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The Safety of Adult Male Circumcision in HIV-Infected and Uninfected Men in Rakai, Uganda

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Abbreviations: AdjOR, adjusted odds ratios; AE, adverse event; CI, confidence interval; GUD, genital ulcerative disease; MC, male circumcision; VCT, voluntary counseling and testing; WHO, World Health Organization

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ABSTRACT

Background

The objective of the study was to compare rates of adverse events (AEs) related to male circumcision (MC) in HIV-positive and HIV-negative men in order to provide guidance for MC programs that may provide services to HIV-infected and uninfected men.

Methods and Findings

A total of 2,326 HIV-negative and 420 HIV-positive men (World Health Organization [WHO] stage I or II and CD4 counts > 350 cells/mm^3) were circumcised in two separate but procedurally identical trials of MC for HIV and/or sexually transmitted infection prevention in rural Rakai, Uganda. Participants were followed at 1–2 d and 5–9 d, and at 4–6 wk, to assess surgery-related AEs, wound healing, and resumption of intercourse. AE risks and wound healing were compared in HIV-positive and HIV-negative men. Adjusted odds ratios (AdjORs) were estimated by multiple logistic regression, adjusting for baseline characteristics and post-operative resumption of sex. At enrollment, HIV-positive men were older, more likely to be married, reported more sexual partners, less condom use, and higher rates of sexually transmitted disease symptoms than HIV-negative men. Risks of moderate or severe AEs were 3.1/100 and 3.5/100 in HIV-positive and HIV-negative participants, respectively (AdjOR 0.91, 95% confidence interval [CI] 0.47–1.74). Infections were the most common AEs (2.6/100 in HIV-positive versus 3.0/100 in HIV-negative men). Risks of other complications were similar in the two groups. The proportion with completed healing by 6 wk postsurgery was 92.7% in HIV-positive men and 95.8% in HIV-negative men ($p = 0.007$). AEs were more common in men who resumed intercourse before wound healing compared to those who waited (AdjOR 1.56, 95% CI 1.05–2.33).

Conclusions

Overall, the safety of MC was comparable in asymptomatic HIV-positive and HIV-negative men, although healing was somewhat slower among the HIV infected. All men should be strongly counseled to refrain from intercourse until full wound healing is achieved.

Trial registration: http://www.ClinicalTrials.gov; for HIV-negative men #NCT00425984 and for HIV-positive men, #NCT00124878.

The Editors' Summary of this article follows the references.
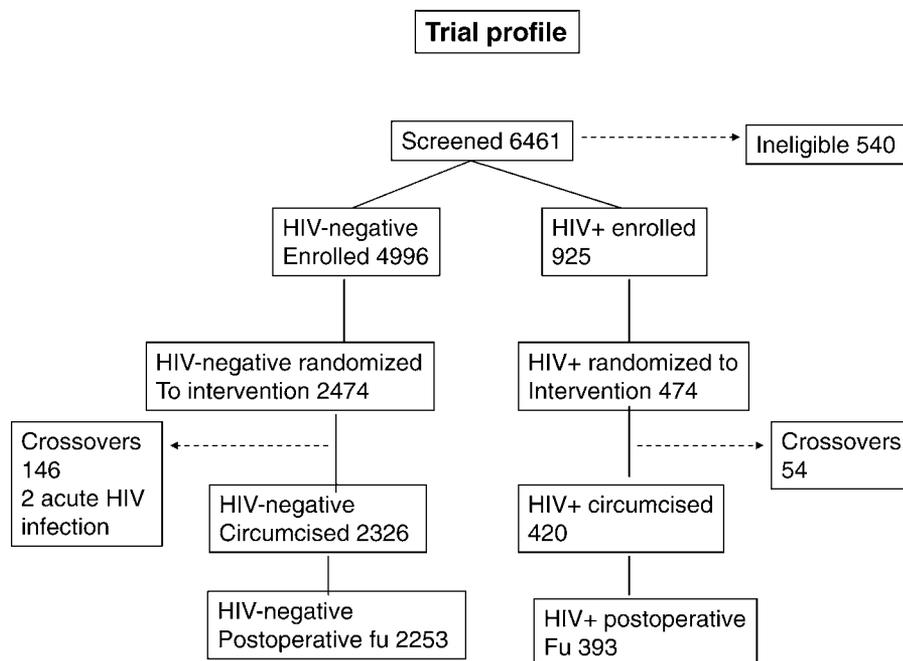
Trial profile

Figure 1. Profile of Trials for HIV-Positive and HIV-Negative Participants

fu, follow up.

