

Male and Female Circumcision Associated With Prevalent HIV Infection in Virgins and Adolescents in Kenya, Lesotho, and Tanzania

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PURPOSE: Remarkable proportions of self-reported virgins and adolescents in eastern and southern Africa are infected with HIV, yet non-sexual routes of transmission have not been systematically investigated in such persons. Many observers in this region have recognized the potential for HIV transmission through unhygienic circumcision procedures. We assessed the relation between male and female circumcision (genital cutting) and prevalent HIV infection in Kenyan, Lesothoan, and Tanzanian virgins and adolescents. **METHODS:** We analyzed data from recent cross-sectional national probability sample surveys of adolescents and adults in households, focusing on populations in which circumcision was common and usually occurred in puberty or later.

RESULTS: Circumcised male and female virgins were substantially more likely to be HIV infected than uncircumcised virgins (Kenyan females: 3.2% vs. 1.4%, odds ratio [OR] = 2.38; Kenyan males: 1.8% vs. 0%, OR undefined; Lesothoan males: 6.1% vs. 1.9%, OR 3.36; Tanzanian males: 2.9% vs. 1.0%, OR 2.99; weighted mean phi correlation = 0.07, 95% confidence interval, 0.03 to 0.11). Among adolescents, regardless of sexual experience, circumcision was just as strongly associated with prevalent HIV infection. However, uncircumcised adults were more likely to be HIV positive than circumcised adults. Self-reported sexual experience was independently related to HIV infection in adolescent Kenyan females, but was unrelated to HIV infection in adolescent Kenyan, Lesothoan, and Tanzanian males.

CONCLUSIONS: HIV transmission may occur through circumcision-related blood exposures in eastern and southern Africa.

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KEY WORDS: Human Immunodeficiency Virus, Circumcision, Female Genital Cutting, Africa, Iatrogenic Disease, Mortality.

INTRODUCTION

A remarkable proportion of self-reported virgins in eastern and southern Africa are infected with human immunodeficiency virus (HIV). For instance, in a 1995 probability sample serosurvey in rural northeast Tanzania, 4.6% of self-reported virgins ages 15 to 24 were HIV positive (1). Similar studies in the last 10 years indicate HIV prevalence in virgins of 0.1%-6.5% in Ethiopia (2, 3), 6.4% in Kenya (4), 2.2% in Malawi (5), 0.7% to 5.5% in South Africa (6–11), 6.5% in Zambia (4), and 0.5% in Uganda (12) (Table 1). Likewise, in recent prospective cohort studies in Malawi and Zimbabwe, the annual incidence of HIV infection in persons reporting no sexual exposures during study intervals was 1.2% to 2.4% (13, 14). Although sexual behavior may be underreported, we know of no evidence that underreporting of sexual experience is related to HIV

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infection. Furthermore, the consistency of these results in both males and females across studies and countries is compelling, and highlights the need to explore non-sexual sources of infection in persons reporting no sexual activity.

For decades, researchers, journalists, and community members (including children) in sub-Saharan Africa have recognized the potential for HIV transmission through circumcision (online references). Most male and female circumcision (genital cutting) procedures in eastern and southern Africa occur outside of formal healthcare settings and are performed by traditional practitioners (online references). Typically, in traditional and some clinical contexts, large numbers of individuals are circumcised in rapid succession, frequently as a rite of passage into adulthood (online references). Especially in traditional settings, the same cutting instrument may be used on many individuals without sterilization or, sometimes, any attempt to clean it whatsoever (online references). Thus, if someone circumcised in such settings were already HIV infected, transmission may occur to those subsequently circumcised.

We examined the relation between circumcision and HIV infection in Kenyan, Lesothoan, and Tanzanian virgins, thereby eliminating, in principle, confounding sexual exposures. Moreover, we investigated the association

Selected Abbreviations and Acronyms

HIV = Human Immunodeficiency Virus DHS = Demographic and Health Survey

between circumcision and HIV infection by age to elucidate the inverse relation often found in men overall (15).

