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Correlates of Bacterial Ulcers and Acute HSV-2 Infection among Men with Genital Ulcer Disease in South Africa: Age, Recent Sexual Behaviors, and HIV

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Abstract

Data from baseline surveys and STI/HIV laboratory tests (n=615 men) were used to examine correlates of bacterial ulcers (*Treponema pallidum*, *Haemophilus ducreyi*, or *Chlamydia trachomatis* L1–L3 detected in ulcer) and acute HSV-2 ulcers (HSV-2 positive ulcer specimen, HSV-2 sero-negative, and negative for bacterial pathogens) vs. recurrent HSV-2 ulcers (sero-positive), separately. Compared to men with recurrent HSV-2 ulcers, men with bacterial ulcers had larger ulcers but were less likely to be HIV-positive whereas men with acute HSV-2 ulcers were younger with fewer partners. Acute HIV was higher among men with bacterial and acute HSV-2 ulcers; the difference was not statistically significant.

Keywords

genital ulcer disease; bacterial ulcers; acute HSV-2; acute HIV; sexual behavior

INTRODUCTION

Genital ulcer disease (GUD), including herpes simplex virus type 2 (HSV-2) infection, is common in sub-Saharan Africa and is associated with HIV acquisition and onward transmission. [1–6] Although some studies have examined demographics and sexual behaviors of men with GUD, [1] less is known about the differences between men with bacterial and other acute ulcers and men with other forms of GUD. Given the relationship

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between HSV-2 and HIV acquisition [7] and the difficulties in the ability to clinically differentiate between specific etiological causes of GUD [8], it is important to examine whether or not men presenting to a clinic with GUD have any demographic or sexual risk differences based on ulcer etiology. Identifying clinical, demographic, and behavioral correlates of GUD by causal infection may aid in the development of targeted counseling messages regarding STI/HIV acquisition and transmission risk as well as STI/HIV prevention practices. Furthermore, identification of differences between men with different ulcer types regarding HIV status and acute HIV infection would be useful for healthcare providers and STD prevention efforts.

Thus, we compared demographics and recent sexual behaviors of men who had either a bacterial or acute HSV-2 ulcer with men who had recurrent HSV-2 ulcers. Finally, we examined the prevalence of HIV sero-positivity and acute HIV among the groups to determine if there was an association between bacterial or acute HSV-2 ulcers and newly acquired HIV infection.

METHODS

As part of larger randomized controlled trial (RCT) on acyclovir therapy conducted in 2006–07, 615 men with GUD aged 18–60 years old were recruited from three primary health care clinics in Gauteng Province, South Africa from a total of 635 men who were found to be eligible for the RCT. [9] We used data from baseline surveys and STI/HIV testing to examine the correlates of 1) bacterial ulcers vs. recurrent HSV-2 ulcers and 2) acute vs. recurrent HSV-2 ulcers. The RCT was approved by U.S. Centers for Disease Control and Prevention and University of Witwatersrand ethics review boards; participants provided informed consent. Study details have been previously published. [9–10]

Our diagnostic approach has been described previously. [9] Briefly, rapid HIV tests [Determine™ (Abbott Laboratories) and Capillus (Trinity Biotech PLC)] were used to screen patients at the clinic; discordant results were further tested in the laboratory using three enzyme-linked immunosorbent assays (Bio-Rad, Abbott Murex, and bioMérieux). Blood serum from antibody negative participants, who consented to have their specimens stored for future testing, were tested to detect acute infection by HIV RNA PCR. The COBAS AmpliScreen HIV-1 Test v.1.5 (Roche, USA) was used for detection of HIV-1 RNA in pooled samples of 6 specimens and individual specimens. Serological screening was undertaken for syphilis with the rapid plasma reagin (Becton Dickinson and Co.) and the *Treponema pallidum* particle-agglutination (Fujirebio Inc.) assays and HSV-2 IgG (Kalon Biological). [11] A previously validated multiplex PCR assay was used to test for *Treponema pallidum*, *Haemophilus ducreyi*, and HSV. [11] A PCR assay was used to type HSV positive specimens to differentiate HSV-1 from HSV-2 infected lesions.[12] A separate real-time PCR assay for *Chlamydia trachomatis* L1–L3 was also performed. [13]