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Introduction

Three randomized trials have shown that male circumcision (MC) reduces the risk of male HIV acquisition in men by 50%–60% [1–3]. This finding suggests that the procedure may be an important means of HIV prevention in areas where circumcision is uncommon and where most HIV transmission is due to heterosexual intercourse. The World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS) has now recommended that MC be promoted as an additional important strategy for preventing heterosexual HIV infection in men [4]. The safety of surgery is a paramount consideration in planning future circumcision programs, both to minimize surgical risks and to provide guidelines for best practices in surgical procedures and postoperative care. Although information is available on postoperative complications in children and in HIV-negative men [1–3,5–8], there is little information on the safety of circumcision in HIV-infected men [3]; this presents an important programmatic issue since future circumcision services are likely to attract both HIV-infected and -uninfected men. Moreover, WHO/UNAIDS guidelines recommend that circumcision be provided to HIV-positive men if medically indicated or if they request the procedure. If surgery were to be unsafe in HIV-positive men, these individuals might have to either be excluded from adult MC programs, which would be potentially stigmatizing, or they might require specialized services for postoperative care, which could add to program costs and complexity.

We conducted two randomized trials of MC in rural Rakai district of southwestern Uganda. One trial, supported by the United States NIH, enrolled HIV-negative men [1]. This trial was stopped for efficacy on December 12, 2006. The other trial, which was supported by the Bill & Melinda Gates Foundation, enrolled HIV-positive men, and enrollment was closed on December 19, 2006. In this paper we report on the safety of circumcision in HIV-negative and HIV-positive men enrolled into the intervention arms of these two trials.

Methods

The Rakai trials enrolled uncircumcised men aged 15–49 y who provided informed consent for screening and for randomization to immediate circumcision (the intervention arm), or circumcision delayed for 24 m (the control arm). The profile of the two parallel trials is provided in Figure 1, and details of trial design are reported elsewhere [1,9] and described in Texts S1 and S2. In brief, 6,461 consenting men were screened. If they were HIV-negative, had no contraindications against or medical indications for surgery, and accepted voluntary counseling and testing (VCT), they were enrolled into an NIH-funded trial of HIV-negative men. Men who were HIV-infected at screening, who did not have symptoms of AIDS (WHO stages I or II) or CD4 count < 350 cells/mm^3, and who did not have contraindications to or indications for MC, were offered VCT and were enrolled into a Gates Foundation-funded trial. There were 540 screened men who were ineligible for either trial or who failed to complete enrollment and were excluded. The trials were conducted in 50 rural communities of southwestern Uganda, thus enrollment and follow-up were decentralized, but all surgery took place in fully equipped outpatient theaters located in a central facility.

In the NIH-supported trial, the primary end points were safety and HIV acquisition. A total of 2,474 participants were randomized to receive immediate circumcision. Of these, 2,328 (94.1%) received surgery within 6 m of enrollment, which was completed in August 2005. Two seronegative men who subsequently seroconverted were found to be PCR

positive but antibody negative at enrollment and are excluded from the analysis, leaving 2,326 HIV-negative men who received circumcision surgery. The Gates Foundation-supported trial enrolled 925 HIV-positive men, and the primary endpoints for male participants were safety and sexually transmitted infection effects. Of these 925 HIV-positive men, 474 were randomized to immediate circumcision and 420 (88.6%) had received surgery by December 19, 2006, when enrollment was closed. The Gates Foundation trial Data Safety Monitoring Board (DSMB) closed enrollment of HIV-positive men because the NIH trial was stopped for efficacy on December 12, 2006, and it was no longer feasible to mask the HIV status of new HIV-positive participants, (since HIV-negative men could no longer be randomized to the control condition). At enrollment, 864/925 (93.4%) of circumcised HIV-positive men accepted VCT.

