

Male Circumcision and Risk of HIV Infection among Heterosexual African American Men Attending Baltimore Sexually Transmitted Disease Clinics

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(See the editorial commentary by Gray et al. and the articles by Nielson et al. and Auvert et al., on pages 1–3, 7–13, and 14–9, respectively.)

Background. Male circumcision has received international attention as an intervention for reducing HIV infection among high-risk heterosexual men; however, few US studies have evaluated its association with the risk of HIV infection.

Methods. We analyzed visit records for heterosexual African American men who underwent HIV testing while attending sexually transmitted disease (STD) clinics in Baltimore, Maryland, from 1993 to 2000. We used multivariable binomial regression to evaluate associations between circumcision and the risk of HIV infection among visits by patients with known and unknown HIV exposure.

Results. Overall, 1096 (2.7%) of 40,571 clinic visits yielded positive HIV test results. Among 394 visits by patients with known HIV exposure, circumcision was significantly associated with lower HIV prevalence (10.2% vs. 22.0%; adjusted prevalence rate ratio [PRR], 0.49 [95% confidence interval [CI], 0.26–0.93]). Conversely, among 40,177 visits by patients with unknown HIV exposure, circumcision was not associated with reduced HIV prevalence (2.5% vs. 3.3%; adjusted PRR, 1.00 [95% CI, 0.86–1.15]), and age ≥ 25 years old and diagnosis of ulcerative STD were associated with increased prevalence.

Conclusions. Circumcision was associated with substantially reduced HIV risk in patients with known HIV exposure, suggesting that results of other studies demonstrating reduced HIV risk for circumcision among heterosexual men likely can be generalized to the US context.

Male circumcision has received international attention as an intervention for reducing sexually acquired

HIV infection among high-risk heterosexual men [1]. This reduction in risk has strong biological plausibility for effectiveness [2–4] and is supported by promising results from observational epidemiological studies [5, 6] and, most recently, by compelling results from 3 randomized controlled trials of adult male circumcision in Africa [7–9]. Although questions have been raised regarding how these findings affect the prevention of HIV infection in the United States, results from these trials have spurred interest in evaluating the possible role played by male circumcision in reducing heterosexually acquired HIV infection in this country [10]. Few US studies [11–13], however, have evaluated the role played by circumcision in preventing heterosexually acquired HIV infection, presumably because the prevalence of HIV infection in the United States is very low (0.4%) [14]

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and because the HIV epidemic in this country is largely concentrated among men who have sex with men [15].

We evaluated the association between male circumcision and the risk of HIV infection among a subset of heterosexual men in the United States by conducting a cross-sectional analysis of visit data from African American patients attending 2 sexually transmitted disease (STD) clinics in Baltimore, Maryland, a city in which HIV prevalence historically has been high. As part of this analysis, we also evaluated the impact of the infection status of patients' sex partners on the observed association between circumcision and risk of HIV infection. Other observational studies, whether international or domestic, generally have not considered key factors that may differ between circumcised and uncircumcised men (such as the infection status of partners) because of difficulties in measuring them; such studies may be subject to confounding [5, 6]. We have empirically demonstrated the importance of measuring the partner's infection status in our other work examining the effectiveness of condoms [16, 17]. Condoms are another method for preventing HIV infection or other STDs in which residual confounding also has been suspected to bias the results of observational studies toward the null hypothesis.

In the present analysis, we compared estimates of the association between male circumcision and the risk of HIV infection based only on those clinic visits for which the patient had documented sexual exposure to an HIV-infected female partner with estimates of this association based on visits for which the HIV infection status of female partners was unknown. We hypothesized that analyses limited to clinic visits by heterosexual men with known HIV exposure—the critical risk factor for transmission of infection—might provide more valid estimates of the association between circumcision and the risk of HIV infection than do analyses based on visits for which the partner's HIV infection status was unknown.

METHODS

Study design and patients. Computerized clinic records were reviewed for heterosexual African American men who underwent HIV testing while attending either of 2 Baltimore STD clinics between 1993 and 2000. During this period, African Americans accounted for the overwhelming majority (96%) of all visits by male patients at the clinics. Patient visits were excluded if HIV testing was not performed during the visit, typically because the patient reported having recently been tested or refused testing. Visits were also excluded if any of the following were documented: risk factors for HIV infection other than penile-vaginal sex (i.e., sex with men [based on reported rectal exposure] or self-reported injection drug use or needle sharing), use of other HIV prevention interventions (i.e., self-reported condom use), or a record of a previous positive or indeterminate HIV test result. Because the analysis included only routinely collected patient

data from a previously de-identified data set, the study protocol and analysis were determined to be exempt from institutional review board review by the Centers for Disease Control and Prevention and were similarly determined to be exempt by Johns Hopkins University.

