Age of male circumcision and risk of prevalent HIV infection in rural Uganda

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Objective: To assess whether circumcision performed on postpubertal men affords the same level of protection from HIV-1 acquisition as circumcisions earlier in childhood.

Design: Cross-sectional study of a population-based cohort.

Setting: Rakai district, rural Uganda.

Methods: A total of 6821 men aged 15–59 years were surveyed and venous blood samples were tested for HIV-1 and syphilis. Age at circumcision was dichotomized into men who were circumcised before or at age 12 years (prepubertal) and men circumcised after age 12 years (postpubertal). Postpubertal circumcised men were also subdivided into those reporting circumcision at ages 13–20 years and ≥ 21 years.

Results: HIV-1 prevalence was 14.1% in uncircumcised men, compared with 16.2% for men circumcised at age ≥ 21 years, 10.0% for men circumcised at age 13–20 years, and 6.9% in men circumcised at age ≤ 12 years. On bivariate analysis, lower prevalence of HIV-1 associated with prepubertal circumcision was observed in all age, education, ethnic and religious groups. Multivariate adjusted odds ratio of prevalent HIV-1 infection associated with prepubertal circumcision was 0.39 [95% confidence interval (CI), 0.29–0.53]. In the postpubertal group, the adjusted odds ratio for men circumcised at ages 13–20 years was 0.46 (95% CI, 0.28–0.77), and 0.78 (95% CI, 0.43–1.43) for men circumcised after age 20 years.

Conclusions: Prepubertal circumcision is associated with reduced HIV risk, whereas circumcision after age 20 years is not significantly protective against HIV-1 infection. Age at circumcision and reasons for circumcision need to be considered in future studies of circumcision and HIV risk.

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Introduction

Epidemiological evidence suggests that male circumcision may reduce the risk of sexually transmitted diseases (STD) and possibly HIV infection. Studies of STD clinic attenders have found that circumcised men are less likely to have gonorrhea, syphilis, herpes, candidiasis, and genital ulcer disease (GUD) [1–3]. Age at circumcision has also been reported as a risk factor in penile cancer [4]. Ecological studies report geographic correlations between HIV seroprevalence and the proportion of uncircumcised men in African populations [5,6], but subsequent cross-sectional and prospective studies found an inconsistent association between male circumcision and HIV-1 and HIV-2 infection in men and women [7–9]. A review of these investigations found 22 cross-sectional studies from six African countries showing protective associations [10,11], and longitudinal studies in Uganda found male circumcision to have a protective effect on incident HIV infection [12]. However, studies in Gambia, Rwanda and Tanzania observe opposite trends with higher HIV prevalence in circumcised men [13–15].

The seemingly protective effect of circumcision led several researchers to propose that male circumcision should be considered a possible preventive intervention to reduce HIV transmission [6,16]. However, the use of circumcision in adult men is a critical question. The wisdom of implementing a circumcision intervention has been criticized due to concern over the epidemiological interpretation of the data on which such a policy would be based [17]. We hypothesize that prepubertal circumcision, performed for religious or traditional reasons, is likely to protect against STD and other genital infections, whereas postpubertal circumcision is likely to be performed as a consequence of infections, such as balantitis, which may be complications of STD. Other questions relevant to the issue include concern over the safety of circumcision, its acceptability due to cultural and religious implications, the feasibility of funding and implementation of a large program [17,18].

In this study, we report recent data from Rakai, Uganda to assess whether circumcision performed on postpubertal men is associated with lower HIV prevalence, as observed with circumcision earlier in childhood.

Methods

The detailed methods of the field studies have been described elsewhere [19], but a brief description follows. Rakai is a rural district in southwest Uganda bordering Tanzania and Lake Victoria and transversed by paved roads carrying traffic from Tanzania, Rwanda, the Democratic Republic of Congo (former Zaïre), and Kenya. In 1989, HIV prevalence among all adults (age $\geq$ 13 years) in Rakai was 38.5% in main road trading centers, 25.4% in smaller local trading villages on secondary dirt roads, and 8.6% in agrarian villages [20]. The incidence of HIV in all adults was 2.1 [95% confidence interval (CI), 1.1–3.1] per 100 person-years [21].