METHODS

Data

We analyzed publicly available data from the Demographic and Health Surveys (DHS; www.measuredhs.com). The DHS are large, standardized, national probability sample household surveys of persons ages 15 to 49 years (15 to 54 years or 15 to 59 years for some surveys/subgroups) conducted periodically in developing countries. We selected surveys in sub-Saharan African countries with the following attributes: male or female circumcision was practiced by a meaningful proportion of the population; circumcision usually occurred in puberty or later; and the DHS data included HIV test results linked to respondents' reports. The age at circumcision criterion was necessary because most persons acquiring HIV infections from unhygienic circumcision procedures in infancy and childhood would not survive to age 15 (16).

Three sets of respondents met our criteria: male (N =2,914) and female (N = 3,268) Kenyans (DHS 2003) (17), male Lesothoans (DHS 2004; N = 2,231) (18), and male Tanzanians (AIS 2003-4; N = 4,771) (19) (see Appendix for the age at circumcision in these groups). In Tanzania, female circumcision generally occurs before puberty (Appendix) and there were no DHS data on female circumcision in Lesotho, thus we did not include Tanzanian or Lesothoan females in analysis. Data from the 1998 Kenya DHS suggest that more than 90% of female circumcisions in Kenya performed in the 1980s and 1990s were clitoridectomies (20). The household response rates for the Kenyan and Tanzanian interviewer-administered surveys were high (96% for Kenya, 95% for Lesotho, and 99% for Tanzania; 85% to 91% of eligible males and 94% of eligible females in responding households participated). In these surveys, dried blood spot samples were obtained from consenting respondents (78% of Kenyan females, 77% of Kenyan males, 80% in Lesothoan males, and 84% of Tanzanian males). HIV serostatus was determined with an enzyme linked immunosorbent assay (ELISA) test and confirmed by a different ELISA test; specimens with discrepant ELISA results were confirmed by Western blot (Kenya) or further ELISA tests (Lesotho and Tanzania). In our analyses, we defined virgins as respondents who reported never having had sexual intercourse. We determined circumcision status from respondents' self-reports of whether they were circumcised.

TABLE 1. HIV prevalence in virgins in general population samples, eastern and southern Africa

	Age	Number of	
Study	range	virgins	Prevalence
Ethiopia			
Addis Ababa, 2001–2004(2)			
Females and males	15+	720	6.5%
National, 2005(3)	13	,20	0,3 70
Females	15-49	1,356	0.1%
Males	15–49	1,754	0.2%
Overall	15–49	3,110	0.1%
Kenya	15 17	3,110	0.170
Kisumu, 1997–1998 ^a (4)			
Females	15-24	67	10.8%
Males	15–24	43	0%
Overall	15–24	110	6.4%
Malawi	13-27	110	0.770
National, 2004(5)			
Females	15-49	247	2.5%
Males	15 -4 9	266	1.8%
Overall	15–49	513	2.2%
South Africa	13-49	515	2.2 /0
Carletonville, 1999(6) Females	14 24	161	6.8%
remaies Males	14-24	161	1.2%
	14-24		
Overall	14–24	323	4.0%
National, 2002(7)	15.	046	T TO/
Females and males	15+	946	5.5%
National, 2003(8)	15 24	2170	2.00/
Females	15–24	2179	3.9%
Males	15–24	2034	2.5%
Overall	15–24	4213	3.2%
National, 2005(11)	15 24	1.620	2.00/
Overall	15–24	1639	3.8%
Overall	15+	1808	4.3%
Orange Farm, 2002–2004(9, 10)			. = 0/
Males	18–24	278	0.7%
Tanzania			
Moishi, 1995(1)			
Females	15–24	163	3.7%
Males	15–24	141	5.7%
Overall	15–24	304	4.6%
Uganda			
National, 2004–2005(12)			
Females	15–49	1,259	0.8%
Males	15–49	1,327	0.2%
Overall	15–49	2,585	0.5%
Zambia			
Ndola, 1997–8(4)			
Females	15–24	106	7.6%
Males	15-24	63	4.8%
Overall	15-24	169	6.5%

Note: Some values in the table reflect estimates calculated from information reported in the original articles.