Applying the methods we first developed to evaluate whether condom use reduced the risk of STDs [17], we used the patient's "reason for visit" to distinguish visits by patients whose sex partners were known to be infected with HIV from visits by patients whose partners were of unknown HIV infection status. Visits by patients with "known HIV exposure" were defined as those made by men who had been recently contacted by disease-intervention specialists regarding sexual exposure to HIV-infected sex partners within the past year as part of the clinic's partner-notification process or were notified of such exposure directly by their sex partners. The remaining visits, which reflected clinic attendance for other reasons (i.e., symptoms, check-up, follow-up for positive STD test result, and sexual contact with a partner with an STD other than HIV infection), were classified as having "unknown HIV exposure." This latter group closely resembles the population used in most studies to assess the association between circumcision and the risk of HIV infection or other STDs (where partner infection status is unknown).

Statistical analysis. HIV infection status was obtained from results of HIV antibody testing documented in the medical record for each included visit. For both groups of patient visits (known vs. unknown HIV exposure), we defined case visits as those for which a positive HIV test result was documented according to the standard enzyme immunoassay/Western blot testing algorithm. Similarly, we defined noncase visits as those for which a negative HIV test result was documented according to this algorithm. Male circumcision status was based on assessment by a clinician and was systematically documented from the physical examination reported in the patient's medical record. Clinicians mark a designated box on the visit record to indicate uncircumcised status. For this analysis, visits for which this box was marked were presumed to be from uncircumcised men, and visits for which it was not marked were presumed to be from circumcised men.

Characteristics of circumcised versus uncircumcised men were compared separately for visits by patients with known and those with unknown HIV exposure status, using the χ^2 statistic of association. We used unconditional multivariable binomial regression with log transformation [18] to evaluate the association between circumcision status and the risk of prevalent HIV infection, with the patient visit representing the unit of analysis. Separate regression models were developed for each group of patient visits and were assessed for goodness of fit and absence of multicollinearity. All regression models for both groups of patient visits used prevalence rate ratios (PRRs) with 95% confidence intervals (CIs) to compare HIV prevalence between testing visits for circum-

Table 1. Characteristics for STD clinic visits made by heterosexual African American male patients, Baltimore, Maryland, 1993–2000, according to knowledge of partner's HIV status and male circumcision status.

Characteristic	Visits by patients with known HIV exposure (n = 394 ^a)		P	Visits by patients with unknown HIV exposure (n = 40,177 ^b)		P
	Circumcised (n = 344)	Uncircumcised (n = 50)		Circumcised (n = 35,062)	Uncircumcised (n = 5115)	
Age			.04			<.001
≥25 years	283 (82)	47 (94)		20,739 (59)	4419 (86)	
<25 years	61 (18)	3 (6)		14,323 (41)	696 (14)	
Ulcerative STD diagnosis (syphilis, herpes) at visit			.17			<.001
Yes	13 (4)	4 (8)		1823 (5)	488 (10)	
No	331 (96)	46 (92)		33,239 (95)	4627 (90)	
Urethral STD diagnosis (gonorrhea, NGU) at visit			.03			<.001
Yes	49 (14)	13 (26)		14,303 (41)	2303 (45)	
No	295 (86)	37 (74)		20,759 (59)	2812 (55)	

NOTE. Data are no. (%) of visits. NGU, nongonococcal urethritis; STD, sexually transmitted disease.

^a No. of visits made by 385 patients.

^b No. of visits made by 26,200 patients.

cised men and those for uncircumcised men, adjusted for potential confounding factors identified in other studies: patient age (≥25 vs. <25 years), new diagnosis of ulcerative (syphilis or genital herpes) or urethral (gonorrhea or nongonococcal urethritis) infection, visit year, and clinic location. In both models, the correlation of multiple clinic visits by the same individual patient was accounted for by using general estimating equations with an exchangeable correlation structure [19, 20].

All statistical analyses were conducted using SAS software (version 9.1; SAS Institute). An α level of .05 was used to determine statistical significance, and all statistical tests were 2-tailed.