Rakai District is the site of a randomized community-based trial of STD control for AIDS prevention that began in November 1994 in 56 communities. In this open cohort, all consenting adults aged 15–59 years at baseline were enrolled, interviewed from the home and asked to provide blood for HIV and syphilis serology. Questionnaire data collected included their knowledge, attitudes, behaviors and practices with regard to STD/HIV; for men, circumcision status, and age and reason for circumcision were also collected. Information was also obtained on sociodemographic characteristics (age, education, ethnic group, religion, marital status and number of wives) and on high-risk sexual behaviors and health (number of sexual partners in past 5 years, use of alcohol in the past month, and reported STD symptoms in past 6 months).

A total of 6994 men initially enrolled in this study. Of these, 5289 men were interviewed at the first survey round (November 1994–June 1995), and 1705 men were interviewed for the first time during the second survey round (July 1995–March 1996). The men interviewed during the second round were either absent during the first round, or were new in-migrants to the study communities. The final study sample was from the 6821 men (97.6%) who gave serum samples and for whom HIV serostatus was available. At the time these data were collected, the men had not been previously exposed to the STD intervention (survey and drug treatment) and did not know their HIV serostatus. Since the results of this analysis are based on prevalent HIV at enrollment and on sociodemographic and behavioral characteristics that temporally precede this study, the treatment or control status of the respondents, or their subsequent request for HIV results, has no bearing on results and are not addressed in this baseline data analysis. The study achieved high participation rates (> 90%), and the enrolled men reflected the general male population of the district [21].

Laboratory analysis

Venous blood samples are tested for HIV-1 and syphilis [19]. HIV was diagnosed by positive results from two enzyme immunoassays (Recombigen EIA, Cambridge Biosciences, Cambridge, Massachusetts, USA; and Organon Teknika, Durham, North Carolina, USA). On discordant samples, Western blot was used to confirm the diagnosis (Cambridge Biosciences). Active or recently treated syphilis was diagnosed with the nontreponemal toludine red unheated serum test (TRUST; New Horizons, Columbia, Maryland, USA) and positive TRUST results were confirmed by a qualitative *Treponema pallidum* hemagglutination test (Sera-Tek, Miles Inc. Diagnostics, Elkhart, Illinois, USA). Serological tests were performed at the Uganda Virus Research Institute, Entebbe, or in the project field laboratory in Rakai, and samples were sent for quality control to Johns Hopkins University (Baltimore, Maryland, USA).

Statistical analysis

Bivariate analysis was used to estimate the odds ratio (OR) of HIV-1 prevalence among men who were circumcised before or at age 12 years (prepubertal circumcision) with men who were circumcised after age 12 years (postpubertal circumcision) and with men who were not circumcised. We used 95% CI of the OR and χ^2 analysis to test the statistical significance of differentials in HIV prevalence by age at circumcision, using the uncircumcised men as the referent group. Multivariate logistic regression [22] was used to estimate the OR of HIV-1 infection among prepubertal and postpubertal circumcised men relative to men who were not circumcised (referent group). We further divided the postpubertal circumcised men into those reporting circumcision at ages 13–20 years (n = 165) and ≥21 years (n = 76). The models included risk factors found to be significant from the bivariate analysis, possible confounders and biologically plausible covariates. Risk factors were grouped and models were constructed separately for distal socioeconomic covariates, and for more proximate behavioral risk factors. A final model was constructed from those covariates in the first two models that were significant at a cut-off level of $P < 0.15$. Significance of the circumcision parameter was assessed by the 95% CI of the OR likelihood ratio test between the model without the circumcision parameter and the model with circumcision. Model goodness of fit was assessed by the Hosmer and Lemeshow test [22]. SPSS version 8.0 statistical computer software was used for all analyses (SPSS, Inc., Chicago, Illinois, USA).

Results

Association of circumcision status with HIV prevalence

Amongst the 6821 men in this study, the overall proportion circumcised was 15.7%, with 12.1% of men circumcised at age ≤ 12 years, and 3.5% of men circumcised at age ≥ 13 years. Amongst the latter, there were 165 (2.4%) men circumcised at age 13–20 years, and 76 (1.1%) circumcised at age ≥ 21 years. There was little variation in circumcision rates by current age (14% in 15–19-year-olds and 15.4% in men aged ≥ 45 years), which suggests that rates of circumcision have been stable over time.

