had little effect on the study results. Moreover, unlike interventions with repeated treatment, often unseen by the study staff, adherence to the intervention was known, and when men missed a visit they were probably protected by circumcision to the same degree as those who did not miss a visit.

Circumcision technique represents one possible source of variation in the protective effect of male circumcision. Although the Orange Farm trial and this study used similar forceps-guided methods,[28] the amount of foreskin tissue remaining after the procedure could vary, depending on the operator. The protective effect of circumcision against HIV infection is thought to derive in part from postsurgical development of a layer of keratinised squamous epithelial cells that limit viral entry to underlying HIV target cells.[16,18] How long it takes the residual tissue to fully heal and become keratinised has not been studied. Our surgical protocol called for retention of 1–1·5 cm of residual inner foreskin. Although the results from the three trials are remarkably consistent, differences in effect sizes could be a result of differences in surgical technique and healing time.

Generalisability of our study results to other populations could be restricted by several factors. The surgical conditions were near optimum, and postoperative wound checks were frequent. Participants were screened to exclude those who were HIV seropositive, who had symptomatic illnesses, or contraindications to surgery. In standard public-health settings, HIV testing might not always be practical or acceptable. Further, if circumcision proves partly protective against HIV transmission to sexual partners, as is now being tested in Uganda, then circumcising HIV-infected men could become a priority. We enrolled only men who were aged 18–24 years, and

almost all were sexually active within the previous year. Ideally, if introduced widely, this intervention will be made available to younger males before they become sexually active. The participants in this study had frequent contact with study staff. They had free medical care, were counselled about safe sexual practices, had unrestricted access to condoms, were tested for sexually transmitted infections, and were treated for bacterial infections. This level of contact, intense counselling, and medical care is unlikely to pertain in standard settings. Finally, almost all the participants in this study identified as belonging to the same ethnic group—the Luo. If Luo males engage in systematically different behaviours from men of other ethnic groups, the results of this study might not apply to other regions of Africa. However, this seems unlikely, since our results are very similar to those from other clinical trials and observational studies, and there is no reason to suspect that Luo men act differently from others in response to circumcision.

Although there is little evidence of risk compensation by the circumcised men in this study, beliefs and attitudes about circumcision could change substantially after the results of the three clinical trials are widely publicised and interventions are put in place to promote male circumcision. A challenge to prevention specialists and clinicians will be to develop circumcision interventions that communicate the benefits of the procedure, while also explaining that circumcision does not offer full protection from HIV acquisition. 13 studies in nine sub-Saharan African countries found that between 29% and 80% of men in traditionally non-circumcising communities would prefer to be circumcised if the procedure could be offered safely, with the minimum of pain, and at low cost.[49] Now that compelling evidence is available that male circumcision reduces risk of HIV acquisition, expectations about the effectiveness of the procedure and demand could increase dramatically, perhaps burdening health facilities and opening opportunities for under-qualified, poorly equipped practitioners with little training in HIV prevention counselling.[50] Circumcision will be most effective if it is not perceived as a stand-alone clinical procedure, but as one component of a full suite of HIV prevention and reproductive health services, including HIV testing and counselling, diagnosis and treatment of sexually transmitted infections, condom promotion, behavioural change counselling and promotion, and other methods as they are proven effective. With commitment to proven prevention methods today, there is the possibility of turning around the HIV epidemic.

Contributors

R C Bailey participated in conceptualising the study, designing the protocol and study instruments, providing scientific and management leadership, reviewing study data, drafting the manuscript and coordinating submission. S Moses participated in conceptualising the study, designing the protocol and study instruments, providing medical, scientific and management leadership, reviewing and analyzing study data, and drafting and editing the manuscript. C B Parker participated in revising the protocol and study instruments, managed and coordinated data input, review and quality control, did the bulk of the data analyses, drafted substantial sections of the manuscript, and reviewed and edited the entire manuscript. K Agot participated in designing the protocol and study instruments, managed and coordinated every aspect of the study operations, ensured outreach to the study community, reviewed and corrected study data, and reviewed and edited the manuscript. I Maclean participated in the design of the protocol and study instruments, established the laboratory and all lab protocols, oversaw management of the laboratory, reviewed study data, and reviewed and edited the manuscript. J N Krieger participated in the design of the protocol and study instruments, trained clinicians and oversaw surgical procedures, reviewed study data, and reviewed and edited the manuscript. C F M Williams participated in review of the protocol and revision of study instruments, provided scientific leadership, and reviewed and edited the manuscript. R T Campbell participated in the analysis of the behavioural study data, and reviewed and edited the manuscript. J O Ndinya-Achola participated in designing the protocol and study instruments, provided overall medical, scientific and management leadership, assisted with study operations, liaised with local, national and university partners, and reviewed and edited the manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