RESULTS

Of 112,703 total STD clinic visits by male patients from 1993 to 2000, 40,571 (36%) were made by 26,448 men who were African American, did not inject drugs, reported sex only with women, and underwent HIV testing during the visit. Of 72,132 visits excluded from analysis, 64,192 were excluded because there was no record of HIV testing. Of visits with a record of HIV testing, 468 were further excluded because of a previous positive or indeterminate HIV test result, 7379 because of acknowledged HIV risk factors other than penile-vaginal sex (i.e., sex with men or injection or needle-sharing behavior) or condom use, and 2203 because the patients were of other racial/ethnic categories. Some visits were excluded for multiple reasons.

Among the 40,571 visits included in the analysis, the majority were made by men who were circumcised (87%) and who were ≥25 years old (63%). Ulcerative and urethral STDs were diagnosed during 6% and 41% of visits, respectively. Overall, 394

visits (1%) were made by male patients who were named as sexual contacts of HIV-infected sex partners within the past year and had been referred by disease-intervention specialists; these visits were considered to involve known HIV exposure. For 237 visits (60%), men received either written or in-person notification of their exposure to HIV by a disease-intervention specialist; for the remaining 157 visits (40%), men had been notified of HIV exposure by their partners.

For the remaining 40,177 visits (99%), HIV exposure status was unknown. For 34,055 clinic visits (85% of all visits with unknown HIV exposure), at least 1 reason for the visit was specified; having symptoms was the most common reason (23,205 visits), followed by seeking a check-up (5943 visits), seeking HIV testing (3123 visits), being a sexual contact of a partner with an STD (other than HIV infection) (4532 visits), and seeking follow-up for an earlier positive test result for gonorrhea, chlamydia, or syphilis (368 visits); some clinic visits were indicated for multiple reasons.

Visits by men who were circumcised differed demographically and clinically from visits by men who were not circumcised, for both visits with known HIV exposure and visits with unknown HIV exposure (table 1). Relative to visits by circumcised men, visits by uncircumcised men were significantly more frequent among patients ≥25 years old and among those who had a urethral STD diagnosed during the visit. Uncircumcised men also were more likely to have an ulcerative STD diagnosed in both visit groups, although this finding was statistically significant only when HIV exposure status was unknown.

Overall, the prevalence of HIV infection was >4 times as high among the 394 clinic visits by patients with known HIV exposure than among the 40,177 visits by patients with unknown HIV

Table 2. Association between male circumcision status and prevalent HIV infection (and between selected covariates and prevalent HIV infection) among STD clinic visits made by heterosexual African American male patients, Baltimore, Maryland, 1993–2000, according to knowledge of partner’s HIV status.

Variable	Visits by patients with known HIV exposure (n = 394)				Visits by patients with unknown HIV exposure (n = 40,177)			
	Visits, no.	HIV positive, %	PRR (95% CI)		Visits, no.	HIV positive, %	PRR (95% CI)	
			Unadjusted	Adjusted ^a			Unadjusted	Adjusted ^a
Circumcised								
Yes	344	10.2	0.46 (0.19–0.85)	0.49 (0.26–0.93)	35,062	2.5	0.77 (0.65–0.90)	1.00 (0.86–1.15)
No	50	22.0	1.00 (referent)	1.00 (referent)	5115	3.3	1.00 (referent)	1.00 (referent)
Age								
≥25 years	330	12.4	1.59 (0.65–3.87)	1.48 (0.60–3.66)	25,158	3.6	3.82 (3.20–4.55)	3.58 (2.97–4.32)
<25 years	64	7.8	1.00 (referent)	1.00 (referent)	15,019	1.0	1.00 (referent)	1.00 (referent)
Ulcerative STD diagnosis								
Yes	17	23.5	2.11 (0.86–5.21)	1.58 (0.56–4.42)	2311	7.0	3.01 (2.56–3.54)	2.33 (2.00–2.71)
No	377	11.1	1.00 (referent)	1.00 (referent)	37,866	2.3	1.00 (referent)	1.00 (referent)
Urethral STD diagnosis								
Yes	62	9.6	0.80 (0.36–1.81)	0.70 (0.30–1.61)	16,606	1.6	0.50 (0.44–0.57)	0.63 (0.56–0.71)
No	332	11.1	1.00 (referent)	1.00 (referent)	23,574	3.3	1.00 (referent)	1.00 (referent)

NOTE. CI, confidence interval; PRR, prevalence rate ratio; STD, sexually transmitted disease.