Enrollment and follow-up procedures were identical for HIV-positive and HIV-negative men. All men provided written informed consent for screening and trial enrollment. Men randomized to the intervention arm in either trial provided written informed consent for surgery, which described the procedure, risks of surgery, and the requirements for postoperative wound care (e.g., personal hygiene, keeping the wound dry, and recognizing signs of complications), and they were strongly advised to refrain from sexual intercourse until the wound was certified to be fully healed. Men were also advised to practice safe sex, including as appropriate sexual abstinence, monogamy with an uninfected partner, and consistent condom use. Attempts were made to contact spouses of male participants, and these female partners were also instructed on wound care, the need for sexual abstinence until wound healing was certified, and were counseled on the subsequent practice of safe sex. Free condoms were offered to all participants. Free individual and couples counseling was also offered to all participants and their spouses.

All participants had a medical examination, and any penile pathology such as genital ulcerative disease (GUD), discharge, or balanitis were treated prior to surgery. Circumcision was performed by trained physicians in fully equipped outpatient operating theaters. The physicians had completed an internship and were trained by the senior urologist (SW). Training consisted of initially observing surgeries and conducting a minimum of 15 supervised procedures prior to certification of competence. The sleeve circumcision procedure was used: details of surgery are provided in the paper reporting the results of the NIH-supported trial in HIV-negative men [1]. All men (HIV-positive or HIV-negative) received the same surgical procedure and postoperative care. Postoperative follow-up visits were scheduled at 24–48 h, 5–9 d, and 4–6 wk. Men could access care at any time if complications occurred between scheduled visits. Follow-up was conducted by health workers (clinical officers and nurses) who were trained to diagnose and treat complications or to refer patients for specialized care if needed. Visits took place at the surgical center, in the participant's home, or at central sites ("hubs") located in the rural communities. At each visit, a structured history was taken to detect symptoms of complications, and the wound was inspected. Wound healing was certified when there was an intact healthy scar with no residual exudate or scab formation, and all sutures had been completely absorbed.

Surgery-related adverse events (AEs) were detected at scheduled as well as at unscheduled postoperative visits. Adverse events were predefined and graded as mild, moderate, and severe. (Protocol definitions are available on request.) Grade 1 or mild AEs required no or minimal treatment, whereas grade 2 (moderate) and grade 3 (severe AEs) required medical or surgical intervention. Thus, the moderate and severe AEs are most relevant to assessment of safety. This report focuses on AEs classified as definitely, probably, or possibly related to surgery. The relationship to surgery was in most cases self evident (e.g., bleeding, wound dehiscence, or infection), but in situations where the relationship to surgery was unclear, we erred on the side of caution and assumed a relationship existed. For example, one severe AE requiring hospitalization involved acute severe herpetic ulceration involving the penile shaft and scrotum, but not the surgical wound. This episode occurred during the postoperative period, and it was assumed that surgery precipitated the reactivation of pre-existing herpes. The anatomical site of any lesion was coded as involving the frenulum or other areas of the penis, and codes were added for AEs associated with external causes such as intercourse or trauma.

All surgery-related AEs were reviewed by a medical officer at the time they were reported. The senior urologist (SW), the NIH Medical Officer (MCB), the trial Medical Officer (GK), and the principal investigator (RHG) each independently reviewed all AEs. Subsequently, a panel of physicians, nurses, and clinical officers reviewed all cases and other available records to establish a final diagnosis, severity grading, and assessment of relatedness to surgery. The panel's final assignation was achieved by consensus.

Statistical Methods

Risks of surgery-related AEs were calculated as the number of men with one or more AEs per 100 surgeries. We also assessed multiple AEs experienced by individual participants and tabulated diagnosis specific rates of AEs graded by severity. Baseline characteristics were compared via chi-squared tests of general association. In comparisons of two proportions, p-values were calculated using chi-squared test for equality of two proportions. Exact binomial confidence intervals (CIs) were calculated for risk estimates.

We compared surgery-related AE risks in HIV-positive and HIV-negative men. We also assessed AE risks by sociodemographic characteristics (age, marital status, education, and occupation), risk behaviors (number of sex partners, condom use), and sexually transmitted disease symptoms (GUD, dysuria, and urethral discharge), which differed in frequency between HIV-positive and HIV-negative men at enrollment, and thus potentially could confound the associations between HIV status and the AE outcomes. Adjusted odds ratios (AdjORs) and 95% CIs for all AEs and moderate and severe AEs were estimated by multiple logistic regression. The covariates included in adjusted analyses were age, marital status, education, sex partners in the past year, condom use, and sexually transmitted infection symptoms at enrollment, and initiation of sex before certified wound healing.

