GENERAL GYNECOLOGY

The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda

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OBJECTIVE: The objective of the study was to assess effects of male circumcision on female genital symptoms and vaginal infections.

STUDY DESIGN: Human immunodeficiency virus (HIV)-negative men enrolled in a trial were randomized to immediate or delayed circumcision (control arm). Genital symptoms, bacterial vaginosis (BV), and trichomonas were assessed in HIV-negative wives of married participants. Adjusted prevalence risk ratios (adjPRR) and 95% confidence intervals (CIs) were assessed by multivariable log-binomial regression, intent-to-treat analyses.

RESULTS: A total of 783 wives of control and 825 wives of intervention arm men were comparable at enrollment. BV at enrollment was higher in control (38.3%) than intervention arm spouses (30.5%, $P = .001$). At 1 year follow-up, intervention arm wives reported lower rates of genital ulceration (adjPRR, 0.78; 95% CI, 0.63-0.97), but there were no differences in vaginal discharge or dysuria. The risk of trichomonas was reduced in intervention arm wives (adjPRR, 0.52; 95% CI, 0.05-0.98), as were the risks of any BV (adjPRR, 0.60; 95% CI, 0.38-0.94) and severe BV (prevalence risk ratios, 0.39; 95% CI, 0.24-0.64).

CONCLUSION: Male circumcision reduces the risk of ulceration, trichomonas, and BV in female partners.

Key words: bacterial vaginosis, female genital ulceration, male circumcision, trichomonas, vaginal infections

Cite this article as: Gray RH, Kigozi G, Serwadda D, et al. The effects of male circumcision on female partners' genital tract symptoms and vaginal infections in a randomized trial in Rakai, Uganda. Am J Obstet Gynecol 2009;200:42.e1-42.e7.

Three randomized trials and multiple observational studies demonstrate that male circumcision reduces the risk of human immunodeficiency virus (HIV) infection in men,[1-3] and World Health Organization has recommended that circumcision be promoted for HIV prevention.[4] However, the effects of male circumcision on male sexually transmitted infections (STIs) are more equivocal. In observational studies[5,6] and 2 randomized trials,[1,7] circumcision was associated with reduced symptomatic genital ulcer disease (GUD) in men but had no effects on symptoms of urethral discharge or dysuria in male participants.

If circumcision becomes widely adopted for HIV prevention in men, it is possible that there may be derivative benefits for female partners if the procedure reduces male carriage of HIV and

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Presented at the 15th Conference on Retroviruses and Opportunistic Infections, Boston, MA, Feb. 3-6, 2008.

Received Dec. 12, 2007; revised June 5, 2008; accepted July 31, 2008.

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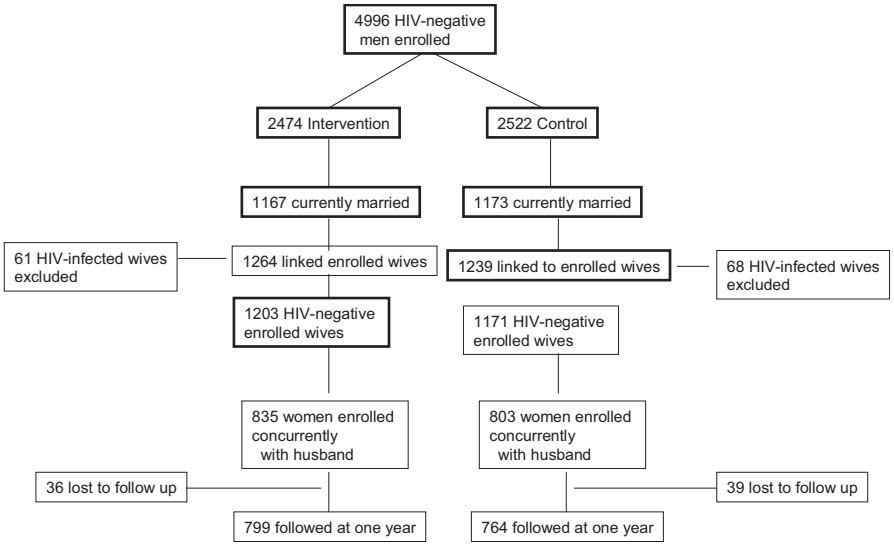
This study was supported in part by Grants (U01 AI11171-01-02) from the National Institutes of Allergy and Infectious Diseases (NIAID), Division of AIDS, National Institutes of Health (NIH), and Grants 2228 and 220062228 from the Bill and Melinda Gates Foundation. The laboratory component was supported in part by the Division of Intramural Research, NIAID, NIH. This publication was supported, in part, by fellowships/grants from the Fogarty International Center/NIH Grant 2 D 43 TW000010-19-AITRP and 5D43TW001508.

