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Aetiology of genital ulcer disease in female partners of male participants in a circumcision trial in Uganda

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Summary

HIV acquisition is associated with herpes simplex virus type 2 (HSV-2) infection and genital ulcer disease (GUD). Three randomized control trials demonstrated that male circumcision significantly decreases HIV, HSV-2, human papillomavirus and self-reported GUD among men. GUD is also decreased among female partners of circumcised men, but it is unknown whether male circumcision status affects GUD pathogens in female partners. For the evaluation of GUD aetiology, two separate multiplex assays were performed to detect *Haemophilus ducreyi*, *Treponema pallidum*, HSV-1 and HSV-2. Of all the female GUD swabs evaluated, 67.5% had an aetiology identified, and HSV-2 was the primary pathogen detected (96.3%). However, there was no difference in the proportion of ulcers due to HSV-2 or other pathogens between female partners of circumcised men (11/15, 73.3%) compared with uncircumcised men (15/25, 60.0%, $P = 0.39$). The seroprevalence of HSV-2 is high in this population and therefore most of the detected HSV-2 infections represent reactivation. Since GUD is associated with HIV acquisition and one-third of GUD in this study did not have an aetiological agent identified, further research is needed to better understand the aetiology of GUD in Africa, and its relationship to circumcision and HIV infection.

Keywords

herpes simplex virus type 2 (HSV-2); *T. pallidum* (TP); *H. ducreyi* (HD); genital ulcer disease (GUD); HIV; circumcision

INTRODUCTION

An association between sexually transmitted infections (STIs), genital ulcer disease (GUD) and HIV acquisition has been shown in observational studies.^{1–5} Three randomized controlled trials demonstrated that male circumcision significantly decreases HIV, herpes simplex virus (HSV)-2, human papillomavirus and self-reported GUD among men.^{6–9} GUD is also

decreased among female partners of circumcised men.¹⁰ We evaluated the aetiology of GUD among female partners linked to men enrolled in the Rakai circumcision trial to determine whether male circumcision status affected GUD pathogens in female partners.

METHODS

We evaluated 6,396 men who were enrolled in two trials of male circumcision for HIV and STI prevention in Rakai, Uganda.^{6,9,11} At enrolment, male trial participants were asked to identify their wives or long-term consensual partners. The design of these studies and the description of HIV and HSV-2 testing have been reported previously.^{6,9–11} Blood samples from both male and female participants were collected at all visits (enrolment, 6, 12 and 24 months) for routine testing, and swab samples were collected from symptomatic ulcerative lesions. Enrolment swabs obtained prior to male circumcision were classified as part of the uncircumcised group. All study participants were evaluated for HSV-2 serostatus, except for one woman who did not have a baseline enrolment sample and for one woman who was negative at enrolment and did not have a follow-up sample.

For the detection of GUD aetiology, two separate multiplex assays were performed for each sample. One reaction was performed for the simultaneous detection of *Haemophilus ducreyi* and *Treponema pallidum*, and the other for HSV-1 and HSV-2 detection, as previously described.¹²

RESULTS

Wives of men were enrolled in a trial in which the men were randomized to immediate or delayed circumcision. Among HIV-negative women married to HIV-negative men, the rates of self-reported GUD were significantly lower in women with circumcised men (12.8%, 102/798) than in women with control partners (16.8%, 128/763, $P = 0.03$) at year one.¹⁰ Among HIV-negative women married to HIV-positive men, GUD symptoms were reported by 20.5% (17/83) of women with circumcised partners and by 12.9% (8/62) of women with control partners ($P = 0.23$). Among HIV-positive women, GUD symptoms were reported by 29.8% (54/181) of women with circumcised partners and by 25.9% (37/143) of women with control partners ($P = 0.43$).

A total of 40 female participants with GUD swabs (15 female partners of circumcised men and 25 female partners of uncircumcised men) were evaluated, of which 67.5% (27/40) had a detected aetiology. HSV-2 accounted for 65.0% (26/40) of GUD and 96.3% (26/27) of GUD with a detected aetiology. *T. pallidum* was detected in one sample, 2.5% (1/40) of total GUD and 3.7% (1/27) of GUD with a detected aetiology. HSV-1 and *H. ducreyi* were not detected in any of the samples. While HIV-infected women had a higher rate of GUD with an aetiology (12/16, 75%) than HIV-negative women (14/24, 58.3%), it was not statistically different ($P = 0.13$).

There was no difference in detectable ulcer aetiology by male partner circumcision status (Table 1). There were 15 (60.0%) women with detectable aetiology for GUD linked to men in the uncircumcised group and 11 (73.3%) women with detectable aetiology for GUD linked to men in the circumcised group ($P = 0.39$).

Of the 39 women evaluated for enrolment HSV-2 status (1 woman did not have a baseline specimen), 74.4% (29/39) were seropositive. Of the individuals who were HSV-2 negative at enrolment and had a detectable GUD by physical examination during the trial 77.8% (7/9) seroconverted to HSV-2 during the trial. Thus, 76.0% (19/25) of HSV-2-positive GUD were due to reactivation and 24.0% (6/25) of HSV-2 positive GUD were due to primary infection.

DISCUSSION

Of all the female GUD swabs evaluated, 67.5% had an STI aetiology identified, and HSV-2 was the primary pathogen (96.3%) detected. These results are consistent with recently published data from other African regions.⁴ Ulcers with no detectable DNA may be due to secondary infections with staphylococcus or streptococcus, the primary pathogen had been cleared, or were traumatic in origin.

Male circumcision decreases HSV-2 incidence and decreases GUD among female partners, but we found no difference in the proportion of ulcers due to HSV-2 or other pathogens between female partners of circumcised men compared with uncircumcised men. The seroprevalence of HSV-2 is high in this population and therefore most of the HSV-2 infections represent reactivation.

The findings in this study and previous studies have demonstrated that the majority of GUD aetiology can be attributed to HSV-2,^{12,13} underscoring the importance of HSV-2 as the causative agent for GUD in sub-Saharan Africa. Since GUD is associated with HIV acquisition¹⁻⁴ and one-third of GUD in this study did not have an aetiological agent identified, further research is needed to better understand the aetiology of GUD in Africa, and its relationship to circumcision and HIV infection.

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Table 1

Aetiology of genital ulcer disease (GUD) in female partners of men participating in a male circumcision trial in Uganda, as determined by two duplex polymerase chain reactions

Aetiology	Female HIV serostatus		Male circumcision status	
	Positive	Negative	Uncircumcised	Circumcised
HSV-2	12/16 (75.0%)	14/24 (58.3%)	15/25 (60.0%)	11/15 (73.3%)
HSV-1	0/16	0/24	0/25	0/15
<i>H. ducreyi</i>	0/16	0/24	0/25	0/15
<i>T. Pallidum</i>	1/16 (6.3%)	0/24	1/25 (4.0%)	0/15
None	3/16 (18.7%)	10/24 (41.7%)	9/25 (36.0%)	4/15 (26.7%)