We assessed the proportion of men who achieved certified wound healing by 30 postoperative d and at 6 wk following surgery, and evaluated surgery-related AEs among men who reported intercourse prior to certified wound healing,

Table 1. Characteristics of HIV-Positive and HIV-Negative Men

Study Group	Categories	Characteristics, Behaviors, and STI Symptoms	HIV-Positive Men		HIV-Negative Men		p-Value[a]
			n	%	n	%	
All			420	100.0	2,326	100.0	—
	Age (y)	15–19	2	0.5	636	27.3	—
		20–24	54	12.9	648	27.9	—
		25–29	115	27.4	415	17.8	—
		30–39	185	44.0	483	20.8	—
		40–49	64	15.2	144	6.2	<0.001
	Marital status	Currently married	291	69.3	1,100	47.3	—
		Previously married	85	20.2	137	5.9	—
		Never married	44	10.5	1,089	46.8	<0.001
	Education	None	23	5.5	139	6.0	—
		Primary	326	77.6	1,545	66.4	—
		Secondary	51	12.1	550	23.6	—
		Tertiary	20	4.8	92	4.0	<0.001
	Sex partners in past year (n)	0	31	7.4	442	19.0	—
		1	187	44.5	1,079	46.4	—
		2	119	28.3	514	22.1	—
		3+	83	19.8	291	12.5	<0.001
Sexually Active Population			389	100	1,884	100	—
	Condom use in past year	Consistent	29	7.5	311	16.5	—
		Inconsistent	177	45.5	654	34.7	—
		None	183	47.0	919	48.8	<0.001
	STI symptoms in past year	GUD	116	29.8	161	8.6	<0.001
		Urethral discharge	51	13.1	77	4.1	<0.001
		Dysuria	66	17.0	115	6.1	<0.001

[a]Chi-square tests of general association. STI, sexually transmitted infection.
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compared with men who resumed intercourse after healing was certified or did not resume sexual activity. Analyses used Intercooled Stata 8 and R.

These trials were reviewed and approved by two Institutional Review Boards (IRBs) in Uganda (The Scientific and Ethics Committee of the Uganda Virus Research Institute, Entebbe, and the AIDS Subcommittee of the National Council on Research and Technology, Kampala) and two IRBs in the US (the Western Institutional Review Board, Bloomberg School of Public Health, Olympia, Washington, and the Johns Hopkins University, Institutional Review Board, Baltimore, Maryland). Each trial was monitored by separate independent DSMBs.

Results

Table 1 shows the characteristics of the circumcised HIV-negative and HIV-positive men enrolled in the two trials. The differences in baseline distributions of all these characteristics were statistically significant. The HIV-positive men were substantially older than the HIV-negative men (median ages 32 versus 23 y, respectively), more likely to be married or divorced/separated, and less likely to have secondary or higher education. The HIV-infected men reported having more sexual partners and being less likely to consistently use condoms than the HIV-negative men. Moreover, the HIV-infected men reported higher levels of genital ulceration, urethral discharge, and dysuria.

The follow-up rates at the 4–6-wk postoperative visit were 93.6% for HIV-positive men (393/420) and 96.9% (2,253/2,326) for HIV-negative men. Twenty-five (6.0%) of the HIV-positive men experienced at least one AE, compared to 172 (7.4%) of

the HIV-negative men (Table 2, $p = 0.29$). Only seven of the HIV-positive men (1.7%) and 31 of the HIV-negative men (1.3%) experienced more than one AE, and one HIV-negative man had three AEs. The risks of moderate or severe (grades 2–3) surgery-related AEs were 3.1/100 in the HIV-infected men and 3.5/100 in HIV-negative men ($p = 0.49$). Risks of infections were similar in the two groups, occurring in 2.6% of surgeries in HIV-positive men and in 3.0% of surgeries in uninfected men ($p = 0.70$). Bleeding/hematoma complications were comparable in HIV-positive (1.9%) and HIV-negative men (2.4%, $p = 0.56$). Wound dehiscence was more common among HIV-positive men (2.6%) compared to HIV-negative men (1.3%), and this was statistically significant ($p = 0.04$). Other individual AEs were infrequent, mostly mild, and were comparable in both groups (e.g., pain 0.2% in HIV-positive versus 0.3% in HIV-negative men, and difficulty voiding 0.2% in HIV-positive versus 0.3% in HIV-negative participants).

