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Male Circumcision and Risk of HIV Acquisition among Men who have Sex with Men from the United States and Peru

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Abstract

Objectives—To assess the association between male circumcision, insertive anal sex practices, and HIV acquisition in a cohort of men who have sex with men (MSM).

Methods—Data were from 1824 HSV-2 seropositive, HIV seronegative MSM, 1362 (75%) from Peru and 462 (25%) from the US, who participated in a randomized placebo controlled trial of HSV-2 suppression for HIV prevention (HPTN 039). Circumcision status was determined by examination at enrollment. HIV testing was done every three months for up to 18 months. Partner-specific sexual behavior for up to the last three partners during the previous three months was analyzed.

Results—There was no significant association between male circumcision and HIV acquisition in univariate analysis (RR=0.84, 95% CI 0.50–1.42). In a pre-specified multivariate analysis that assumed a linear relationship between the proportion of insertive acts and effect of circumcision on HIV acquisition, the interaction between circumcision and proportion of insertive acts was not significant (p=0.11). In an exploratory analysis that categorized behavior with recent partners by proportion of insertive acts (<60% or ≥60% insertive acts), circumcision was associated with a non-statistically significant 69% reduction in the risk of HIV acquisition (RR=0.31, 95% CI 0.06–1.51) among men who reported ≥60% of insertive acts with recent male partners.

Conclusion—Circumcision does not have a significant protective effect against HIV acquisition among MSM from Peru and US, although there may be reduced risk for men who are primarily insertive with their male partners. This association needs to be investigated across diverse cohorts of MSM.

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Keywords

HIV acquisition; male circumcision; men who have sex with men

Introduction

In the Americas, Asia and Europe, HIV disproportionately affects men who have sex with men (MSM) [1–3], and MSM are recognized as an important but neglected risk group in sub-Saharan Africa [4]. Three randomized trials have demonstrated that male circumcision reduced HIV acquisition risk among heterosexual men by ~60% [5–8]. These results have generated discussion about the potential efficacy of circumcision to reduce HIV susceptibility among MSM.

Unprotected receptive anal intercourse (URAI) is the highest risk behavior for HIV acquisition among MSM. Circumcision is unlikely to reduce URAI risk, but could partially protect against HIV for MSM practicing unprotected insertive anal intercourse (UIAI) [9]. A cohort study of MSM in the US found that lack of male circumcision was associated with a doubling in HIV risk [10]. However, a meta-analysis found that circumcised MSM had only a 14% decreased risk of HIV infection versus non-circumcised MSM, with a 30% lower risk among MSM who primarily engaged in insertive sex; these differences were not statistically significant [13].

Research is needed from longitudinal studies of diverse populations of MSM with data on the proportion of sexual exposure through insertive and receptive anal sex to evaluate the relationship between male circumcision status and risk of HIV acquisition. We conducted an analysis of male circumcision, sexual practices, and HIV acquisition among MSM from Peru and the US enrolled in the HIV Prevention Trials Network (HPTN) 039 study [14].

Material and Methods

Study Population

HPTN 039 was a randomized trial of acyclovir suppression of herpes simplex virus type 2 (HSV-2) for prevention of HIV acquisition among HSV-2 seropositive MSM and women; acyclovir did not significantly reduce HIV incidence [14]. HIV seronegative, HSV-2 seropositive MSM from New York, San Francisco, and Seattle (US) and Iquitos, Lima, and Pucallpa (Peru) were enrolled. Inclusion criteria included age ≥18 years, ≥1 episode of anal sex during the previous six months, and not in a mutually monogamous relationship with a known HIV negative partner in the past year. To assure recruitment of men at highest HIV risk [12], more restrictive eligibility criteria were used in Peru, including one of the following: no condom use during last anal intercourse, self-identification as a sex worker, or, in the prior six months, diagnosis of a sexually transmitted infection, anal intercourse with ≥ five partners, or sex with an HIV-infected man.

The study protocol was approved by Division of AIDS Prevention Science Review Committee, US National Institute of Allergy and Infectious Diseases; Family Health International Regulatory Affairs; and institutional review boards at the University of Washington and collaborating institutions.

