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.

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. 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. Effective new HIV preventive interventions are needed.

That male circumcision might reduce risk of HIV acquisition was first proposed in 1986. Ecological studies have shown that, in regions where HIV transmission is predominantly heterosexual, the prevalence of HIV and of male circumcision are inversely correlated. 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, and 14 prospective studies all show a protective effect, ranging from 48% to 88%. 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. 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.

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. The number of preputial target cells is increased in men with a history of recent sexually transmitted infections. 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. In explant culture, several times more HIV-1 is taken up by Langerhans' cells, CD4+ T cells, and macrophages than does cervical tissue. The virus does not infiltrate the cells on the outer surface of the foreskin. Other possible mechanisms by which the presence of the foreskin could lead to greater risk for HIV infection include poor hygiene, greater incidence of ulcerative sexually transmitted infections, and susceptibility of the foreskin to abrasions.

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—e.g., condom use, health-seeking behaviour, and sexual behaviour—the protective effect was much the same (61%).

Upon announcement of the Orange Farm results in July, 2005, 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. A Cochrane review had also cautioned against implementation of male circumcision as a preventive strategy in the absence of more data from clinical trials.

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. 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. In 2003, HIV prevalence was about 25% in Luo women and 18% in Luo men.

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 treated. Inclusion and exclusion criteria are listed in the panel. 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
- Haemophilic 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. 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 $\alpha=0.05$ (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 $\alpha_1=0.000518$ 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 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 $\alpha_2=0.0183$. 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 $\alpha_3=0.0269$, 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 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 seroincidence and corresponding standard errors obtained by Greenwood’s formula 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 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. 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 0, 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
6686 registered at the clinic  
6159 tested for HIV  
5622 screened according to protocol  
4489 eligible  
2784 randomised  
1393 control group  
1391 circumcision group  

Exclusions  
78 age outside range or undocumented  
261 non-resident of Kisumu/uncertain stay  
114 non-consenting to HIV testing/examination  
108 not completely uncircumcised  
337 HIV seropositive or indeterminate  
671 absence of sexual relations in previous 12 months  
32 contraindication to surgery  
63 condition preventing sexual activity  
9 hypoplasia  
58 absolute indication for surgery  
176 medical problem—unsolved/no return  
157 unreliable  
44 client wants to be circumcised  
201 insufficient understanding  
1407 client undecided/not returned  
53 client declined further participation  

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 \( \chi^2 \) 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
### Demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Circumcision group</th>
<th>Control group</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>20 (19–22; 18–28; 1391)</td>
<td>20 (19–22; 17–24; 1393)</td>
<td>20 (19–22; 17–28; 2784)</td>
</tr>
<tr>
<td><strong>Ethnic group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luo</td>
<td>1361 (98%)</td>
<td>1378 (99%)</td>
<td>2739 (98%)</td>
</tr>
<tr>
<td>Other</td>
<td>30 (2%)</td>
<td>15 (1%)</td>
<td>45 (2%)</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than secondary</td>
<td>468 (34%)</td>
<td>479 (34%)</td>
<td>947 (34%)</td>
</tr>
<tr>
<td>Any secondary or above</td>
<td>923 (66%)</td>
<td>914 (66%)</td>
<td>1837 (66%)</td>
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<tr>
<td><strong>Employment status</strong></td>
<td></td>
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<tr>
<td>Employed and receiving a salary</td>
<td>128 (9%)</td>
<td>134 (10%)</td>
<td>262 (9%)</td>
</tr>
<tr>
<td>Self-employed</td>
<td>374 (27%)</td>
<td>355 (25%)</td>
<td>729 (26%)</td>
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<tr>
<td>Unemployed</td>
<td>889 (64%)</td>
<td>904 (65%)</td>
<td>1793 (64%)</td>
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<tr>
<td><strong>Occupation</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Professional/managerial</td>
<td>25 (2%)</td>
<td>39 (3%)</td>
<td>64 (2%)</td>
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<tr>
<td>Skilled worker</td>
<td>141 (10%)</td>
<td>113 (8%)</td>
<td>254 (9%)</td>
</tr>
<tr>
<td>Semi-skilled worker</td>
<td>95 (7%)</td>
<td>86 (6%)</td>
<td>181 (7%)</td>
</tr>
<tr>
<td>Unskilled worker</td>
<td>668 (50%)</td>
<td>758 (54%)</td>
<td>1456 (52%)</td>
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<tr>
<td>Farm labour/fisherman</td>
<td>107 (8%)</td>
<td>90 (6%)</td>
<td>197 (7%)</td>
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<tr>
<td>Student</td>
<td>325 (23%)</td>
<td>307 (22%)</td>
<td>632 (23%)</td>
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<tr>
<td><strong>Marital status</strong></td>
<td></td>
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<tr>
<td>Not married (no live-in partner)</td>
<td>1296 (93%)</td>
<td>1291 (93%)</td>
<td>2587 (93%)</td>
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<tr>
<td>Not married (with live-in partner)</td>
<td>9 (0·6%)</td>
<td>11 (0·8%)</td>
<td>20 (0·7%)</td>
</tr>
<tr>
<td>Married (not living with wife)</td>
<td>11 (0·8%)</td>
<td>19 (1%)</td>
<td>30 (1%)</td>
</tr>
<tr>
<td>Married (living with wife)</td>
<td>71 (5%)</td>
<td>65 (5%)</td>
<td>136 (5%)</td>
</tr>
</tbody>
</table>