We estimated the AdjORs of any AE and of moderate/severe AEs by HIV status, controlling for characteristics and behaviors found to differ significantly between the two groups at enrollment (Table 1), and for initiation of sex before certification of completed wound healing. The AdjOR of any surgery-related AE in HIV-positive men relative to HIV-negative men was 0.79 (95% CI 0.49–1.27), and the AdjOR for moderate or severe AEs was 0.91 (95% CI 0.47–1.74). GUD at enrollment was associated with an increased rate of moderate or severe AEs (odds ratio = 1.68, 95% CI 0.91–3.10, $p = 0.095$), despite the fact that GUDs were treated prior to surgery. No other baseline covariates were found to be associated with moderate/severe AEs.

The median time to wound healing could not be estimated

Table 2. Surgery-Related AEs by Severity

AEs	Category AE	Grades	HIV-Positive (n = 420 Men)		HIV-Negative (n = 2,326 Men)		
			Number of Men with AEs	Percentage (95% CI)	Number of Men with AEs	Percentage (95% CI)	p-Value[a]
AEs related to surgery		1	12	2.9	90	3.9	—
		2	13	3.1	77	3.3	—
		3	0	0.0	5	0.2	—
Total AEs			25	6.0 (3.9–8.7)	172	7.4 (6.4–8.5)	0.29
Common cause-specific AEs	Infection	1	3	0.7	16	0.7	—
		2	8	1.9	52	2.2	—
		3	0	0.0	1	0.04	—
	All infections		11	2.6 (1.3–4.6)	69	3.0 (2.3–3.7)	0.70
	Bleeding/hematoma	1	3	0.7	31	1.3	—
		2	5	1.2	22	9.5	—
		3	0	0.0	2	0.1	—
	All bleeding/hematoma		8	1.9 (0.8–3.7)	55	2.4 (1.8–3.1)	0.56
	Wound dehiscence	1	11	2.6	27	1.2	—
		2	0	0.0	2	0.1	—
		3	0	0.0	1	0.04	—
	All dehiscence		11	2.6 (1.3–4.6)	30	1.3 (0.9–1.8)	0.04

[a]Chi-square tests for comparison of two proportions.
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because men were observed at 1 wk and then again at 4–6 wk or thereafter, and completed healing had to precede the scheduled visit at which time the wound was observed and certified. However, follow-up by 30 d postoperatively was available for 393 out of 420 HIV-positive men (93.6%), and 2,258 out of 2,326 HIV-negative men (97.1%). By 30 d following surgery, completed wound healing was certified in 73.0% (287/393) of HIV-positive men, compared with 83.2% (1,879/2,258) of HIV-negative men ($p < 0.001$), suggesting more rapid wound healing in the HIV-uninfected participants. Men who were not completely healed at 4–6 wk were followed weekly until healing was complete. At 6 wk after surgery, 92.7% (364/393) of HIV-positive and 95.8% (2,163/2,258) of HIV-negative men had complete wound healing certified ($p = 0.007$).

The risks of surgery-related AEs by self-reported timing of intercourse relative to certification of wound healing were assessed (Table 3). We classified participants as men who initiated intercourse early ($\geq$ 5 d before certification of wound healing), and men who either initiated sex within 5 d of certification or after healing was complete. Among the

HIV-positive circumcised participants, 66 (15.7%) reported that they had resumed sex before the wound was certified as healed, whereas among HIV-negative circumcised men, 250 (10.7%) reported resumption of sex before certification of healing. This difference was statistically significant ($p = 0.003$). A higher proportion of HIV-positive men were married, and married men were more likely to resume sex prior to healing certification than were unmarried men. Among 266 HIV-positive currently married men with follow-up information, 74 (27.8%) reported resuming intercourse before wound healing, whereas among 116 HIV-positive unmarried men, 16 (13.8%) resumed sex before healing was certified ($p = 0.003$). Similarly, among 1,047 currently married HIV-negative men, 305 (29.1%) reported resumption of sex before healing, compared to 75 (6.3%) out of 1,182 unmarried men ($p < 0.001$). Early resumption of intercourse was associated with an increased risk of all surgery-related AEs in HIV-negative and HIV-positive men, although this was statistically significant only for the HIV-uninfected. Early resumption of intercourse prior to wound healing is of programmatic concern because HIV-infected men who resumed sex before wound healing