Table 1 shows HIV prevalence associated with circumcision status and other covariates. HIV prevalence was 14.5% for men circumcised at age ≥ 13 years (postpubertal circumcision), 14.1% in uncircumcised men, compared with 6.9% in men circumcised at age ≤ 12 years. Stratifying for sociodemographic characteristics, the lower prevalence of HIV associated with prepuber-

Table 1. HIV seroprevalence among men and odds ratios (OR) by circumcision status, age at circumcision and sociodemographic characteristics (n = 6821).

Selected sociodemographic characteristics	No. men (% HIV-positive)			OR (95% CI) relative to those uncircumcised	
	Not circumcised	Circumcised			
		≤ 12 years	> 12 years	≤ 12 years	> 12 years
Total	5750 (14.1)	830 (6.9)	241 (14.5)	0.45 (0.34–0.60)	1.03 (0.75–1.41)
Age (years)					
15–24	2554 (3.5)	385 (0.8)	37 (5.4)	0.22 (0.04–0.65)	1.56 (0.18–6.25)
25–29	974 (20.6)	133 (15.0)	47 (23.4)	0.68 (0.40–1.15)	1.18 (0.55–2.45)
30–34	676 (33.1)	113 (14.2)	42 (19.0)	0.33 (0.18–0.59)	0.47 (0.20–1.09)
35–39	474 (28.5)	74 (4.1)	35 (20.0)	0.11 (0.03–0.36)	0.63 (0.24–1.55)
40–44	303 (21.8)	41 (12.2)	24 (12.5)	0.50 (0.16–1.40)	0.51 (0.12–1.89)
≥ 45	769 (12.4)	84 (11.9)	56 (7.1)	0.96 (0.45–1.99)	0.55 (0.16–1.62)
Education					
None/primary	4084 (14.5)	578 (7.4)	154 (9.0)	0.47 (0.34–0.66)	0.59 (0.32–1.05)
Secondary/further	1665 (13.2)	252 (5.6)	87 (24.1)	0.39 (0.21–0.70)	2.10 (1.22–3.59)
Religion					
Non-Muslim	5737 (14.1)	97 (9.3)	132 (16.7)	0.62 (0.29–1.28)	1.21 (0.74–1.97)
Muslim	13 (0)	733 (6.5)	109 (11.9)	–	–
Ethnic group					
Baganda	4548 (14.4)	708 (7.5)	146 (15.8)	0.48 (0.36–0.65)	1.11 (0.69–1.78)
Banyankole	468 (14.3)	39 (2.6)	29 (17.2)	0.16 (0.01–0.97)	1.25 (0.40–3.60)
Banyarwanda	196 (11.2)	9 (11.1)	13 (7.7)	0.44 (0.02–3.39)	0.66 (0.03–5.32)
Other	538 (12.5)	74 (2.7)	53 (11.3)	0.20 (0.03–0.76)	0.90 (0.33–2.29)

CI, Confidence interval.

tal circumcision was observed in all age (except for ≥ 45 years), education, religious and ethnic groups (except for Banyarwanda, a small minority group). Within each circumcision category, HIV prevalence was highest between the 25–29-year or 30–34-year age-groups. The differentials for men with late circumcision was not as clear and analysis was limited by small numbers, but men circumcised later in life had significantly higher rates of HIV amongst the younger (15–29 years) and better educated men, relative to uncircumcised men.

Religious affiliation was, as expected, strongly associated with circumcision status: 98.5% of all Muslim men were circumcised, whereas only 3.8% of non-Muslims were circumcised. The correlation between being Muslim and being circumcised in prepuberty was 0.83. Muslims accounted for 79% of all circumcised men. Thirteen Muslim men reported that they were uncircumcised and none were found to have HIV infection. However, the HIV prevalence for prepubertal circumcised Muslim men was significantly lower than among Muslims with postpubertal circumcision (6.5% and 12%, respectively; OR, 1.82; 95% CI, 1.02–3.25). The same pattern was found in non-Muslims, where early circumcision, but not late circumcision, was associated with a protective effect on HIV infection, although this was not statistically significant.

Controlling for proximate risk behaviors, HIV prevalence increased with the number of sex partners reported within the past 5 years in all circumcision categories (Table 2). However, HIV prevalence was significantly lower in the prepubertal circumcision group irrespective of the reported number of partners. The differences between uncircumcised men and those circumcised in postpubescence were less pronounced and not statistically significant when stratified by sexual activity. A test for trend in number of sex partners within the past 5 years by circumcision status was statistically significant for non-circumcision ($P < 0.0001$) and prepubertal circumcision ($P < 0.0001$), but only borderline significant for postpubertal circumcision ($P = 0.054$).