Procedures

At quarterly visits for up to 18 months of follow-up, participants were asked about sexual behavior in the previous 3 months, with assessment of partner-specific risk behaviors for a maximum of three of their most recent partners, including number of protected and

unprotected receptive and insertive sex acts. Physical examination for circumcision status was performed at enrollment [14]. At quarterly visits, HIV testing was performed; HIV seroconversion was confirmed by Western blot. Condoms and risk reduction counseling were provided at each visit.

Statistical Analyses

Cox proportional hazards analysis, with time-dependent covariates, was used to assess the association between circumcision status and time to HIV acquisition. Factors that confounded or modified this relationship were included in a multivariate analysis, stratified by study site. Analyses were performed using Intercooled Stata 9.1 (Stata Corporation, College Station, TX).

To assess whether the association between male circumcision and HIV acquisition differed for insertive versus receptive anal sex, we quantified the proportion of insertive anal sex acts (defined as the ratio of total insertive acts over all sexual acts reported with the last three partners at each quarterly visit), and analyzed this as a continuous, time-dependent covariate (total number of sexual acts with the last three partners in the last three months was also included in the model to control for overall level of risk). If a participant reported partners in a given quarter but did not provide partner-specific behavioral information, this proportion was treated as missing, which occurred in 5% (n=467) of quarterly visits. In a pre-specified analysis, the proportion of insertive anal sex acts was included as an effect modifier of the relationship between circumcision status and HIV acquisition risk. In an exploratory analysis, relative risks of circumcision and HIV acquisition were calculated for categories for proportion of insertive sex acts with male partners (1–20%, 21–40%, 41–60%, 61–80% and 81–100%). The population attributable risk (PAR) due to lack of circumcision was calculated for relevant categories of proportion of insertive anal sex [15].

Results

Among the 1822 MSM included in the analysis, 457 (25.1%) were circumcised. Circumcision prevalence differed by country: 378 (81.8%) men in the US were circumcised compared to 79 (5.8%) Peruvian men (Table 1). Circumcised men were older and had higher levels of education. Peruvian men reported higher numbers of sexual partners in the past year than US men, but there was little difference in the number of partners between circumcised and uncircumcised men within each country (12 vs. 10 in Peru and 5 vs. 6 in the US). Fewer circumcised men reported having a known HIV positive partner compared to uncircumcised men (1.5% vs. 1.6% in Peru and 17.1% vs. 24.1% in the US).

Uncircumcised men reported similar rates of new partners, less protected and unprotected receptive anal intercourse (PRAI and URAI), and more UIAI compared to circumcised men. Among Peruvian participants, the proportion of insertive acts with the last three partners was higher for circumcised than uncircumcised men (0.46 vs. 0.28), but among US participants, the proportion was similar between circumcised and uncircumcised men (0.53 vs. 0.51). A higher proportion of uncircumcised men reported exclusively receptive anal sex compared to circumcised men, particularly among Peruvian men (65.8% vs. 46.0%).

Drug use was more frequently reported by US than Peruvian participants (42.4% vs. 5.2%), particularly among uncircumcised men. Among US men, alcohol use was higher among circumcised men than uncircumcised men (45.2% vs. 36.1%). Uncircumcised men in both regions reported more sex in exchange for money, gifts or shelter than circumcised men (27.6% vs. 18.4% in Peru and 5.6% vs. 4.3% in the US).

Circumcision, Sexual Role and HIV Acquisition

Eighty-five men (67 uncircumcised and 18 circumcised) seroconverted to HIV (incidence 3.2/100 person-yrs). HIV incidence was 2.28 per 100 person-years (95% confidence interval [CI] 0.96, 4.56) during periods when men reported exclusively insertive sex.. In univariate analysis, being circumcised was not significantly associated with reduced HIV acquisition risk (risk ratio [RR]=0.84, 95% CI 0.50–1.42, p=0.512). In the pre-specified multivariate analysis, there was a non-statistically significant suggestion of a lower relative risk of HIV acquisition associated with circumcision for primarily insertive men (p-value for linear relationship by proportion of anal sex acts insertive=0.11) (Figure 1). In this multivariate model, including the interaction between circumcision and proportion of sex acts that were insertive, the predicted relative risk of HIV acquisition associated with circumcision among men who were 80% insertive and exclusively insertive was 0.83 (95% CI 0.30–2.32) and 0.65 (95% CI 0.19–2.27), respectively. PAR percentages for lack of circumcision and HIV acquisition among men who were exclusively (100%) or mainly (80% of acts) insertive were 28.7% and 13.3%, respectively. These estimates differed by country, due to differences in circumcision rates: 55.9% and 48.8% in Peru and 8.9% and 3.6% in the US.