Table 3. Risks of Surgery-Related AEs by Timing of Resumption of Intercourse in HIV-Positive and HIV-Negative Men

Risks of Surgery-Related AEs	Resumption of Intercourse before Healing	HIV-Positive				HIV-Negative				All Men			
		AEs	n	%	RR (95% CI)	AEs	n	%	RR (95% CI)	AEs	n	%	RR (95% CI)
All AEs	Yes	6	66	9.1	1.63 (0.68–3.93)	29	250	11.6	1.67 (1.14–2.43)	35	316	11.1	1.64 (1.16–2.32)
	No	19	341	5.6	1.00	143	2,056	7.0	1.00	162	2,397	6.8	1.00
Grade 2 and 3 AEs	Yes	2	66	3.0	0.94 (0.21–4.14)	8	250	3.2	0.89 (0.43–1.82)	10	316	3.2	0.89 (0.49–1.70)
	No	11	341	3.2	1.00	74	2,056	3.6	1.00	85	2,397	3.5	1.00
Grade 2 and 3 infections	Yes	2	66	3.0	1.72 (0.36–8.35)	7	250	2.8	1.25 (0.57–2.74)	9	316	2.8	1.31 (0.65–2.64)
	No	6	341	1.8	1.00	46	2,056	2.2	1.00	52	2,397	2.2	1.00

Unadjusted risk ratios (RRs) are presented. AdjORs estimated by multiple logistic regression are given in the text.
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were more likely to infect their female partners (see Discussion) [9], so we assessed the frequency of AEs for both groups combined. The AdjOR of any AE associated with resumption of sex before certified wound healing was 1.56 (95% CI 1.05–2.34, $p = 0.029$). However, early resumption of intercourse was not associated with increased moderate or severe AEs (AdjOR = 0.83, 95% CI 0.42–1.63).

We assessed condom use after resumption of sex at an interview 6 mo postenrollment. Among 314 sexually active HIV-positive participants, 53 (16.9%) reported consistent condom use during follow-up compared with 1,755 sexually active HIV-negative men, of whom 330 (18.8%) reported consistent condom use ($p = 0.42$). However, postoperative consistent condom use by the HIV-positive participants during follow-up increased relative to use at enrollment (16.9% versus 7.7%, respectively, $p < 0.001$). Among HIV-positive men, 45.2% reported inconsistent condom use compared with 37.0% of HIV-negative men ($p = 0.006$).

Discussion

We found that the risks of moderate or severe AEs following adult MC were 3.1% in HIV-infected and 3.5% in HIV-negative men. Thus, we conclude that circumcision performed by adequately trained and equipped medical personnel is likely to be safe in HIV-infected men with WHO stage I or II disease and with a CD4 count > 350 cells/mm^3. Completed wound healing was more rapid in the HIV-negative than in the HIV-positive men, but over 90% of wounds were certified as completely healed by 6 wk postoperatively. Resumption of intercourse before wound healing was associated with higher rates of surgical complications; thus both circumcised men and their partners should be strongly counseled to delay intercourse until full wound healing is achieved.

It is difficult to compare complication rates following adult MC between the three trials of circumcision for HIV prevention [1–3] or case series [7,8] because of differences in AE definitions, and in methods used for detection of AEs and for reporting of events. Further, with the exception of the three HIV prevention trials reported to date [1–3], adult MC is usually performed for medical indications, and the underlying medical conditions (e.g., balanitis, phimosis, ulceration) may contribute to postoperative morbidity. Adult MC complication rates reported in the literature range from 2% to 10% in HIV-negative men [8]. Thus, the complication rates observed in the Rakai trial are compatible with rates associated with circumcisions performed by medically trained practitioners elsewhere. Among HIV-negative men, the rates of surgery-related AEs were 1.7% in the Kenyan trial [2] (although an earlier publication reported a rate of 3.5% [7]), and 3.6% in the South African trial [3]. These rates are compatible with moderate and severe events observed in the present study, but lower than the total AEs observed here (Table 2). However, differences in methods of ascertainment and diagnosis make strict comparisons of AEs between these trials problematic. For example, in the present study in a rural area, AEs were detected by clinical officers mainly during field visits. Review of the AEs suggested that the clinical officers were concerned about access to health services in this setting and tended to overtreat and possibly overdiagnose minor complications. In the South African and Kenyan trials ascertainment of AEs occurred in a central clinic and in settings with better access to services. Thus, the context of the study may have affected reporting. There is little experience with circumcision in HIV-positive adults. The circumcision trial in South Africa reported a surgery-related AE rate of 8.2% in 73 HIV-infected men [3], which is similar to the total AE rate of 6.0% observed in the present trial (Table 2).