Since 79% of the circumcised men were Muslim, their reported number of partners is more likely to represent polygamy rather than extramarital relationships, so we examined the associations with HIV among polygamous men. For polygamous men, HIV prevalence increased with the number of sexual partners regardless of circumcision status. For those who reported more than three sexual partners, polygamous men circumcised in prepubescence had a significantly lower HIV prevalence than uncircumcised men (OR, 0.16; 95% CI, 0.05–0.50). Circumcision provides a non-significant protective effect for polygamous men

Table 2. HIV seroprevalence among men and odds ratios (OR) by circumcision status, age of circumcision, risk behaviors and symptoms of sexually transmitted diseases (n = 6821).

Selected sociodemographic characteristics	No. men (% HIV-positive)			OR (95% CI) relative to those uncircumcised	
	Not circumcised	Circumcised			
		≤ 12 years	> 12 years	≤ 12 years	> 12 years
Total	5750 (14.1)	830 (6.9)	241 (14.5)	0.45 (0.34-0.60)	1.03 (0.75–1.41)
Sex partners in last 5 years*					
0	984 (2.2)	126 (0.8)	12 (8.3)	0.35 (0.02–2.47)	3.98 (0.09–29.58)
1	2022 (12.7)	243 (4.9)	71 (14.1)	0.36 (0.19–0.67)	1.13 (0.54–2.32)
2	1228 (15.6)	219 (8.2)	64 (9.4)	0.48 (0.28–0.82)	0.56 (0.21–1.37)
≥ 3	1470 (22.2)	237 (11.0)	91 (19.8)	0.43 (0.28–0.67)	0.87 (0.49–1.51)
Travel					
Kampala and out of country	1949 (16.0)	398 (7.0)	104 (20.2)	0.40 (0.26–0.61)	1.33 (0.79–2.24)
Rakai and other Uganda	3634 (13.1)	416 (6.7)	129 (10.9)	0.48 (0.32–0.72)	0.81 (0.44–1.46)
None	166 (14.5)	16 (6.3)	8 (0)	0.39 (0.02–3.09)	0 (0)
Ever used condoms					
Yes	1577 (16.7)	262 (8.0)	78 (20.5)	0.44 (0.27–0.71)	1.29 (0.70–2.34)
No	4169 (13.1)	568 (6.3)	163 (11.7)	0.45 (0.31–0.64)	0.88 (0.52–1.45)
Sexually transmitted disease symptoms					
Genital ulcer					
Yes	489 (36.6)	49 (14.3)	31 (32.3)	0.29 (0.12–0.69)	0.82 (0.35–1.89)
No	5261 (12.0)	781 (6.4)	210 (11.9)	0.50 (0.37–0.68)	0.99 (0.63–1.54)
Genital discharge					
Yes	252 (31.3)	28 (10.7)	13 (15.4)	0.26 (0.06–0.95)	0.40 (0.06–1.97)
No	5498 (13.3)	802 (6.7)	228 (14.5)	0.47 (0.35–0.63)	1.10 (0.74–1.63)
Painful/frequent urination					
Yes	500 (20.4)	78 (11.5)	34 (20.6)	0.51 (0.23–1.10)	1.01 (0.39–2.52)
No	5250 (13.5)	752 (6.4)	207 (13.5)	0.44 (0.32–0.60)	1.00 (0.65–1.53)
Positive syphilis test					
Yes	479 (24.8)	59 (11.9)	31 (16.1)	0.46 (0.34–0.62)	1.10 (0.73–1.66)
No	5268 (13.1)	770 (6.5)	210 (14.3)	0.41 (0.16–0.96)	0.58 (0.19–1.64)

*Test for trend by circumcision status: non-circumcised, $P < 0.0001$; age ≤ 12 years, $P < 0.0001$; age ≥ 12 years, $P = 0.054$. CI, Confidence interval.

circumcised in postpubescence compared with uncircumcised men (OR, 0.55; 95% CI, 0.24–1.25). Use of condoms (ever) and travel to Kampala (the capital city) or internationally, covariates that are proxies for high-risk sexual behavior, were associated with higher HIV prevalence, but the apparent protective effects of prepubertal circumcision were observed irrespective of these behaviors.