0002-9378/$36.00 • • doi: 10.1016/j.ajog.2008.07.069

FIGURE
Trial Profile



Gray. Effects of circumcision on female partners' genital symptoms and vaginal infections. Am J Obstet Gynecol 2009.

STIs or directly affects male-to-female transmission. One observational study suggested that there may be a reduction of HIV, bacterial vaginosis (BV), and *Trichomonas vaginalis* infections in female partners of circumcised men.[8] However, 2 US studies observed no association between a man's circumcision status and female BV.[9,10] Therefore, we examined data on vaginal infections from female partners of men enrolled in a randomized trial of male circumcision for HIV prevention, in Rakai District, Uganda.

Materials and Methods

The trial of male circumcision, supported by the National Institutes of Health has been described elsewhere.[1] In brief, 4996 HIV-negative men aged 15-49 years who accepted voluntary counseling and receipt of their HIV results were enrolled and randomized to immediate circumcision (the intervention arm, n = 2474) or circumcision delayed for 2 years (the control arm, n = 2522). The trial was closed early on Dec. 12, 2006, because an interim analysis showed evidence of circumcision efficacy for male HIV acquisition.

At enrollment, male trial participants were asked to identify their wives or long-term consensual partners. Consenting men who provided this information were then linked to their female partners who were enrolled and followed up in a separate study supported by the Bill and Melinda Gates Foundation. Because the male circumcision trial was closed, we felt it appropriate to assess the potential effects of male circumcision on the health of their female partners because this could be of relevance to future policy decisions with regard to promotion of male circumcision.

The trial profile is given in the Figure. There were 1264 wives currently married or in long-term union with 1167 men enrolled in the intervention arm (1.08 wives per married man), and there were 1239 female spouses of 1173 men enrolled in the control arm of the trial (1.06 wives per married man). The number of linked, enrolled women exceeded the number of enrolled men because of polygamous relationships.

At the time of female enrollment, 1203 wives of intervention arm men were HIV negative (95.2%); and in the control arm 1171 were uninfected with HIV (94.5%). Among these HIV-negative married women, 835 (69.4%) were enrolled concurrently with their husbands in the intervention arm (ie, before the man's circumcision surgery), and 803 (68.6%) were enrolled concurrently with their control arm husbands. These HIV-uninfected women who were enrolled at the same time as their husbands constitute the primary analysis sample for this study (Figure).

A minority of women (368 in the intervention arm and 368 in the control arm) were enrolled 6 or more months after their husband's enrollment date. These women were excluded from the primary intent-to-treat analysis because if circumcision affected female vaginal symptoms or infections, the baseline information for these women could have been biased by the interval of exposure between their male partner's circumcision and the woman's initial enrollment visit.

Among the 835 HIV-negative concurrently enrolled HIV-negative female partners of HIV-uninfected intervention arm men, 799 (95.7%) were followed up at 1 year after enrollment, and among the 803 concurrently enrolled female partners of control arm, men 764 (95.1%) were followed up at 1 year. At the time of the closure of the National Institutes of Health male trial, 90% of men had completed 12 months of follow-up, but only 44% of male participants had the opportunity to complete 24 months follow-up. Therefore, the female follow-up was truncated at 1 year.

The married women were visited after their husbands had enrolled in the trial and were then followed up at annual intervals. At each study visit, women were interviewed to ascertain sociodemographic characteristics, sexual risk behaviors, and health status, including symptoms of genital tract infections (GUD, vaginal discharge, and dysuria). Symptomatic women were treated syndromically.

At each visit, women were asked to provide a self-collected vaginal swab for diagnosis of BV and *T vaginalis*. BV was detected by Gram-stained slides from vaginal swabs using the criteria of Nugent et al,[11] a quantitative morphology that has a standardized 0 to 10 point scoring system, whereby 0-3 is normal, 4-6 is intermediate (transitional state), and 7-10 is BV. Severe BV was defined as a score of 9-10. Enrollment information on BV was available for 825 of 835 con-

currently enrolled wives of intervention arm men (98.8%) and 783 of 803 wives of control arm men (97.5%).