Foremost, we thank the young men of Kisumu who volunteered to participate in this study. We also thank Richard Muga and Allan Ronald for their helpful advice and constant support; George Magoha and James Otieno for their surgical expertise and support; Erastus Irungu and Nancy Kayere (University of Nairobi WHO Collaborating Centre for STD Research and Training), staff at the Canadian National Laboratory for HIV Reference Services and Julie Overbaugh and Dana DeVange Panteleeff (Fred Hutchinson Cancer Research Center) for laboratory analyses of study specimens; the matron and staff of Lumumba Health Centre; Christine Mattson, Martha Schnell, Nelli Westercamp, Norma Pugh, Bonnie Knoke, Kathy Mason, Pablo Destefanis, Carol Sigurdson, and Lynn Gauthier for their continuous devotion and invaluable assistance; Melanie Bacon for advice and medical oversight; and the following UNIM Project staff for their long hours of work and devotion to sound research: Millicent A Ogosi, Virginia Akach, Martha A Chumba, Merab Ndinya, James A Ogollah, Thomas O Pittchar, Habil O Agoro, Rosemary A Onyango, John C Opeya, Juma S Hayombe, Benard Ayieko, Felix A Opiyo, Dickens Omondi, Rachel A Okune, Michael Otieno, Fanuel Odundo, Edward Odawa, Maurice Orao, George Ogano, Erick Owino, Charles Opondo, Robert Ogol, Stephen Onyango, Bernard Andalla, Ken Owiyo, Alex Wadegu, Collins Rading, Maurice Onyango, Erastus Aroko, George Awino, James Ogutu, Fidel Asol, Tobias Agutu, Edith Nyagaya, Lawrence Agunda, Walter Agingu, Ruth Murugu, Erick Onyuro, Retunoi Lesaigor, Mathews Onyango, Martin Okumu, and Joshua Okeyo. This research was supported by grant number AI50440 from the Division of AIDS, National Institute of Allergies and Infectious Disease of the United States National Institutes of Health, and by grant number HCT 44180 from the Canadian Institutes of Health Research (CIHR). S Moses was supported by a CIHR Investigator Award.

References

1 UNAIDS. Report on the global HIV/AIDS epidemic. Geneva: UNAIDS, 2006.
2 The Lancet. Betting on HIV prevention. *Lancet* 2006; **368:** 424.
3 Alcena V. AIDS in third world countries. *N Y State J Med* 1986; **86:** 446.
4 Fink A. A possible explanation for heterosexual male infection with AIDS. *N Engl J Med* 1986; **314:** 1167.
5 Bongaarts J, Reining P, Way P, Conant F. The relationship between male circumcision and HIV infection in African populations. *AIDS* 1989; **3:** 373–77.
6 Drain P, Halperin D, Hughes J, Klausner J, Bailey R. Male circumcision, religion, and infectious diseases: an ecologic analysis of 118 developing countries. *BMC Infect Dis* 2006; **6:** 172.
7 Halperin DT, Bailey RC. Male circumcision and HIV infection: 10 years and counting. *Lancet* 1999; **354:** 1813–15.
8 Moses S, Bradley JE, Nagelkerke NJ, Ronald AR, Ndinya-Achola JO, Plummer FA. Geographical patterns of male circumcision practices in Africa: association with HIV seroprevalence. *Int J Epidemiol* 1990; **19:** 693–97.

9 Bailey RC, Plummer FA, Moses S. Male circumcision and HIV prevention: current knowledge and future research directions. *Lancet Infect Dis* 2001; **1:** 223–31.