Glynn and colleagues (98) reported slightly different numbers for the same subset of participants: 8/67 (11.9%) of virgins were HIV-infected.

Statistical Analyses

We conducted our analyses separately by sex and country. We assessed the association between circumcision and prevalent HIV infection in virgins with bivariate odds ratios (OR) and algebraically related phi (Pearson) correlations (21, 22) (some 2 × 2 contingency tables had a null cell rendering undefined ORs). Because circumcision often varies by ethnicity (available for the Kenyan survey only), religion, and region in Kenya and Tanzania, we estimated the association between each of these variables and circumcision with Goodman and Kruskal's tau (with circumcision as the dependent variable) (23, 24). This proportional reduction in error measure of association between nominal scale variables ranges between 0 and 1. We then assessed the relation between circumcision and HIV within subsets of respondents defined by the variable most strongly associated with circumcision. We also measured the association between circumcision and HIV within different age groups. Furthermore, we assessed the association between lifetime history of sexual intercourse and HIV infection in adolescents and calculated partial correlations to predict HIV serostatus from sexual experience and circumcision. We performed χ^2 tests to evaluate the homogeneity of correlations across samples and also computed weighted mean correlations and corresponding 95% confidence intervals (CI) to obtain the best estimate of the association between circumcision and HIV infection from multiple samples (25, 26).

RESULTS

HIV prevalence ranged between 1% and 3% in virgins (1.7% in Kenyan females, 1.3% in Kenyan males, 2.8% in Lesothoan males, and 2.2% in Tanzanian males). In each sample, the median age of virgins with data on circumcision and HIV status was 17 (90th percentile = 22). No self-reported virgin with data on HIV status and circumcision acknowledged ever having been married, ever having been pregnant, or ever having children (virgins were not asked about STD history or symptoms).

Circumcised virgins were substantially more likely to be HIV positive than uncircumcised virgins in every sample (Table 2). The phi correlations for the four samples were homogenous ($\chi^2(3) = 0.63$, p = 0.89). Table 1 shows the weighted mean correlation for all four samples; the weighted

mean phi correlation for just the three male samples was the same (.07, 95% $\rm CI=0.03$ to 0.12). The small absolute magnitude of the correlations is due to the relatively low HIV prevalence (22, 27); nonetheless, the correlations correspond to sizable odds ratios (when calculable; Table 2).

Circumcision was common among Kenyan (75%) and Tanzanian (63%) male virgins, but comparatively uncommon among Kenyan female (18%) and Lesothoan male (21%) virgins. Circumcision varied considerably by ethnicity (tau = 0.54 and .44 for Kenyan females and males, respectively) and region (tau = 0.43 for Tanzanian males) (see Tables 3 and 4 in Appendix). Among virgins in those ethnic groups/regions where a majority of virgins were circumcised (for Kenyan and Tanzanian males) or uncircumcised (for Kenyan females), the association between circumcision and HIV remained robust (phi = 0.04 to 0.05), despite the reduced variation in circumcision.

In contrast to the pattern in virgins, among all respondents (regardless of sexual experience), circumcised persons were usually less likely to be HIV infected than uncircumcised persons (Figure 1; Table 5 in Appendix). However, in each sample, the association between circumcision and prevalent HIV infection varied dramatically, consistently, and significantly by age (Figure 1; Appendix). The relation between circumcision and HIV infection was moderately to strongly positive (circumcision associated with infection, as in virgins) in adolescents (age < 18 years), abruptly changed direction (lack of circumcision associated with infection) in early adulthood, and remained inverse for older age groups. The correlations between circumcision and HIV infection in adolescents were homogeneous (range = 0.05 to 0.07; χ^2 (3) = 0.37, p = 0.95) and as strong as those for virgins only (weighted mean phi = 0.06, 95% CI 0.02 to 0.10).