Twelve month follow-up data on BV were available for 785 intervention arm women (98.7% of women followed up), and 751 control arm wives (98.4%) of women followed up. The number of women with information on BV was less than the number of women seen because some participants declined to provide self-collected vaginal swabs.

Trichomonas vaginalis was detected from cultures of vaginal swabs using the InPouch TV culture method (BioMed Diagnostics, San Jose, CA). Because of financial constraints, trichomonas culture was initiated only late in the study, and there were limited data available at the time of female enrollment. At the 12 month follow-up visit, data on trichomonas were available for 408 intervention arm wives (51.1% of those followed up) and for 402 control arm wives (52.7% of those followed up). Assays for human papillomavirus and herpes simplex virus type 2 (HSV-2) are ongoing, so this report focuses on vaginal infections with trichomonas and BV.

We conducted an intent-to-treat analysis to assess the prevalence of symptoms of genital tract infections and diagnoses of BV and trichomonas during follow-up in concurrently enrolled HIV-negative wives of male participants in the intervention, compared with the control arm of the randomized trial.

STI symptoms reported over the 6 month period preceding the 1 year follow-up visit were used to estimate the period prevalence of symptoms per 100 women. Diagnoses of BV and trichomonas at the 12 month visit were used to estimate the point prevalence of these conditions per 100 women. In addition, tabulations of BV scores at follow-up were stratified by BV scores at enrollment to determine rates of progression to BV from normal or intermediate baseline flora scores, and among women with BV at enrollment, we determined persistence of BV at follow-up.

Unadjusted prevalence risk ratios (PRRs) and 95% confidence intervals (CIs) were estimated. Adjusted prevalence risk ratios (adjPRRs) were estimated using multiple log-binomial regression, with adjustment for age (15-19, 20-24, 25-29, and 30 years or older), monogamous or polygamous marriage at enrollment, self-reported numbers of sexual partners (1, 2, 3, or more), and use of condoms (none, consistent, or inconsistent) during the 1 year follow-up interval. Because the prevalence of BV differed between study arms at enrollment, we also adjusted the follow-up prevalence of BV for the presence of BV at enrollment. The percent efficacy of circumcision was estimated as follows: (1-adjPRR) $\times$ 100%.

We also conducted an as-treated analysis whereby men allocated to the intervention arm but who failed to return for surgery within 6 months of enrollment were classified as uncircumcised (n = 36). Two control participants received circumcision from other sources during the first year of follow-up and were circumcised crossovers.

Enrollment of the HIV-negative male trial participants was funded by the National Institutes of Health, and the trial was registered (ClinicalTrials.Gov number NCT00425984). The enrollment and follow-up of female partners of trial participants was funded by the Gates Foundation and is registered (Clinical.Trials.Gov number NCT00124878).

The study was reviewed and approved by 2 institutional review boards (IRBs) in Uganda (the Scientific and Ethics Committee of the Uganda Virus Research Institute and the Uganda National Committee of Science and Technology) and 2 IRBs in the United States (the Johns Hopkins Bloomberg School of Public Health IRB and Western IRB). A community advisory board provided guidance for the study and 2 data safety monitoring boards, 1 for the NIH and the other for the Gates-funded study, provided oversight.

RESULTS

Table 1 shows the characteristics of the women at enrollment. Randomization of male trial participants produced a high degree of comparability in female partner enrollment characteristics and sexual behaviors between arms. There was also comparability with respect to STI symptoms. Only a small minority of women had enrollment cultures for trichomonas because these tests were initiated late in the study, so the overall baseline prevalence cannot be assessed.

BV at enrollment was less frequent among women married to intervention arm men (30.6%) than women married to control men (38.3%), and this difference was statistically significant (P = .001). Severe BV (scores 9-10) were also lower in the intervention than control arm wives (1.8% vs 2.6%), but this difference was not statistically significant (P = .4).

As shown in Table 2, the rates of self-reported GUD were significantly lower in the wives of intervention arm men (12.8%) than in women with control arm partners (16.8%, P = .03). However, there were no differences in the frequency of female symptoms of discharge or dysuria by their husband's arm of randomization. The prevalence of trichomonas was significantly lower among women with intervention arm husbands (5.9%), compared with women with control arm husbands (11.2%, P = .01). BV prevalence was significantly lower among the wives of intervention arm men (40.3%), compared with wives of control arm men (50.6%, P = .00006).