Bacterial ulcers were those with *Treponema pallidum (*syphilis*)*, *Haemophilus ducreyi (*chancroid*)*, or *Chlamydia trachomatis* L1–L3 (Lymphogranuloma Venereum, LGV) detected in the ulcer specimens. Recurrent HSV-2 ulcers were those among men with HSV-2 positive serology and HSV-2 detected in the ulcer. Acute HSV-2 ulcers where those among

men with HSV-2-positive ulcer specimen and HSV-2-negative serology. Among all participants, men with bacterial ulcers were compared to men with recurrent HSV-2. Among men who did not have a bacterial ulcer, men with acute HSV-2, were compared to men with recurrent HSV-2 ulcers. Correlates that were examined, separately, for both ulcer outcome measures included demographics, recent sexual behaviors and HIV test results (HIV sero-positivity or acute HIV). In the absence of anti-HIV antibodies at baseline, acute HIV was defined by either detection of HIV RNA at baseline or by HIV seroconversion at one month follow-up.[6] Ulcer size (determined by measurements of largest ulcer) and mean number of ulcers were also included in analyses. Chi-squares, Fisher's Exact tests (acute HIV analyses), and t-tests were used for bivariate analyses. Variables with $p < .10$ in bivariate analyses were included in adjusted logistic regression models.

RESULTS

Of the 615 participants with GUD, 7.0% had a bacterial ulcer (n=43), 21.3% had acute HSV-2 (n=131), 0.8% had both a bacterial and acute HSV-2 ulcer (n=5), 50.1% had recurrent HSV-2 (n=308), and 20.8% had an ulcer of undetermined etiology (n=128). Among bacterial ulcers (n=48), 30 were attributed to syphilis, 10 to chancroid, and 8 to LGV. For this analysis, we categorized the 0.8% (5/615) of men who had a bacterial and acute HSV-2 ulcer has having a bacterial ulcer. No men had a dually-infected bacterial and recurrent HSV-2 ulcer. Of men who had a bacterial or recurrent HSV-2 ulcer (n=356), men who had a bacterial ulcer were significantly younger than men with recurrent HSV-2 ulcers (p=.02), and the majority were single (Table 1). Also, men with bacterial ulcers reported more casual sex partners in the past 3 months than men with recurrent HSV-2 ulcers (p=.01). There were no differences between the groups for other sexual behaviors, in the average time it took men to seek care for their ulcer, or number of ulcers. As compared to men with recurrent HSV-2 ulcers, men with bacterial ulcers had larger ulcers (p<.0001), and fewer were HIV-positive (24/48; 50.0% vs. 237/308; 77.0%, p<.0001). There was no difference in the prevalence of acute HIV between the two groups. In adjusted analyses, men with a bacterial ulcer were significantly more likely to have large ulcers (AOR=6.82; 95%CI 3.26 to 14.29) as compared to men with recurrent HSV-2 ulcers. Men with bacterial ulcers were also less likely to test positive for HIV antibodies (AOR=0.26; 95%CI 0.12 to 0.55).

Of men with HSV-2 who did not have a bacterial ulcer (n=444), 30.6% had acute herpes (n=136) and 69.4% had recurrent herpes (n=308). Similar to findings for bacterial vs. recurrent HSV-2 ulcers, in bivariate analyses, men with acute HSV-2 were younger (p<.0001) (Table 2). Conversely, as compared to men with recurrent HSV-2, men with acute HSV-2 had lower reports of multiple regular sex partners (p<.01), but also fewer reports of always using condoms with these partners p=.09), although this difference was not significant. It is worth noting that the majority (> 75%) of men in both groups reported multiple regular sex partners in the past 3 months and consistent condom use was low (<20%). Men with acute HSV-2 did not differ from those with recurrent HSV-2 in ulcer size. However, men with acute HSV-2 sought care more quickly than men with recurrent HSV-2 ulcers (p=.01). Fewer men with acute HSV-2 tested positive for HIV infection (55/136; 40.4% vs. 237/308; 77.0%, p<.0001). Although the percent with acute HIV was higher among those with acute HSV-2 (5/81; 6.2%) compared to those with recurrent HSV-2 ulcers

(1/71; 1.4%), the difference did not reach statistical significance (p=.22). In adjusted analyses, men with acute HSV-2 were more likely to be 18–25 years (AOR=6.61, 95%CI 2.96–14.77) and were less likely to report multiple regular partners (AOR=0.53, 95%CI 0.30–0.96). Finally, as compared to men with recurrent HSV-2, men with acute HSV-2 were less likely to test positive for HIV antibodies at baseline (AOR=0.31, 95%CI 0.19–0.50).