Men were asked about any STD symptoms in the 6 months prior to interview. Men with prepubertal circumcision reported significantly less GUD than non-circumcised men [5.8% and 8.4%, respectively; odds ratio (OR), 0.67; 95% CI, 0.49–0.91], whereas men who were circumcised postpubescence reported significantly more cases of GUD (12.5%) than the uncircumcised reference group (RR, 1.56; 95% CI, 1.06–2.30). There were no significant differences with respect to circumcision status in the frequencies of reported genital discharge or painful urination. However, the reduced risks of prevalent HIV infection associated with early age of circumcision was observed in men with or without symptoms suggestive of STD (Table 2).

Questions were asked regarding the reasons for circumcision and then we investigated whether these reasons differed by age of circumcision. Overall, circumcisions were conducted for traditional/religious reasons (87%), health reasons (11%), or other reasons (2%). The majority of traditional/religious circumcisions were performed in early childhood (85%), whereas the majority of circumcisions performed for health reasons were performed after puberty (79%). In men circumcised for health reasons, the prevalence of HIV was significantly higher for those with postpubertal circumcision (18.0%), compared with those circumcised before puberty (4.3%; OR, 4.82; 95% CI, 0.60–38.44). In those circumcised for traditional/religious reasons, HIV prevalence was 7.0% for men circumcised at age ≤ 12 years compared with 12.1% for those circumcised later (OR, 1.83; 95% CI, 1.03–3.26). We further analyzed subgroups of men with postpubertal circumcision adjusting for age by direct standardization. In 165 men circumcised at age 13–20 years, the prevalence of HIV was 10.0%, whereas in 76 men circumcised at ≥ 21 years, the prevalence of HIV was 16.2%. A χ^2 test of linear trend for HIV prevalence by age at circumcision (< 12, 13–20, ≥ 21 years) was highly significant ($P < 0.0001$).

Multivariate models were created to estimate the adjusted risks of HIV-1 seropositivity and circumcision status (Table 3). The first model adjusted for the more distal socioeconomic variables of age, marital status, number of wives, religion, and education. A second model included number of sex partners, use of condoms (ever), alcohol use, history of syphilis, reported history of GUD, genital discharge or pain on urination, and history of travel. A final combined model contained all significant covariates from previous models. These models were constructed with prepubertal age at circumcision (≤ 12 years) and with postpubertal age at circumcision divided at ages 13–20 and ≥ 21 years. The reduced risk of prevalent HIV infection associated with prepubescent circumcision was significant in all models; in the final model, the adjusted OR was 0.39 (95% CI, 0.29–0.53). For postpubescent circumcision, relative to the uncircumcised, the OR were 0.46 (95% CI, 0.28–0.77) for those circumcised at ages 13–20 years, and 0.78 (95% CI, 0.43–1.43) for those circumcised at age ≥ 21 years. We created an additional combined model with men circumcised at ages ≤ 20 years (OR, 0.41; 95% CI, 0.31–0.53) versus men circumcised at ≥ 21 years (OR, 0.78; 95% CI, 0.43–1.43). The lack of a protective effect for men circumcised after age 20 years also held for men who did not have known risk factors for STD.

Religion was dropped from the final model due to the very high correlation between being Muslim and prepubertal circumcision (r = 0.83). A combined model including religion found only prepubertal circumcision

Table 3. Odds ratio (OR) of age at circumcision as a predictor for positive HIV serostatus with non-circumcised as the comparison group (n = 6772).

	OR (95% CI)						
	Circumcised in prepubescence (≤ 12 years)	Circumcised in postpubescence		−2 log likelihood	χ^2 (df)	Goodness of fit test	
		13–20 years	≥ 21 years			χ^2 (df)	Probability > χ^2
Model 1*	0.52 (0.31–0.88)	0.59 (0.34–1.03)	1.01 (0.55–1.85)	4457	8.95 (3)§	12.06 (8)	0.1483
Model 2†	0.56 (0.41–0.76)	0.70 (0.42–1.15)	1.29 (0.72–2.32)	4753	18.41 (3)¶	8.12 (8)	0.4215
Model 3‡	0.39 (0.29–0.53)	0.46 (0.28–0.77)	0.78 (0.43–1.43)	4236	53.46 (3)¶	9.55 (8)	0.2982