The proportion of women reporting 2 or more sex partners during the follow-up interval was higher in the control than intervention arm women (5.6% and 3.4%, respectively, P = .02), but there were no differences between study arms in self-reported condom use or consistency of use during follow-up.

Because BV prevalence differed significantly between study arms at enrollment with a higher prevalence in the control arm (Table 1), the differentials observed at follow-up could reflect this preexisting differential at enrollment. Therefore, we assessed BV at follow-up, stratified by enrollment vaginal flora scores. Our reasoning was that if circumcision affected BV, the effects should be observed among women without BV at enrollment, and this should not be affected by disparities in BV prevalence at enrollment. The results are shown in Table 3.

Among women with normal flora (scores 0-3) at enrollment, progression to BV during follow-up was significantly lower in the wives of intervention than control arm men (PRR, 0.80; 95% CI, 0.65-0.97; $P = .005$). Progression to BV among women with intermediate flora scores (4-6) at enrollment was less in the intervention than the control arm, but this was not statistically significant (PRR, 0.83; 95% CI, 0.65-1.06; $P = .2$). However, in women who had BV at enrollment, persistent BV at 1 year follow-up was significantly lower in the intervention arm than control arm women (PRR, 0.83; 95% CI, 0.72-0.96; $P = .02$.)

We also assessed women with severe BV (scores 9-10) at follow-up (Table 3). In the control arm wives with initially normal vaginal flora, 4.0% progressed to severe BV, whereas no intervention arm wives developed severe BV ($P = .0002$). Similarly, among women with intermediate flora at enrollment, progression to severe BV was lower in the intervention (0.7%) than in the control arm (5.6%) wives, and this difference was of borderline statistical significance (PRR, 0.13; 95% CI, 0.02-1.06; Fisher $P = .03$). Among women with BV at enrollment, severe BV was lower in the wives of intervention than control arm at follow-up, although the difference was not statistically significant (PRR, 0.61; 95% CI, 0.33-1.12).

After adjustment for enrollment characteristics and sexual risk behaviors during follow-up, the log binomial adjusted prevalence risk ratio of GUD among wives of intervention, compared with control arm participants, was 0.78; 95% CI, 0.61-0.99; $P = .04$, suggesting a circumcision efficacy of 22% (95% CI, 1-39%). For trichomonas infection in the intervention relative to control arm wives, the adjPRR was 0.55, 95% CI, 0.34-0.89; $P = .02$ (efficacy 45%; 95% CI, 11-66%). The adjusted risk of trichomonas was increased among women reporting 2 (adjPRR, 2.02; 95% CI, 1.05-4.33) and 3 or more sex partners (adjPRR, 5.12; 95% CI, 1.05-25.77), compared with 1 partner. For BV at follow up, the adjPRR was 0.82 (95% CI, 0.74-0.91; $P = .0003$), with an efficacy of 18% (95% CI, 9-26%.) Compared with women without BV at enrollment, the adjusted risk of BV at fol-

TABLE 1
Enrollment characteristics of HIV-negative women by their husband's study arm

	Control		Intervention	
	n	%	n	%
All	803	100	835	100
Age, y				
15-17	22	2.7	29	3.5
18-19	95	11.8	109	13.1
20-24	290	36.1	274	32.8
25-29	212	26.4	233	27.9
30-39	155	19.3	167	20.0
40-49	29	3.6	23	2.8
Marital status				
Monogamous	687	85.6	690	82.6
Polygamous	116	14.4	143	17.1
Religion				
Catholic	494	61.5	516	61.8
Protestant	218	27.1	230	27.5
Saved	68	8.5	66	7.9
Muslim	23	2.9	22	2.6
Education				
None	108	13.4	118	14.1
Primary	581	72.4	604	72.3
Secondary	98	12.2	96	11.5
Tertiary	16	2.0	16	1.9
Sex partners past year				
0	3	0.4	1	0.1
1	763	95.0	810	97.0
2	34	4.2	20	2.4
3+	3	0.4	4	0.5
Condom use				
Consistent	4	0.5	4	0.5
Inconsistent	143	17.8	127	15.2
No use	656	81.7	704	84.3
Drank alcohol with sex				
Never	543	67.6	565	67.7
Sometimes	260	32.4	269	32.2
Always	0	0.0	1	0.1
STD past year				
GUD	105	13.1	113	13.5
Discharge	360	44.8	386	46.2
Dysuria	164	20.4	160	19.2