Compared with adolescent male virgins, sexually experienced adolescent males were less or equally likely to be HIV positive (Kenya: phi = -0.07, 95% CI -0.17 to 0.02; Lesotho: phi = -0.01, 95% CI -0.10 to 0.09; Tanzania: phi = 0.00, 95% CI -0.08 to 0.08). After controlling for circumcision, these correlations did not change, just as the correlation between circumcision and HIV infection stayed the same after adjusting for sexual experience (range of partial

TABLE 2. Association between female and male circumcision and prevalent HIV infection in virgins, Kenya (2003), Lesotho (2004), and Tanzania (2003-2004)

	Kenyan females		Kenyan males		Lesothoan males		Tanzanian males		
	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	
Uncircumcised	98.6 (438)	1.4 (6)	100 (118)	0 (0)	98.1 (310)	1.9 (6)	99.0 (302)	1.0 (3)	
Circumcised	96.8 (92)	3.2 (3)	98.2 (333)	1.8 (6)	93.9 (77)	6.1 (5)	97.1 (505)	2.9 (15)	
OR (95% CI)	2.38 (0.59	2.38 (0.59–9.69)		<u> </u>		3.36 (1.00–11.28)		2.99 (0.86–10.4)	
Phi	0.05	0.05		0.07		10		.06	
Weighted mean phi (95% CI)		0.07 (0.03–0.11)							

Note: Cells in cross-tabulations show percentages with frequencies in parentheses.

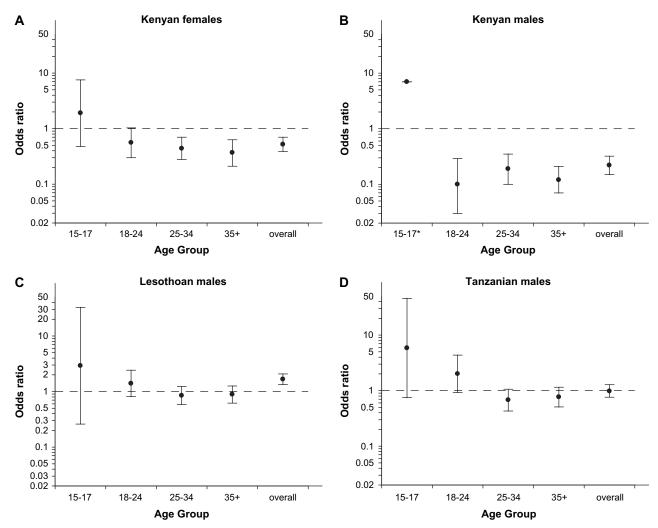


FIGURE 1. Association (odds ratio) between circumcision and prevalent HIV infection by age group, with 95% confidence intervals shown as bars. Odds ratios above the dashed reference line indicate circumcised persons were more likely to be infected and odds ratios below the line indicate uncircumcised persons were more likely to be infected. *Odds ratio computed from a pseudo-Bayesian smoothing of the table to compensate for the 0 count in the uncircumcised and infected cell (see Appendix). No conventional confidence interval calculable.

correlations = 0.05 to 0.07; homogeneity χ^2 (2) = 0.2, p = 0.90; weighted mean partial correlation = 0.07, 95% CI 0.02 to 0.12). Sexually experienced Kenyan female adolescents, however, were more likely to be HIV infected than adolescent virgins (phi = 0.11, 95% CI 0.01 to 0.20). Circumcision and sexual experience were independent correlates of HIV infection in Kenyan adolescent females (partial correlation for circumcision = 0.07, 95% CI -0.03 to 0.17; partial correlation for sexual experience = 0.11, 95% CI 0.01 to 0.21).