^a PRR for HIV infection for patient visits by circumcised vs. uncircumcised men, adjusted for age (≥25 vs. <25 years), new diagnosis of ulcerative (syphilis and/or genital herpes) or urethral (gonorrhea and/or nongonococcal urethritis) STD, year of visit, and clinic location.

exposure (11.7% vs. 2.6%). The association between circumcision and the risk of prevalent HIV infection varied depending on whether visits were made by patients who had known sexual contact with an HIV-infected partner (table 2). Among the 394 visits by patients with known HIV exposure, circumcision was associated with a significant 51% reduction in HIV prevalence after adjustment for demographic and behavioral characteristics (10.2% vs. 22.0%; adjusted PRR, 0.49 [95% CI, 0.26–0.93]). Although the point estimates for older age and diagnosis of ulcerative STD suggested a moderately elevated risk, these factors did not reach significance in multivariable analyses. By contrast, among the 40,177 visits by patients with unknown HIV exposure, circumcision was not associated with reduced HIV prevalence in multivariable analyses comparing circumcised and uncircumcised men (2.5% vs. 3.3%; adjusted PRR, 1.00 [95% CI, 0.86–1.15]) (table 2). For this group, HIV prevalence was significantly higher among visits by patients who were ≥25 years old (adjusted PRR, 3.58 [95% CI, 2.97–4.32]) and for those who had an ulcerative STD diagnosed at the visit (adjusted PRR, 2.33 [95% CI, 2.00–2.71]) and was significantly lower for visits by patients who had a urethral STD diagnosed (adjusted PRR, 0.63 [95% CI, 0.56–0.71]).

DISCUSSION

Consistent with recently published results from 3 randomized controlled trials in South Africa, Uganda, and Kenya [7–9] and numerous observational studies [5, 6], our finding among Afri-

can American men in Baltimore with known HIV exposure further corroborates the theory that circumcision reduces the risk of heterosexually acquired HIV infection. The ~50% reduction in prevalence observed among patients with known HIV exposure is of comparable magnitude to the risk reduction reported across the 3 African trials (range, 48%–60% [7–9]). This analysis also provides a rare examination of the association between male circumcision status and heterosexual risk of HIV infection among a cohort of men in the United States, a group for which existing data are limited. To our knowledge, only 3 other US-based evaluations have reported on this association—2 were conducted among attendees at STD clinics [11, 12], and 1 was conducted among participants in the National Health and Nutrition Examination Surveys [13]. Although these studies suggested that circumcision may be associated with reduced HIV risk, their findings were limited by either a small sample [11, 12] or extremely low HIV prevalence [13], with no findings attaining statistical significance.

We documented that the protective association between male circumcision and the risk of HIV infection in this populations of heterosexual STD clinic patients was evident and significant only when analyses were restricted to visits by patients with known exposure to infected sex partners. Given the difficulties of measuring exposure to infection [21, 22], our ability to isolate reduced HIV risk associated with circumcision among patients with known HIV exposure represents a significant methodological advancement over most other observational studies. Such studies generally examine circumcision and HIV risk among en-

ture populations, in which the overall HIV prevalence is considerably lower and key unmeasured factors related to the risk of infection may differ between circumcised and uncircumcised men. (The single notable exception was a prospective cohort study in Uganda among HIV-discordant couples [23], in which the incidence of HIV infection among men with infected female partners was lower for circumcised than for uncircumcised men.) The magnitude of protection provided by circumcision may thus have been underestimated in most other observational studies because of several factors, possibly including confounding by differences in HIV risk between circumcised and uncircumcised men and a lower prevalence of HIV infection among the pool of female sex partners (compared with the present study).

Our examination of male circumcision and HIV risk among sexual contacts of HIV-infected partners represents a new application of the technique we first employed to reduce confounding in observational studies estimating the protective effect of condom use [17]. In that evaluation, there was a markedly stronger association between condom use and the prevention of gonorrhea and chlamydia when analyses were restricted to STD clinic patients with known exposure to these diseases than when analyses included all patients. Collectively, these and other recent analyses [16, 23–26] illustrate that, in studies that are not randomized, the expected benefits of interventions to prevent STD (including circumcision and use of condoms) are most likely to be demonstrated when the exposed and unexposed groups are similar with regard to potentially confounding factors and when the prevalence of infection in the partner pool is higher. They also lend further evidence that restricting the study population to persons with infected sex partners is useful for estimating the risk reduction associated with interventions in situations in which confounding is suspected and randomized trials are either unethical or not feasible.