The risks of complications following circumcision observed in this and other trials represent the "best case" for safe surgery and were lower than rates of surgical complications observed in public hospitals (11.1%), private medical facilities (22.5%), and traditional practitioners (34.3%) in Kenya [9,10–12]. High complication rates and deaths have been reported with traditional pubertal circumcision in South Africa [13]. Thus, in the scale-up of circumcision programs it will be imperative to provide services under the best feasible circumstances and to upgrade existing personnel and facilities. Efforts will also be required to minimize surgeries by traditional practitioners or to ensure that they have requisite skills.

There is limited experience with the widespread use of surgery as a public health intervention. Mass sterilization programs in India during the 1970s reported serious complications and deaths due to inadequate attention to surgical quality, asepsis, and postoperative care. This led to wide-scale social protest and ultimately rejection of the program [14,15]. Thus, when circumcision is adopted for HIV prevention, it will be imperative to provide safe surgery and good postoperative care, and to mitigate the possible harm that could arise if traditional procedures are promoted, or if inexperienced medical personnel perform the operation under less than optimal circumstances. Future studies are needed in nonresearch settings to determine the safety of circumcision in programs.

Our finding that complications of circumcision are similar in HIV-positive and HIV-negative men has important programmatic implications. Inclusion of HIV-positive men in future circumcision programs could avoid potential stigmatization and may be of benefit to these men by reducing GUD [9]. Although the addition of VCT to circumcision programs is highly desirable, under WHO/UNAIDS guidelines it would not have to be a mandatory precondition for provision of safe surgery [4], and this could reduce barriers for persons unwilling to be tested for HIV, as well as reduce the costs and complexity of circumcision services. An additional finding of programmatic relevance is that resumption of sex before completed wound healing was associated with increased AEs, and that wound healing was complete for more than 90% of participants by 6 wk postoperatively. Also, in a separate analysis of male-to-female HIV transmission following circumcision in the Rakai trial, HIV-infected men who resumed intercourse before certified wound healing were more likely to transmit HIV to their initially uninfected female partners [9]. This suggests that, if follow-up to certify wound healing cannot be conducted, it would be prudent for programs to recommend sexual abstinence for a minimum of 6 wk after surgery both to avoid complications of surgery and to minimize risks to female partners.

In summary, our findings suggest that circumcision is as safe in HIV-infected men with WHO stage I or II or CD4

counts > 350 cells/mm^3, as in uninfected men, and the rates of moderate or severe AEs are acceptably low. However, healing was slower among HIV-positive men, and resumption of intercourse before full wound healing was associated with higher complication rates, irrespective of HIV status, so there is a need to strongly advise men and their female partners of the necessity to abstain from sex until full wound healing is achieved.

Acknowledgments

Supporting Information

Text S1. Protocol for the Gates Foundation-Funded Trial of MC in HIV-Positive Men

Found at doi:10.1371/journal.pmed.0050116.sd001 (707 KB DOC).

Text S2. Protocol for the NIH Funded Trial of MC for HIV Prevention in HIV-Negative Men

Found at doi:10.1371/journal.pmed.0050116.sd002 (573 KB DOC).

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Editors' Summary

Background Worldwide over 33 million people are thought to be living with HIV, and in the absence of a vaccine, preventing its spread is a major health issue. The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimate that 68% of 2.5 million new infections worldwide in 2007 took place in sub-Saharan Africa, where 76% of 2.1 million AIDS-related deaths also took place.