These data suggested a threshold for the relationship between circumcision status and insertive anal sex acts with HIV acquisition risk: circumcision was not protective for men who were primarily receptive (men who were insertive ≤60% of acts), but among men who were insertive for ≥60% of acts with recent partners, there appeared to be a non statistically-significant decreased risk for circumcised men compared to uncircumcised men (RR=0.31, 95%CI: 0.06–1.51). The interaction between these two categories (<60% vs. ≥60% insertive) and the circumcision effect was statistically significant (p=0.018). Based on this model, the PAR associated with circumcision among men who were primary insertive (≥60%) was 62.4% overall, or 74.0% and 28.7% in Peru and the US, respectively.

Discussion

In this longitudinal study of over 1800 Peruvian and US MSM with a significant risk of HIV acquisition, male circumcision was not associated with decreased HIV risk either overall or among men with primarily or exclusively insertive anal sex behavior. However, in an exploratory multivariate analysis, there was a suggestion that male circumcision may reduce risk of HIV acquisition by 69% among men who reported ≥60% of acts insertive with their last three partners. Our findings are consistent with a meta-analysis that reported a non-significant RR of 0.86 among all MSM and a trend towards lower HIV risk among MSM who primarily practiced insertive anal sex (RR 0.70, 95% CI 0.2–2.2) [13].

Observational data have not consistently found that circumcision reduces HIV risk for MSM. In an Australian study, circumcision was associated with a lower risk of HIV acquisition among MSM whose preferred sexual role was insertive, after controlling for age and number of insertive unprotected anal intercourse acts with HIV positive or status unknown partners (hazard ratio 0.15, 95% CI 0.03–0.80) [16]. In a cross-sectional study of African MSM, where most men reported exclusively practicing insertive anal intercourse, circumcision was associated with lower HIV prevalence (adjusted odds ratio 0.2, 95% CI 0.1–0.2) [17]. While one study among US MSM found that circumcision was not protective against HIV infection among men who reported unprotected insertive anal sex with HIV-infected partners [18], another study observed a trend towards higher risk of HIV acquisition among uncircumcised men with recent unprotected insertive anal sex (adjusted hazard ratio 1.78, p=0.09) [19].

In this cohort, all men were seropositive for HSV-2, which may limit the generalizability of these findings [20]; HSV-2 seroprevalence among MSM in other cohorts is 30%–60% [12,

21]. Participants were asked about sexual role for only the last three sex partners in the past three months, which could lead to misclassification of sexual role, with potential attenuation of the relationship between the proportion of insertive acts and RR of circumcision for HIV acquisition. Given an average of six anal sex acts reported at quarterly follow-up visits, our ability to discriminate differences in risk for small differences in proportion of acts insertive (e.g., 60 versus 80%) may have been limited.

In conclusion, our data indicate no overall protective benefit from male circumcision among MSM from Peru and the US. Further studies are needed among populations of MSM with different rates of role segregation and male circumcision, such as from Africa and Latin America [17, 22, 23], to further evaluate whether circumcision is protective among men whose main exposure to HIV with recent partners was through UIAI. Public health messages for MSM should summarize available data on male circumcision and HIV risk and reinforce the importance of condom use for HIV prevention.

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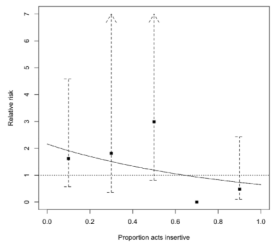

Fig. 1. Multivariate relative risk of HIV acquisition for circumcised versus uncircumcised men under two modeled conditions

1) The solid line depicts the predicted relative risk in a model in which the proportion of sex acts that were insertive was considered as a continuous variable (i.e., assuming a linear relationship for the proportion of acts insertive). 2) The individual point estimates (with 95% confidence interval whiskers) are from a multivariate model in which the proportion of acts that were insertive was considered as five categories: 1–20%, 21–40%, 41–60%, 61–80% and 81–100%. For both models, the proportion of sex acts that were insertive was considered as a time-dependent measure. Both multivariate models were adjusted for age, education, genital ulcer disease during follow-up, alcohol or drug use with sex, giving or receiving drugs money and/or gifts for sex, total number of sex acts, total number of described partners and having sex with a known HIV positive individual and were stratified by study site.