Gray. Effects of circumcision on female partners' genital symptoms and vaginal infections. Am J Obstet Gynecol 2009.
(continued)

TABLE 1
Enrollment characteristics of HIV-negative women by their husband's study arm *(continued)*

	Control		Intervention	
	n	%	n	%
Vaginal infections				
Trichomonas	1/1	100	0/1	0
Any BV	300/783	38.3	252/825	30.5[a]
Severe BV	20/783	2.6	15/825	1.8

[a] $P = .001$.

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low-up was also significantly increased if the woman had BV at enrollment (adjPRR, 1.51; 95% CI, 1.35-1.568).

The as-treated analyses yielded similar results to the intent-to-treat analyses because crossovers were few in number (n = 36). For trichomonas, the as-treated adjusted PRR was 0.55 (95% CI, 0.34-0.88; $P = 0.14$), and for BV the adjPRR was 0.82 (95% CI, 0.74-0.92).

Comment

This trial of HIV uninfected female partners of HIV uninfected men found that female partners of circumcised men had reduced risks of GUD (efficacy 22%), trichomonas (efficacy 45%), and BV (efficacy 18%). This strongly suggests that male circumcision may have direct benefits for prevention of GUD and vaginal infections in female partners.

The findings from this randomized trial are consistent with those from a prior observational study in Rakai, which reported significantly reduced risks of GUD (PRR, 0.6; 95% CI, 0.4-1.0), BV (PRR, 0.79; 95% CI, 0.69-0.91), and trichomonas (PRR, 0.55; 95% CI, 0.55-0.77).[8] However, our findings are contrary to 2 small US studies that found no association between male circumcision and BV in female partners, but a high proportion of men in these studies were circumcised, and there was limited power to detect an effect relative to women with uncircumcised partners.[9,10] We are not aware of other studies examining female GUD or vaginal infections associated with male circumcision.

The mechanisms for the protective effects of male circumcision on female GUD and vaginal infections are unknown. However, it is known that circumcised men are less likely to have symptomatic genital ulcer disease,[12] and a metaanalysis suggested that circumcision is associated with reduced rates of

TABLE 2
Vaginal symptoms, trichomonas, and BV during follow-up visits for HIV-negative women, by male partner's randomization arm

Outcomes at 1 y follow-up and sexual behaviors	Control		Intervention		Unadjusted PRR (intervention/control)	95% CI
	n/N	%	n/N	%		
Vaginal symptoms						
Genital ulceration	128/763	16.8	102/798	12.8	0.76	0.60-0.97
Discharge	323/763	42.3	336/798	42.1	0.99	0.89-1.12
Dysuria	114/763	14.9	113/798	14.2	0.97	0.75-1.21
Vaginal infections						
Trichomonas	45/402	11.2	24/408	5.9	0.53	0.33-0.85
BV	380/751	50.6	316/785	40.3	0.80	0.71-0.89
Severe BV	49/751	6.52	16/785	2.04	0.31	0.18-0.54
Sexual behaviors						
Number of sex partners						
1	715/760	94.1	786/795	96.6	1.03	1.00-1.05
≥ 2	45/760	5.6	27/795	3.4	0.57	0.36-0.91
Condom use						
None	607/763	79.6	655/798	82.1	1.03	0.98-1.08
Inconsistent	148/763	19.4	134/798	16.8	0.87	0.70-1.07
Consistent	8/763	1.1	9/798	1.1	1.08	0.42-2.77

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TABLE 3
Bacterial vaginosis at follow-up by vaginal flora score at enrollment

Vaginal flora score at enrollment	Control		Intervention		PRR (intervention/control)	95% CI
	BV at follow-up/n at enrollment	BV at follow-up, %	BV at follow-up/n at enrollment	BV at follow-up, %		
0-3	124/325	38.2	122/402	30.3	0.80	0.65-0.97
4-6	67/124	54.0	60/134	44.8	0.83	0.65-1.06
7-10	185/285	64.9	130/240	54.2	0.83	0.72-0.96
	Severe BV		**Severe BV**			
	(9-10)		(9-10)			
0-3	13/325	4.0	0/402	0.0	0.00	0.00-0.24[a]
4-6	7/124	5.6	1/134	0.7	0.13	0.02-1.06
7-10	29/285	10.2	15/240	6.3	0.61	0.33-1.12

[a] Unconditional exact interval (StatXact 6.0).