10 Buchbinder SP, Vittinghoff E, Heagerty PJ, et al. Sexual risk, nitrite inhalant use, and lack of circumcision associated with HIV seroconversion in men who have sex with men in the United States. *J Acquir Immune Defic Syndr* 2005; **39:** 82–89.

11 MacDonald KS, Malonza I, Chen DK, et al. Vitamin A and risk of HIV-1 seroconversion among Kenyan men with genital ulcers. *AIDS* 2001; **15:** 635–39.

12 Reynolds SJ, Shepherd ME, Risbud AR, et al. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet* 2004; **363:** 1039–40.

13 Sateren WB, Bautista CT, Shaffer DN, et al. Male circumcision and HIV infection risk among tea plantation residents in Kericho, Kenya: incidence results after 1·5 years of follow-up. Sixteenth International AIDS Conference; Toronto, Canada; Aug 13–18, 2006. Abstract TUAC0202.

14 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000; **14:** 2361–70.

15 Quinn TC, Wawer MJ, Sewankambo N, et al. A study in rural Uganda of heterosexual transmission of human immunodeficiency virus. *N Engl J Med* 2000; **343:** 364.

16 Patterson BK, Landay A, Siegel JN, et al. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. *Am J Pathol* 2002; **161:** 867–73.

17 Donoval BA, Landay AL, Moses S, et al. HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections. *Am J Clin Pathol* 2006; **125:** 386–91.

18 McCoombe SG, Short RV. Potential HIV-1 target cells in the human penis. *AIDS* 2006; **20:** 1491–95.

19 O'Farrell N, Morison L, Moodley P, et al. Association between HIV and subpreputial penile wetness in uncircumcised men in South Africa. *J Acquir Immune Defic Syndr* 2006; **43:** 69–77.

20 Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect* 2006; **82:** 101–09.

21 Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 trial. *PLoS Med* 2005; **2:** 1–11.

22 Auvert B, Puren A, Taljaard D, Lagarde E, Sitta R, Tambekou J. Impact of male circumcision on the female-to-male transmission of HIV. 3rd IAS Conference on HIV Pathogenesis and Treatment; Rio de Janeiro; July 24–27, 2005. Abstract TuOa0402.

23 UNAIDS/WHO/UNFPA/UNICEF. Press statement: UNAIDS statement on South African trial findings regarding male circumcision and HIV. Rio de Jeneiro: UNAIDS, World Health Organization, United Nations Population Fund, United Nations Children's Fund, 2005.

24 Siegfried N, Muller M, Deeks J, et al. HIV and male circumcision—a systematic review with assessment of the quality of studies. *Lancet Infect Dis* 2005; **5:** 165–73.

25 Central Bureau of Statistics (Kenya). Ministry of Finance and Planning. Kenya 1999 population and housing census. Volume VII: analytical report on population projections, 2002.

26 Buve A, Auvert B, Langarde E, Kahindo M, Hayes R, Carael M. Male circumcision and HIV spread in sub-Saharan Africa. XIII International Conference on AIDS; Durban, South Africa; July 9–14, 2000. Abstract MoDrC192.

27 Central Bureau of Statistics (Kenya). Ministry of Health (MOH), ORC Macro. Kenya demographic and health survey: 2003. Calverton, Maryland: CBS, MOH, ORC Macro, 2003.

28 Krieger JN, Bailey RC, Opeya J, et al. Adult male circumcision: results of a standardized procedure in Kisumu District, Kenya. *BJU Int* 2005; **96:** 1109–13.

29 Lan KK, DeMets DL. Design and analysis of group sequential tests based on the type 1 error spending function. *Biometrika* 1983; **74:** 149–54.

30 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.

31 Greenwood M. A report on the natural duration of cancer. *Rep Public Health Med Subj (Lond)* 1926; **33:** 23–25.

32 Cox DR. Partial likelihood. *Biometrika* 1975; **62:** 269–76.

33 Cox DR. Regression models and life tables (with discussion). *J R Stat Soc Ser B* 1972; **34:** 187–220.

34 Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986; **73:** 13–22.

35 Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet* 2007; **369:** 657–66.

36 Williams BG, Lloyd-Smith JO, Gouws E, et al. The potential impact of male circumcision on HIV in sub-Saharan Africa. *PLoS Med* 2006; **3:** e262.