*Socioeconomic variables only: adjusting for age of circumcision, marital status, current age (15–24, 25–29, 30–34, 35–39, 40–44, ≥ 45 years), number of wives, education, and religion. †Behavioral variables only: adjusting for age of circumcision, number of sexual partners in past 5 years, foreign and domestic travel, use of condoms ever, alcohol consumption in past month, reported presence of genital discharge, genital ulcers or pain during urination in past 6 months, positive syphilis test. ‡Combined socioeconomic and behavioral variables: adjusting for age of circumcision, marital status, current age (15–24, 25–29, 30–34, 35–39, 40–44, ≥ 45 years), number of wives, number of sexual partners in past 5 years, reported presence of genital ulcer, positive syphilis test. §Significant at $P \leq 0.05$. ¶Significant at $P \leq 0.001$. CI, Confidence interval.

protective: age ≤ 12 years (OR, 0.56; 95% CI, 0.41–0.76), 13–20 years (OR, 0.70; 95% CI, 0.42–1.15), and ≥ 21 years (OR, 1.29; 95% CI, 0.72–2.32).

Discussion

This study used the Rakai cohort, established in a high HIV-1 prevalence area, to assess the association between circumcision and HIV-1 seroprevalence. Unlike many prior reports, our analysis distinguished age at circumcision dichotomized into prepubertal (age ≤ 12 years) and postpubertal (age 13–20 years and ≥ 21 years). We used this dichotomy because, *a priori*, we postulated that the age of circumcision might interact with risk of HIV infection in complex ways. This complexity would help explain why several similar studies in sub-Saharan Africa produced conflicting results [9].

As hypothesized, we found that men who were circumcised before puberty had a much reduced risk of prevalent HIV infection than men who were uncircumcised (adjusted OR, 0.39). Analyses of postpubertal circumcised men suggested that reduced risk of HIV is found largely among men circumcised at age 13–20 years (OR, 0.46), but there was no statistically significant association with circumcision at age ≥ 21 years (OR, 0.78; 95% CI, 0.43–1.41). This lack of significance was true regardless of the presence or absence of risk factors for STD. The findings in non-circumcised men were in agreement with other population-based studies in Africa [23].

There are biological and behavioral interpretations of our findings. First, the protective effect against HIV infection for men who were circumcised during early childhood may be explained by biological mechanisms. The presence of a foreskin may increase the risk of HIV acquisition because the recesses of the preputial sac are non-keratinized predisposing the area to physical trauma during sex. In addition, the moist environment under the foreskin may facilitate the presence or persistence of microbial flora [3,4], which, via inflammatory changes, may lead to a higher concentration of HIV target cells in the foreskin [24]. Men who were circumcised in postpubescence may have a higher risk of HIV, possibly because these men were predominantly circumcised for health reasons, such as treatment for strictures or balantitis [23,25]. Although we do not know whether HIV infection occurred before or after circumcision for men in the subgroup circumcised postpubertally, it is reasonable to assume that these men had been circumcised after possible exposure to STD infections through high-risk sexual behaviors. Such behaviors and the putative STD are likely to place men at risk of HIV. Nevertheless, we cannot determine whether adult circumcision might have moderated this assumed higher risk of infection.

This study was cross-sectional and we were not able to determine the temporality of circumcision to HIV infection. However, given the late onset of HIV among men in this population [19], with a peak prevalence in the 25–34-year age-groups (Table 1), it is likely that circumcision preceded HIV infection in the majority of subjects. In the future we will have information on incident HIV infections for discordant couples, and analysis of these data will provide information on both the susceptibility and infectivity of men in relation to their circumcision status. Our data did not allow us to explore the mediating effects of penile hygiene in these baseline data, but questions relating to personal hygiene, asked in subsequent survey rounds, will also be addressed in future studies.

Circumcision status was verified by physical examination only in the cases where genital ulcers were reported. Physical examinations were not performed on all men because interviews were conducted in the home, and our purpose was to avoid intrusive survey methods. Urassa *et al.* [23] found the agreement between actual and reported circumcision status, in a Tanzanian population similar to Rakai, to be 81%. Although the possibility of misclassification may exist, we feel there is no reason that it would be differential.

Circumcision after the age of 20 years was not significantly protective against HIV infection in our data. This raises questions about the feasibility and utility of proposed circumcision programs for adults [14]. We believe that the protection afforded by prepubertal circumcision is likely to be due to a biological mechanism and that there may be utility to providing circumcision to newborn infants or children, particularly if this is a cultural norm. Future studies should obtain information on both age of circumcision and the reasons for circumcision in order to better understand the potential role of this procedure as a means of HIV prevention.

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