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ulceration caused by HSV-2, *Haemophilus ducreyi*, and syphilis.[13] Therefore, reduced male carriage of these pathogens may reduce transmission of these ulcerative STIs to women. In addition, the subpreputial space in uncircumcised men is moist,[14] and this may enhance survival of trichomonas and possibly the Gram-negative anaerobes associated with BV, so removal of the foreskin could reduce female exposures to these pathogens.

We considered potential biases that might affect these results. Our findings with respect to the effects of male circumcision on BV are complicated by the fact that BV was more common among the control than the intervention arm women at enrollment, so differentials observed at follow-up could have been due to preexisting differences between women in the 2 arms rather than a direct effect of circumcision on BV per se.

We do not know why randomization did not result in comparability of BV at enrollment, and we have been unable to identify any factor, from randomization to the selection of the final analysis set, that would have made a systematic difference in the proportions with BV at enrollment. However, circumcision significantly reduced the risk of progression to BV among women with normal flora at enrollment and reduced the risks of persistent BV among women with BV at enrollment (Table 3). This strongly suggests that male circumcision provides partial protection from BV in female partners.

Although there were no differentials in sexual risk behaviors reported by women at enrollment (Table 1), the wives of control arm men did report more sexual partners during follow-up (Table 2), and this could have affected their risks of vaginal infections. This apparent disinhibition among wives of control arm men could have occurred by chance or might arise if uncircumcised men experienced more difficulties with intercourse (eg, caused by phimosis), which caused a minority of their wives to seek other partners. However, we adjusted for these differentials in behaviors between arms by multivariate analyses, and there were no differentials in sexual risk behaviors reported by male trial participants.[1] Thus, confounding because of differential risk behaviors is unlikely.

The questions with regard to STI symptoms were asked prior to questions on the woman's partner's circumcision status, so interviewer bias is also unlikely. Moreover, if such bias occurred, it would probably have affected questions on all vaginal symptoms, whereas the only protective effects were observed with symptomatic GUD but not with vaginal discharge or dysuria. A similar protective effect of circumcision specifically against GUD was also observed among men in the randomized trial.[1]

Laboratory bias in the diagnosis of trichomonas or BV is extremely unlikely because technicians were blinded to the male partner's circumcision status. Retention rates were high and comparable in both study arms, so selective loss to follow-up cannot explain the study findings. Thus, we conclude that the protective effects of male circumcision on female GUD and vaginal infections is likely to be a valid observation.

These findings may have implications for future programs providing male circumcision for HIV prevention because GUD and vaginal infections are potential cofactors for HIV acquisition,[15-19] and reductions in these conditions because of circumcision may potentially protect women from HIV infection. Observational studies suggest that male circumcision is associated with decreased risks of HIV in female partners.[20,21] Thus, male circumcision might protect women from HIV risk by lowering infectivity (eg, reduced male HIV shedding from the preputial mucosa), reducing HIV cofactors such as GUD in both men and women, and reducing vaginal infections in women. In addition, because circumcision prevents male HIV acquisition, it is also likely to have an indirect effect via reduced female exposures to the virus, thus lowering secondary HIV transmissions to women.

We conclude that male circumcision prevents genital ulceration, trichomonas, and BV in female partners and that this benefit to women should be considered when planning scale-up of male circumcision programs for HIV prevention. ■

ACKNOWLEDGMENTS

The laboratory component was supported in part by the Division of Intramural Research, National Institutes of Allergy and Infectious Diseases, National Institutes of Health. We would like to acknowledge the members of the National Institutes of Health and Bill and Melinda Gates Foundation data safety monitoring boards, which monitored this trial, as well as the institutional review boards, which provided oversight (the Scientific and Ethics Committee of the Uganda Virus Research Institute, the Committee for Human Research at Johns Hopkins, and the Western Institutional Review Board). We also are grateful for the advice provided by the Rakai Community Advisory Board. Finally, we wish to express our gratitude to study participants whose commitment and cooperation made the study possible.

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