DISCUSSION

Circumcised male and female virgins in nationally representative samples of Kenyans, Lesothoans, and Tanzanians were

substantially more likely to be HIV infected than uncircumcised virgins. Among adolescents, regardless of sexual experience, circumcision was just as strongly associated with prevalent HIV infection. However, the relation between circumcision and HIV infection changed direction (uncircumcised persons more likely to be HIV positive) in adults. Self-reported sexual experience was unrelated to HIV infection in adolescent males.

The frequent serious complications of circumcision, including death, in sub-Saharan Africa, especially in traditional settings, attest to the often unhygienic and crude nature of such operations (28–39). In the Middle East and eastern Africa, circumcision (both female and male) performed in groups or by traditional providers has repeatedly been independently associated with hepatitis B and C

infection in adolescents and adults (40-46). Because most circumcision in Kenya, Lesotho, and Tanzania is ritually motivated, it seems very unlikely that the association between circumcision and infection with blood-borne pathogens is caused by infected persons seeking circumcision. It is much more probable that circumcision-related exposures precede and cause infection. Beyond the use of shared, contaminated cutting instruments in circumcision, many blood exposures may accompany or follow circumcision. Some examples include: potentially unsafe tetanus vaccinations in formal healthcare settings in anticipation of unhygienic traditional circumcisions (47), blood (of the circumciser or of persons circumcised earlier in the sequence) on the circumciser's hands or fingers during the procedure, and possibly contaminated sharps or other equipment and supplies in formal or informal healthcare settings for treatment of complications. Furthermore, the apparent lack of association between female circumcision and sexually transmitted infections (48, 49) suggests that the age-varying association between female circumcision and HIV infection reflects nonsexual HIV transmission. Regardless of the specific blood exposures underlying the circumcision-HIV association in youth, our analyses add to the accumulating evidence that routes other than penile-vaginal sex and mother-tochild transmission may play a significant role in the spread of HIV in sub-Saharan Africa (50-55). Circumcision cannot account for all HIV infections among virgins and adolescents in most of the DHS data sets we analyzed, as some uncircumcised virgins and adolescents were infected, which may also point to other nonsexual modes of transmission.

Consistent with our results, previous research showed that male circumcision was associated with prevalent HIV infection in South African and Ugandan samples when most persons were within a few years of the typical age at circumcision (6, 56). In earlier studies, when the bulk of a sample was more than a few years older than the typical age at circumcision, the circumcision-HIV relation for both females and males was absent or inverse (i.e., uncircumcised were more likely infected) (6, 49, 56-65). Mortality of infected, circumcised persons may be one reason for the inversion of the relation among older persons. Because circumcised adolescents have a higher HIV prevalence than uncircumcised adolescents, circumcised persons suffer higher mortality by early to mid-adulthood, consequently reducing HIV prevalence, or slowing its growth, in surviving circumcised adults relative to uncircumcised adults. Indeed, such mortality would be enough to produce similar prevalence in circumcised and uncircumcised Tanzanian and Lesothoan men age 25 and older (Table 5 in Appendix).

However, mortality alone cannot account for the markedly lower HIV prevalence in circumcised Kenyan adults relative to their uncircumcised counterparts. It is possible that male circumcision protects against sexual acquisition through yet unsubstantiated physical or physiologic mechanism(s) involving the penis (9), and that this effect is not apparent until adulthood, when transmission through circumcision-related exposures has ceased, most of those so infected have died, and sexual activity is more frequent. This explanation, though, does not apply to female circumcision and cannot account for our results in Kenyan females. HIV specific immunity acquired from circumcision-related exposures might also contribute to lower HIV prevalence and incidence (15) in circumcised adults (Appendix). The large reduction in HIV incidence in circumcised males relative to uncircumcised males in the recent South African randomized trial (9) would seem to negate this latter possibility, but several alternate explanations for the trial's results have not yet been investigated (Appendix).