37 Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med* 2006; **3:** e517.

38 Anon. Circumcision policy statement. American Academy of Pediatrics. Task Force on Circumcision. *Pediatrics* 1999; **103:** 686–93.

39 Cathcart P, Nuttall M, van der Meulen J, Emberton M, Kenny SE. Trends in paediatric circumcision and its complications in England between 1997 and 2003. *B J Surg* 2006; **93:** 885–90.

40 Kaplan GW. Complications of circumcision. *Urol Clin North Am* 1983; **10:** 543–49.

41 Bailey RC, Egesah O. Assessment of clinical and traditional male circumcision services in Bungoma District, Kenya: complications rates and operational needs, 2006. http://pdf.usaid.gov/pdf_docs/PNADG558.pdf (accessed Feb 9, 2007).

42 Magoha GA. Circumcision in various Nigerian and Kenyan hospitals. *East Afr Med J* 1999; **76:** 583–86.

43 Manji KP. Circumcision of the young infant in a developing country using the Plastibell. *Ann Trop Paediatr* 2000; **20:** 101–04.

44 Krieger JN, Bailey RC, Opeya JC, et al. Adult male circumcision outcomes: experience in a developing country setting. *Urol Int* (in press).

45 Bailey RC, Neema S, Othieno R. Sexual behaviors and other HIV risk factors in circumcised and uncircumcised men in Uganda. *J Acquir Immune Defic Syndr* 1999; **22:** 294–301.

46 Seed J, Allen S, Mertens T, et al. Male circumcision, sexually transmitted disease, and risk of HIV. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995; **8:** 83–90.

47 Agot KE, Kiarie JN, Nguyen HQ, Odhiambo JO, Onyango TM, Weiss NS. Male circumcision in Siaya and Bondo Districts, Kenya: prospective cohort study to assess behavioral disinhibition following circumcision. *J Acquir Immune Defic Syndr* 2007; **44:** 66–70.

48 Cassell MM, Halperin DT, Shelton JD, Stanton D. Risk compensation: the Achilles' heel of innovations in HIV prevention? *BMJ* 2006; **332:** 605–07.

49 Westercamp N, Bailey RC. Acceptability of male circumcision for prevention of HIV/AIDS in sub-Saharan Africa: a review. *AIDS Behav* published online Oct 20, 2006. DOI:10.1007/S10461-006-9169-4.

50 Mattson CL, Muga R, Poulussen R, Onyango T, Bailey RC. Feasibility of medical male circumcision in Nyanza Province, Kenya. *East Afr Med J* 2004; **81:** 230–35.

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

Ronald H Gray, Godfrey Kigozi, David Serwadda, Frederick Makumbi, Stephen Watya, Fred Nalugoda, Noah Kiwanuka, Lawrence H Moulton, Mohammad A Chaudhary, Michael Z Chen, Nelson K Sewankambo, Fred Wabwire-Mangen, Melanie C Bacon, Carolyn F M Williams, Pius Opendi, Steven J Reynolds, Oliver Laeyendecker, Thomas C Quinn, Maria J Wawer

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.**

Lancet 2007; 369: 657–66

See **Editorial** page 615

See **Comment** page 617

See **Perspectives** page 635

See **Articles** page 643

See **Viewpoint** page 708

Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA (Prof R H Gray MD, Prof L H Moulton PhD, M A Chaudhary PhD, M Z Chen MSc, Prof M J Wawer MD); **Rakai Health Sciences Program, Entebbe, Uganda** (G Kigozi MBChB, F Nalugoda MHS, N Kiwanuka MBChB, P Opendi MBChB); **Makerere University, Institute of Public Health, Kampala, Uganda** (D Serwadda MBChB, F Makumbi PhD, F Wabwire-Mangen PhD); **Makerere University, Mulago Hospital, Department of Surgery, Urology Unit, Kampala, Uganda** (S Watya MBChB); **Makerere University, Department of Medicine, Kampala, Uganda** (N K Sewankambo MBChB); **National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA** (M C Bacon MPH, C F M Williams PhD, S J Reynolds MD, O Laeyendecker MSc, Prof T C Quinn MD); **and Johns Hopkins Medical Institutions, Baltimore, MD, USA** (S J Reynolds, O Laeyendecker, T C Quinn)