One of the principal means of person-to-person transmission of HIV is through sex without the protection of a condom. In parts of Africa, male circumcision is performed in infancy or childhood for religious or cultural reasons or is a traditional rite of passage that marks the transition from child to man. Three trials, in South Africa, Kenya, and Uganda, each found that circumcised men were around half as likely as uncircumcised men to contract HIV from HIV-positive female partners. After reviewing the results, WHO and UNAIDS issued joint advice that male circumcision should be promoted for preventing HIV infection in heterosexual men. As male circumcision does not provide complete protection against HIV infection, they advised that it should be promoted in addition to existing strategies of promoting condom use, abstinence, and a reduction in the number of sexual partners.

Why Was This Study Done? Although earlier studies had shown that adult male circumcision, when performed in Africa under optimal conditions, is a safe procedure for HIV-negative men, it was not known whether it would also be a safe procedure for HIV-positive men. WHO guidelines recommend that HIV-positive men who request the procedure or have a medical need and no contraindications for it should be circumcised. Also, exclusion of HIV-positive men from circumcision programs may result in stigmatization of these men, and discourage participation by men who do not wish to be tested for HIV. Therefore, it is important to know whether the procedure is safe for HIV-positive men.

What Did the Researchers Do and Find? The authors compared results from two separate clinical trials carried out with identical procedures in rural Rakai, Uganda. The first, which compared the effect of circumcision with no circumcision in HIV-negative men, was one of the three trials that persuaded the WHO and UNAIDS to promote male circumcision as an HIV prevention strategy. The second Rakai trial did the same comparison but in men who were HIV positive and without symptoms. In this present study, the authors used data from both trials to compare the likelihood of surgery-related complications following circumcision for HIV-negative and HIV-positive men.

The trials recruited men aged 15–49, who were randomly assigned to be circumcised either on enrollment or two years later and were followed up to monitor complications related to the procedure, such as infections, as well as wound healing and when the participant first had sex after the operation. Condom use was recorded at enrollment and six months after enrollment.

The researchers found that most complications were infrequent, mild, and comparable in both groups, with moderate-to-severe complications occurring in only 3%–4% of men in each group. However, delayed wound healing was more frequent in HIV-positive men. Complications were more likely among men who had sex before healing was complete; such men were more likely to be HIV-positive and/or married. Similarly,

moderate or severe complications were more likely where men had symptoms of sexually transmitted disease at enrollment, although these were treated before surgery, and these men were more likely to be HIV-positive. Six months after enrollment, similar proportions of HIV-positive and HIV-negative men used condoms consistently, but HIV-positive men were more likely to report using condoms inconsistently than HIV-negative men. However, consistent use of a condom increased among the HIV-positive men compared to when they enrolled.

What Do these Findings Mean? Circumcision in HIV-positive men without symptoms of AIDS has a low rate of complications, although healing is slower than in HIV-negative men. Because of the greater risk of complications if sex is resumed before full healing, both men and their women partners should be advised to have no sex for at least six weeks after the operation. A separately reported analysis from one of these studies found that women partners are more likely to become HIV infected by HIV-positive men who resume sex prior to complete wound healing. Therefore, for protection of both men and their female partners, it is essential to refrain from intercourse after circumcision until the wound has completely healed.

Because the study found no increased risk of surgical complications in HIV-positive men who undergo circumcision, it should not be necessary to screen men with no symptoms of HIV in future circumcision programs. This should reduce the complexity of implementing such programs and reduce any stigma resulting from exclusion, making it likely that more men will be willing to be circumcised. The rise in consistent condom use among HIV-positive men suggests that messages of safe sex are reaching an important target group and changing their behavior, and that circumcision does not make men less likely to use a condom.

The authors also noted that the rates of complications they observed were low compared with those following traditional circumcision procedures. Others have found that circumcision carried out under unsafe conditions has a high rate of complications. The authors of this study comment that the resources and standards of surgery during the trial represented best practice and that to attain similarly low rates of complications—and the confidence of men in the safety of the procedure—there is a need to ensure sufficient resources and high standards of training.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed. 0050116.

- WHO and the UNAIDS issued a joint report recommending male circumcision for HIV prevention and another on the HIV epidemic worldwide in December 2007
- An information pack here on male circumcision and HIV prevention has also been developed jointly by WHO/UNAIDS, the United Nations International Children's Emergency Fund (UNICEF), the United Nations Population Fund (UNFPA), and the World Bank
- The University of California San Francisco's HIV InSite provides information on HIV prevention, treatment, and policy
- AEGIS is the world's largest searchable database on HIV and AIDS
- The National AIDS Trust provides information on HIV prevention