Although prior research has demonstrated moderate to very good validity of self-reported male circumcision status in Kenya and Tanzania (57, 66, 67) there may be some error in the measurement of circumcision in the data we analyzed. We are not aware of methodological assessments of selfreported female circumcision status in populations where circumcision occurs in adolescence, but such reports displayed moderate validity in one community where female circumcision typically occurred in childhood (49). We likely underestimated the association between circumcision and HIV infection in virgins and adolescents because circumcision-related mortality likely already had affected the youngest age group surveyed. Next steps for investigating the role of circumcision in HIV transmission might include direct examination of circumcision procedures and cutting instruments in multiple settings combined with observational studies among youth in particular communities and safer circumcision intervention trials. Perhaps most crucial for determining modes of HIV transmission is tracing of incident cases and uninfected controls' contacts for all possible sexual and nonsexual exposures, coupled with sequencing of cases' HIV isolates and analysis of time and place of exposures (68).

Circumcision procedures in many clinical settings in sub-Saharan Africa may still involve risk for HIV transmission. Circumcision in formal healthcare settings involves more exposures to sharps (e.g., injections for anesthesia as well as cutting tools) than in other settings. None of the 10 health facilities inspected in a recent study in western Kenya had all the necessary instruments and supplies to perform male circumcision safely (3 lacked appropriate sterilizers), and some clinicians had performed circumcision without prior training (69). Blood-contaminated instruments and unhygienic procedures are also widespread in formal health care settings in sub-Saharan Africa (54, 70-78). Furthermore, a mass circumcision at a Turkish hospital—an event consciously designed for hygienic care—involved a rate of complications (including infections) nearly three times as high as circumcisions performed singly (79). Recently, safer injection initiatives have been piloted in selected local areas in sub-Saharan Africa and these may improve the situation (80), although their impact on hygiene of injections and other invasive procedures is not yet known. In light of the evidence, people seeking male or female circumcision (or other lacerating or puncturing procedures) in ritual, cosmetic, or healthcare (formal or informal) contexts should insist on demonstrably sterile instruments and hygienic procedures (81). Before promoting male circumcision as an HIV preventive intervention, large and sustained investments and improvements in the safety of care in all of these settings must be made (Appendix). Otherwise, such initiatives may well facilitate transmission of HIV and other blood-borne pathogens.

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APPENDIX

Age at Circumcision

Data from the 1998 Kenyan DHS indicate the median age of female circumcision is 11 to 12 (20), based on mothers' reports of the age at which their oldest daughters (up to age 15) were circumcised. The 2004-2005 Tanzanian DHS data show that most females are circumcised before puberty (82). In the ethnographic and health science literature, authors routinely refer to male circumcision in most of

TABLE 3. Ethnic variation in circumcision in Kenyan (2003) virgins

	K	enyan females	Kenyan males		
Ethnic group	N	% Circumcised	N	% Circumcised	
Embu	7	29	1	100	
Kalenjin	54	11	24	38	
Kamba	52	15	48	98	
Kikuyu	138	8	107	65	
Kisii	36	86	38	100	
Luhya	94	0	70	93	
Luo	47	2	44	16	
Masai	3	33	4	0	
Meru	22	14	15	47	
Mijikenda/Swahili	32	3	28	100	
Somali	24	100	53	100	
Taita/Taveta	13	15	5	80	
Turkana	7	0	5	40	
Kuria	4	100	5	0	
Other	6	17	10	80	

contemporary Kenya, Lesotho, and Tanzania as a rite of passage into adulthood. Several sources indicate that male circumcision typically occurs in puberty or young adulthood in these countries (online references).