Correspondence to:
Prof Ronald H Gray, Johns Hopkins University, Bloomberg School of Public Health, Suite E4132, 615 N Wolfe Street, Baltimore, MD 21215, USA
rgray@jhsph.edu

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

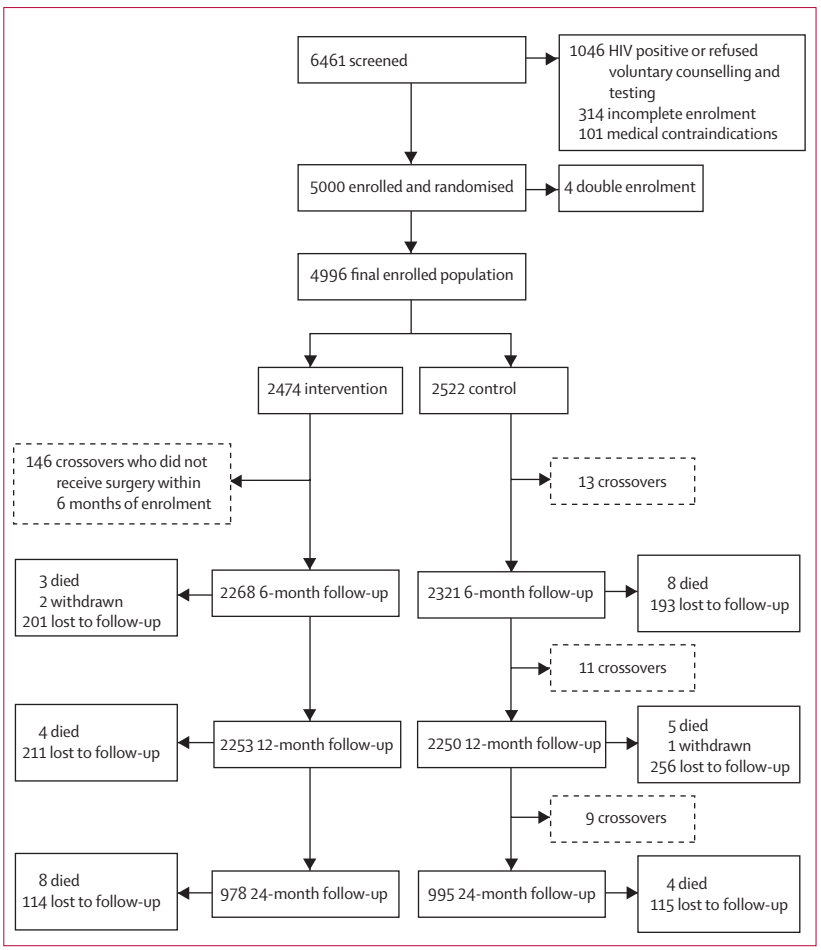


Figure 1: **Trial profile**

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.

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**

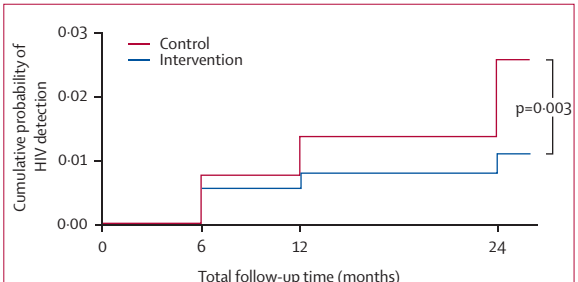


Figure 2: **Kaplan-Meier cumulative probabilities of HIV detection by study group**

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.

Acknowledgments

The study was supported by a grant (UO1 AI11171-01-02) from the National Institutes of Allergy and Infectious Disease (NIAID), Division of AIDS, National Institutes of Health (NIH), and in part by the Division of Intramural Research, NIAID, NIH. This publication was supported, in part, by a fellowship/grant from the Fogarty International Center/USNIH: grant number 2 D 43 TW000010-19-AITRP. We thank the members of the NIH data safety monitoring board who monitored this trial, as well as the institutional review boards that provided oversight (the scientific and ethics committee of the Uganda Virus Research Institute, the committee for human research at Johns Hopkins, and Western Institutional Review Board). We are also grateful for the advice provided by the Rakai community advisory board. Finally, we wish to express our gratitude to study participants whose commitment and cooperation made the study possible.