Table 1

Demographic and behavioral and clinical characteristics of participants at enrollment

	Peru[#] (n=1360, 74.6%)		US (n=462, 25.4%)	
N (%)	**Circumcised n=79 (5.8%)**	**Uncircumcised n=1281 (94.2%)**	**Circumcised n=378 (81.8%)**	**Uncircumcised n=84 (18.2%)**
Demographics				
Age (years)*	30 [25–35]	27 [23–34]	41 [34–49]	37 [29–46]
Education				
Less than High School	1 (1.3%)	56 (4.4%)	0 (0%)	1 (1.2%)
Some High School	20 (25.3%)	781 (61.0%)	52 (13.8%)	19 (22.6%)
More than High School	58 (73.4%)	444 (34.6%)	326 (86.2%)	64 (76.2%)
Behavioral characteristics				
No. of partners in the last year *	12 [5–30]	10 [5–30]	5 [3–12]	6 [3–14]
All partners in the last month				
Any partner	66 (83.5%)	1147 (89.5%)	281 (74.3%)	58 (69.1%)
Any HIV + partner	1 (1.5%)	18 (1.6%)	48 (17.1%)	14 (24.1%)
Any unknown HIV status partner	44 (66.7%)	934 (81.4%)	98 (34.9%)	28 (48.3%)
Any HIV - partner	29 (43.9%)	352 (30.7%)	198 (70.5%)	35 (60.3%)
Up to three most recent partners during the last 3 months				
At least one partner	76 (96.2%)	1233 (96.3%)	347 (91.8%)	72 (85.7%)
Any new partner	59 (77.6%)	838 (68.0%)	254 (73.2%)	51 (70.8%)
Any URAI with any of 3 most recent partners	38 (50.0%)	717 (58.2%)	131 (37.8%)	33 (45.8%)
Any UIAI with any of 3 most recent partners	28 (36.8%)	263 (21.3%)	162 (46.7%)	31 (43.1%)
Any PRAI with any of 3 most recent partners	52 (68.4%)	845 (68.5%)	169 (48.7%)	37 (51.4%)
Any PIAI with any of 3 most recent partners	35 (46.1%)	306 (24.8%)	205 (59.1%)	41 (56.9%)
Total # of sex acts with 3 most recent partners*	6 [4–14]	7 [3–15]	5 [3–12]	5 [3–15]
Proportion of insertive acts^	0.46	0.28	0.53	0.51
Participant totally insertive	17 (22.4%)	183 (14.8%)	110 (31.7%)	17 (23.6%)
Participant totally receptive	35 (46.0%)	811 (65.8%)	70 (20.2%)	15 (20.8%)
Participant both insertive and receptive	24 (31.6%)	239 (19.4%)	167 (48.1%)	40 (55.6%)
Any alcohol use with sex	40 (52.6%)	660 (53.5%)	157 (45.2%)	26 (36.1%)
Any drug use with sex	2 (2.63%)	66 (5.4%)	145 (41.8%)	32 (44.4%)
Exchange for money, drug or shelter for sex	14 (18.4%)	340 (27.6%)	15 (4.3%)	4 (5.6%)
Clinical characteristics				

	Peru[#] (n=1360, 74.6%)		US (n=462, 25.4%)	
N (%)	**Circumcised n=79 (5.8%)**	**Uncircumcised n=1281 (94.2%)**	**Circumcised n=378 (81.8%)**	**Uncircumcised n=84 (18.2%)**
History of GUD (previous 3 months)	14 (17.7%)	214 (16.7%)	103 (27.3%)	29 (34.5%)
GUD on exam	1 (1.3%)	38 (3.%)	10 (2.7%)	5 (6.0%)
Syphilis seropositive (based on RPR)	15 (19.0%)	406 (31.7%)	16 (4.2%)	4 (4.5%)

[*] Median [Interquartile range]

[^] Proportion insertive acts over all reported sex acts

[#] Two observation excluded due to lack of circumcision status

Definitions: URAI = Unprotected receptive anal intercourse, UIAI = Unprotected insertive anal intercourse, PRAI = Protective receptive anal intercourse, PIAI = Protective insertive anal intercourse; GUD = Genital ulcer disease; RPR = Rapid plasma reagin serologic test for syphilis