Pseudo-Bayesian Smoothing of the Kenyan Adolescent Males' Circumcision-HIV Table

To estimate the odds ratio for the association between circumcision and HIV infection for Kenyan adolescent males, we used a method described by Bishop and colleagues (83) for pseudo-Bayesian smoothing of observed values in a contingency table. In this approach, cell values are assumed to come from a multinomial distribution, with a Dirichlet prior distribution for the multinomial probabilities. (The method is pseudo-Bayesian because it uses an estimate from the data for one of the prior distribution's parameters.) The smoothed values reflect estimates of the posterior expected cell probabilities, which are a function of the prior cell probabilities and the observed data. With non-zero prior probabilities for all cells, the smoothing eliminates cell values of 0 in the observed table (as in the uncircumcised and infected cell for Kenyan adolescent males).

Empirically based prior probabilities are generally desirable. We used the empirical proportions from the Tanzanian adolescent males' table as the prior cell probabilities. The available evidence suggests male circumcision procedures are similar in Kenya and Tanzania, and the phi correlation between circumcision and HIV infection and the

TABLE 4. Geographic variation in circumcision in Tanzanian (2003-2004) male virgins

Region	N	% Circumcised
Dodoma	27	96
Arusha	61	93
Kilimanjaro	36	92
Tanga	24	88
Morogoro	29	97
Pwani	33	97
Dar es Salaam	36	86
Lindi	11	82
Mtwara	14	100
Ruvuma	26	73
Iringa	39	36
Mbeya	47	23
Singida	64	77
Tabora	33	30
Rukwa	45	24
Kigoma	61	61
Shinyanga	26	0
Kagera	62	19
Mwanza	40	23
Mara	42	79
Manyara	69	93

TABLE 5. Association between circumcision and prevalent HIV infection, stratified by age group, Kenya (2003), Lesotho (2004), and Tanzania (2003-2004)

	Kenyan females		Kenyan males		Lesothoan males		Tanzanian males	
Age group HIV	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+
15-17								
Uncircumcised	98.0 (343)	2.0 (7)	100 (154)	0 (0)	99.4 (339)	0.6(2)	99.6 (248)	0.4(1)
Circumcised	96.3 (77)	3.8 (3)	98.6 (276)	1.4 (4)	98.3 (58)	1.7(1)	97.7 (423)	2.3 (10)
OR (95% CI)	1.91 (0.48–7.55)		-		2.92 (0.26-32.8)		5.85 (0.75–45.5)	
18-24								
Uncircumcised	91.6 (657)	8.4 (60)	9.18 (90)	8.2 (8)	92.2 (285)	7.8 (24)	97.8 (364)	2.2 (8)
Circumcised	95.2 (256)	4.8 (13)	99.1 (696)	0.9 (6)	89.4 (288)	10.6 (34)	95.8 (883)	4.2 (39)
OR (95% CI)	0.56 (0.3	30–1.03)	0.10 (0.03–0.29)		1.40 (0.81–2.42)		2.01 (0.93–4.35)	
25-34								
Uncircumcised	85.5 (537)	14.5 (91)	78.7 (70)	21.3 (19)	65.2 (116)	34.8 (62)	92.1 (372)	7.9 (32)
Circumcised	93.0 (348)	7.0 (26)	95.1 (638)	4.9 (33)	68.8 (245)	31.2 (111)	94.5 (997)	
OR (95% CI)	0.44 (0.28–0.70)		0.19 (0.10–0.35)		0.85 (0.58–1.24)		0.68 (0.43–1.06)	
35+		,	, , ,	,		.,		,
Uncircumcised	87.8 (402)	12.2 (56)	74.6 (88)	25.4 (30)	71.2 (166)	28.8 (67)	89.2 (313)	10.8 (38)
Circumcised	95.2 (373)	4.8 (19)	96.0 (770)	4.0 (32)	73.7 (319)	26.3 (114)	91.5 (901)	8.5 (84)
OR (95% CI)	0.37 (0.2	21–0.63)	0.12 (0.07–0.21)		0.89 (0.62–1.26)		0.77 (0.51–1.15)	
Overall								
Uncircumcised	90.1 (1939)	9.9 (214)	87.6 (402)	12.4 (57)	85.4 (906)	14.6 (155)	94.3 (1297)	5.7 (79)
Circumcised	94.5 (1054)	5.5 (61)	96.9 (2380)	3.1 (75)	77.8 (910)	22.2 (260)	94.4 (3204)	
OR (95% CI)	0.52 (0.3		0.22 (0.1		1.67 (1.34–2.08)		0.98 (0.75–1.28)	