As we have noted elsewhere [17], several advantages are offered by this retrospective design for evaluating whether interventions reduce the risk of acquiring an STD. By using the patient's clinic referral as evidence of having an infected partner, this design uses the existing STD clinic framework for partner notification to identify persons with infected sex partners and thus avoids the additional expense of HIV or STD testing or the active recruitment and enrollment of subjects. Although our analysis assessed the association between circumcision and the risk of HIV acquisition among men who have sex with women, this method of identifying patients with infected partners could be extended to men who have sex with men, among whom published studies of the benefits of circumcision are limited in number, lack information on the infection status of partners, and have yielded conflicting results [27–31]. Application of this method to populations of men who have sex with men is particularly important in the United States, given that the majority of

HIV infections diagnosed here have been concentrated in this population.

Our findings are subject to some limitations. First, unlike the 3 randomized trials of adult circumcision [7–9], our analysis was based on observational data. However, the conduct of a randomized trial of circumcision among heterosexual men would probably be impractical or prohibitively expensive in the United States [10] given that the incidence of HIV infection is very low [14], particularly among men who do not have sex with men and do not inject drugs, and that the proportion of men who are circumcised is high (~80%) [13, 32]. Second, in part because our analysis was based on existing clinic records, we lacked information as to whether patients had intercourse with their partners while they were infected, the frequency of sexual exposure, and the stage of disease in the HIV-infected partner—or whether these factors varied by circumcision status. This type of information (particularly high-frequency exposure to HIV-infected partners [33]) may be related to the reduction in HIV risk observed for circumcised men in other studies. Similarly, because we examined only patients who sought care at an STD clinic and specifically visits during which patients agreed to HIV testing, we could not address the possibility of selection bias associated with these factors.

Third, because of how circumcision status was ascertained in the clinic record (i.e., the default was to classify men as circumcised), the prevalence of circumcision may have been overestimated because of incomplete marking of the clinical record. Any misclassification of circumcision status should have been independent of the HIV infection status of patients, however, given that circumcision status was assessed before HIV test results were available; such misclassification generally biases associations toward the null hypothesis [34]. Finally, although we attempted to restrict potential HIV exposures to penile-vaginal intercourse, some patients may have been unwilling to report other HIV risk behaviors, such as intravenous drug use and sex with other men. Taken together, these limitations likely bias our results toward showing no protective effect of male circumcision against HIV infection.

Our analysis also had several strengths. First, we were able to identify a sufficiently large cohort of men with known exposure to HIV-positive partners to evaluate whether male circumcision was associated with reduced risk of infection. Second, we assessed circumcision status as determined by clinicians during the standard physical examination rather than from patient self-reports. Although imperfect [34], clinician-determined measures of circumcision are less prone to error and misclassification [6]. Third, although our analysis was cross-sectional, the reverse-causality problem typically associated with such studies may not have been applicable in this case, because nearly all circumcised men in the United States undergo the procedure as infants [10]. Finally, our findings of different associations between circumcision status and HIV infection status in patients

with known versus those with unknown HIV exposure are reinforced by the fact that we observed many of the same predictors of HIV infection seen in other studies [12, 35, 36].

Whether a randomized trial examining the use of circumcision for preventing heterosexually acquired HIV infection is warranted in the United States was among the questions considered at a recent consultation convened by the Centers for Disease Control and Prevention [37]. Experts who discussed this question concluded that such a trial was probably not necessary, given the biological plausibility for risk reduction and the consistency of results observed across epidemiologic studies, particularly the 3 recent randomized trials. (For men who have sex with men, the consultants concluded that there were insufficient data on the impact of circumcision and recommended that such data be gathered.) Future studies should examine how many heterosexually acquired HIV infections could be averted in the United States by adding adult male circumcision to existing HIV prevention intervention efforts.

In summary, circumcision was associated with significantly reduced HIV prevalence among a cohort of African American heterosexual men with known HIV exposure who were attending Baltimore STD clinics. This study provides evidence that the results of randomized trials in Africa as well as other observational studies that have been conducted among heterosexual men can be generalized to the US context. These findings also demonstrate that the benefits of circumcision may be most evident in observational studies of male patient populations with documented exposure to HIV-infected female partners.

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