References

1 Weiss HA, Quigley MA, Hayes RJ. Male circumcision and risk of HIV infection in sub-Saharan Africa: a systematic review and meta-analysis. *AIDS* 2000; **14:** 2361–70.

2 Gray RH, Kiwanuka N, Quinn TC, et al. Male circumcision and HIV acquisition and transmission: cohort studies in Rakai, Uganda. Rakai Project Team. *AIDS* 2000; **14:** 2371–81.

3 Reynolds SJ, Shepherd ME, Risbud AR, et al. Male circumcision and risk of HIV-1 and other sexually transmitted infections in India. *Lancet* 2004; **363:** 1039–40.

4 Lavreys L, Rakwar JP, Thompson ML, et al. Effect of circumcision on incidence of human immunodeficiency virus type 1 and other sexually transmitted diseases: a prospective cohort study of trucking company employees in Kenya. *J Infect Dis* 1999; **180:** 330–36.

5 Baeten JM, Richardson BA, Lavreys L, et al. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. *J Infect Dis* 2005; **191:** 546–53.

6 Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med* 2005; **2:** e298.

7 Walsh PC, Retik AB, Stamey TA, Vaughan ED, eds. Campbell's urology, 6th edn. WB Saunders Co, 1992: 2972–73.

8 Zablotska IB, Gray RH, Serwadda D, et al. Alcohol use before sex and HIV acquisition: a longitudinal study in Rakai, Uganda. *AIDS* 2006; **20:** 1–6.

9 Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983; **70:** 659–63.

10 O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; **35:** 549–56.

11 Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet* 2007; **369:** 643–56.

12 Gray RH, Li X, Kigozi G, et al. The impact of male circumcision on HIV incidence, and cost-per infection prevented: a stochastic simulation model from Rakai, Uganda. *AIDS* (in press).

13 Weiss HA, Thomas SL, Munabi SK, Hayes RJ. Male circumcision and risk of syphilis, chancroid, and genital herpes: a systematic review and meta-analysis. *Sex Transm Infect* 2006; **82:** 101–09.

14 Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS* 2006; **20:** 73–83

15 Reynolds SJ, Risbud AR, Shepherd ME, et al. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. *J Infect Dis* 2003; **187:** 1513–21.

16 Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sex Transm Dis* 2001; **28:** 579–97.

17 Gray RH, Azire J, Serwadda D, et al. Male circumcision and the risk of sexually transmitted infections and HIV in Rakai, Uganda. *AIDS* 2004; **18:** 2428–30.

18 Hussain LA, Lehner T. Comparative investigation of Langerhans' cells and potential receptors for HIV in oral, genitourinary and rectal epithelia. *Immunology* 1995; **85:** 475–84.

19 Donoval BA, Landay AL, Moses S, et al. HIV-1 target cells in foreskins of African men with varying histories of sexually transmitted infections. *Am J Clin Pathol* 2006; **125:** 386–91.

20 McCoombe SG, Short RV. Potential HIV-1 target cells in the human penis. *AIDS* 2006; **20:** 1491–95.

21 Patterson BK, Landay A, Siegel JN, et al. Susceptibility to human immunodeficiency virus-1 infection of human foreskin and cervical tissue grown in explant culture. *Am J Pathol* 2002; **161:** 867–73.

22 Szabo R, Short RV. How does male circumcision protect against HIV infection? *BMJ* 2000; **320:** 1592–94.

23 Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med* 2006; **3:** e517.

24 Bailey RC, Egesah O. Assessment of clinical and traditional male circumcision services in Bungoma district, Kenya. Complication rates and operational needs. Special report. Washington, DC: USAID, PSI AIDSMark, 2006: 1–39.

25 Kabra SG, Narayanan R. Sterilisation camps in India. *Lancet* 1990; **335:** 224–25.

26 Kumar S. Health-care camps for the poor provide mass sterilisation quota. *Lancet* 1999; **353:** 1251.

27 Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA* 2005; **294:** 2203–09.