Note: Cells in cross-tabulations show percentages with frequencies in parentheses.

prevalence of circumcision and HIV in adolescents were also similar in these two countries.

Comparison of Circumcision-HIV Association in Adolescents and Adults

In each sample, we compared adolescents (ages 15 to 17 years) and adults (age 18+ years) in terms of the association between circumcision and prevalent HIV infection. We assessed the significance of the differences between adolescents and adults' phi correlations with a Z test within samples (25) and the cumulative Z test across samples, weighted by sample size (84). The relation was consistently positive in adolescents and inverse in adults (weakly positive in Lesothoan adults), and these differences were statistically significant (Kenyan females: adolescent phi = 0.05, adult phi = -0.10, Z = 2.74; Kenyan males: adolescent phi = 0.07, adult phi = -0.23, Z = 5.85; Lesothoan males: adolescent phi = 0.07, adult phi = 0.07,

Possibility of HIV-Specific Immunity in Surviving Circumcised Adults

Some circumcised but uninfected persons may be immune to HIV. In this scenario, some circumcised persons are exposed to HIV through circumcision or related procedures, and many of them seroconvert. Other persons exposed in this context may experience transient infections but not sero-convert (85, 86), reflecting acquired or genetic immunity. Such persons might resist infection in subsequent exposures more effectively than previously unexposed persons, parallel to the corresponding phenomenon of acquired immunity to simian immunodeficiency virus in macaques (87–89).

We predict that circumcised HIV-negative women (if several or more years older beyond the typical age at circumcision) have lower HIV incidence than uncircumcised HIV-negative women, mirroring the relation observed in men (15). Similarly, we also hypothesize that circumcised seronegative young adults have higher HIV-specific immune responses than uncircumcised seronegative young adults, exhibiting the same signs of resistance in seronegative healthcare workers occupationally exposed to HIV-infected blood (90, 91).

Alternate Explanations of South African Circumcision Trial Results

One potential reason for the lower incidence in circumcised men is that circumcision may have lowered incidence of some genital symptoms arising from sexually transmitted and urinary infections (92, 93), resulting in fewer exposures to contaminated sharps in treatment for such, especially in sexually transmitted infection clinics and by informal healthcare providers. Another possibility, among many, is

related to the belief, not uncommon in sub-Saharan Africa, that anal sex involves lower risk of HIV transmission than vaginal sex (53, 94, 95). Newly circumcised men who previously and mistakenly practiced anal sex as a protective behavior may feel less at risk for acquiring HIV and therefore shift to vaginal sex with its lower actual risk of transmission. The investigators of the South African trial apparently did not assess many fundamental exposures (e.g., anal sex, blood exposures in informal healthcare, cosmetic, and ritualistic settings, etc.) and have also not yet reported HIV incidence by trial arm in men who reported no sexual contact during follow-up (9, 10, 96).

Efforts to Improve Hygiene and Safety of Circumcision in Sub-Saharan Africa

Considerable development of infrastructure will be needed before hygienic and safe circumcision can be delivered on a broad scale in sub-Saharan Africa (97). Recently, some communities in eastern and southern Africa instituted campaigns for or laws requiring safe circumcision (online references), although the impact of these efforts on complications and transmission of blood-borne pathogens is unknown.

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