### Physical and laboratory findings

<table>
<thead>
<tr>
<th></th>
<th>Circumcision group</th>
<th>Control group</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>61 (59–68; 42–91; 1391)</td>
<td>62 (58–67; 40–100; 1392)</td>
<td>61 (59–67; 40–100; 2783)</td>
</tr>
<tr>
<td><strong>Haemoglobin (g/L)</strong></td>
<td>154 (143–163; 90–199; 1386)</td>
<td>153 (142–164; 83–201; 1391)</td>
<td>153 (142–163; 83–201; 2777)</td>
</tr>
<tr>
<td><strong>Herpes simplex virus 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>405 (29%)</td>
<td>363 (26%)</td>
<td>768 (28%)</td>
</tr>
<tr>
<td>Negative</td>
<td>980 (71%)</td>
<td>1029 (74%)</td>
<td>2009 (72%)</td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>19 (1%)</td>
<td>9 (0·6%)</td>
<td>28 (1%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1369 (99%)</td>
<td>1379 (99·4%)</td>
<td>2748 (99%)</td>
</tr>
<tr>
<td><strong>Trichomonas vaginalis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27 (2%)</td>
<td>31 (2%)</td>
<td>58 (2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1351 (98%)</td>
<td>1350 (98%)</td>
<td>2701 (98%)</td>
</tr>
<tr>
<td><strong>Neisseria gonorrhoeae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>32 (2%)</td>
<td>25 (2%)</td>
<td>57 (2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1342 (98%)</td>
<td>1355 (98%)</td>
<td>2697 (98%)</td>
</tr>
<tr>
<td><strong>Chlamydia trachomatis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>73 (5%)</td>
<td>55 (4%)</td>
<td>128 (5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>1300 (95%)</td>
<td>1325 (96%)</td>
<td>2625 (95%)</td>
</tr>
<tr>
<td><strong>Haemophilus ducreyi</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Negative</td>
<td>21 (100%)</td>
<td>8 (100%)</td>
<td>29 (100%)</td>
</tr>
</tbody>
</table>

### Sexual history with women

<table>
<thead>
<tr>
<th></th>
<th>Circumcision group</th>
<th>Control group</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first sexual encounter (years)</strong></td>
<td>16 (14–17; 5–23; 1346)</td>
<td>16 (14–17; 6–24; 1354)</td>
<td>16 (14–17; 5–24; 2700)</td>
</tr>
<tr>
<td>Sexual intercourse with any partner in previous 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1196 (86%)</td>
<td>1195 (86%)</td>
<td>2391 (86%)</td>
</tr>
<tr>
<td>No</td>
<td>192 (14%)</td>
<td>194 (14%)</td>
<td>386 (14%)</td>
</tr>
</tbody>
</table>

(Continues on next page)
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 circumcision. An analysis excluding all 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 (95% CI 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 group (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. 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

![Figure 2: Cumulative HIV seroincidence across follow-up visits by treatment](image-url)
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 and resolved with treatment within hours or days. We note that erectile dysfunction was reported post-randomisation and resolved with treatment within hours or days.

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

<table>
<thead>
<tr>
<th>Table 3: Adverse events recorded by severity and relatedness to the surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of occurrences</td>
</tr>
<tr>
<td>-----------------------</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Disruption</td>
</tr>
<tr>
<td>Delayed healing</td>
</tr>
<tr>
<td>Swelling</td>
</tr>
<tr>
<td>Anaesthetic-related event</td>
</tr>
<tr>
<td>Wound at base of penis</td>
</tr>
<tr>
<td>Pubic abscess</td>
</tr>
<tr>
<td>Folliculitis</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
</tr>
</tbody>
</table>

5154 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 12 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 (I), 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.

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 lower proportion of men reporting unprotected sexual intercourse with any partner, sexual intercourse with a lower proportion of men reporting unprotected sexual intercourse with any partner.
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 consistent condom use (p=0·0349), 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.

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.44 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.21 44 These lessons will be important for implementation of wide-scale medical male circumcision interventions.

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 month 6. These gains were sustained for the duration during the previous 6 months rose from baseline to 6 months. Similarly, the proportion of men practising and having two or more sexual 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.
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. However, the Orange Farm trial found that circumcised men had slightly higher levels of risk, as measured by five behavioural factors. 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. 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* (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, 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. 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 persist 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. 8 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. 9 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.

References

Articles