DISCUSSION

Our study found that bacterial infections accounted for a lower proportion of ulcers. Specifically, less than 10% of participants had a bacterial ulcer but nearly one-third of men had acute HSV-2 infection at clinical presentation. Also, we found that men with acute ulcers tended to have larger ulcers than men with recurrent HSV-2 ulcers. HIV positivity at the time of GUD clinical presentation was high among men with bacterial (50%) and acute HSV-2 ulcers (40%); however, they were less likely to be infected with HIV as compared to men with recurrent HSV-2 ulcers (77%). Furthermore, 4% of men with a bacterial ulcer and 6.2% of men with acute HSV-2 had acute HIV. Acute and early HIV infection may help drive HIV transmission in sub-Saharan Africa. [14] Our data emphasize the importance of testing, with a rapid, sensitive HIV screening assay, all men with GUD for HIV co-infection at the first clinical presentation [15] and to re-test HIV sero-negative men for possible HIV seroconversion at the end of the ‘window period’ (ideally, 4–6 weeks later).

Other places in Africa, such as a study in Namibia have found that bacterial infections accounted for a low proportion of ulcers.[16] In comparison, bacterial ulcers accounted for a higher proportion GUD in etiological studies conducted among men and women in both Malawi in 2004–06 [3] and Madagascar in 2011 (D A Lewis, personal communication).

Recent sexual behaviors and age were associated with ulcer type, although these findings were not significant in adjusted analyses for bacterial ulcers. We did find that younger men (18–34 years old) were more likely to have acute HSV-2 as compared to recurrent HSV-2 in bivariate and adjusted analyses. It is important to note that, across all ulcer groups (bacterial ulcers, acute HSV-2, and recurrent HSV-2), the majority of men reported multiple partners (2 or more regular and casual partners) and half reported never using condoms). Thus, given the lack of consistent behavioral and demographic findings across our ulcer groups, a broader rather than targeted approach to the delivery of prevention messages may be useful for men presenting to primary healthcare clinics with GUD. Specifically, it may be useful to discuss STD/HIV prevention efforts with all men who present with GUD. These could include correct and consistent condom use, reduction in number of partners, early treatment of symptomatic STIs, and the benefits for couples to know their HIV serostatus.

Our study has limitations. The small number of bacterial ulcers precluded examining syphilis, chancroid, and LGV ulcers separately. It is possible that some correlates may vary for the different bacterial ulcer types. The small number of acute HIV infections limits our interpretations of those data. Finally, it is possible that the epidemiology and predictors of the ulcer types have changed over time.

CONCLUSION

Finally, our findings emphasize the importance of HIV testing and retesting and strengthening STI/HIV prevention programs for men in South Africa, particularly HIV negative youth that may benefit from prevention services. GUD diagnosed among HIV-negative young adult men can be sentinel public health opportunities to engage this high risk group in STI/HIV prevention counseling/education. It is important that men are equipped with the appropriate knowledge and skills to either avoid acquiring, or to seek early treatment for, STIs including GUD. Furthermore, given the high levels of risk behavior we observed, it is also important for prevention messages to be disseminated to all men including those with recurrent HSV-2 infections.

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Table 1

Characteristics of Men with Bacterial Ulcers as Compared to Recurrent HSV-2 Ulcers, South Africa, 2006–07

Correlate	Bivariate Analyses			Adjusted Model (n=354) AOR (95%CI)
	Bacterial ulcer (n=48) n (%)	Recurrent HSV-2 (n=308) n (%)	Unadjusted P value	
Demographics				
Age (years)			.02	
18–24	13 (27.1%)	38 (12.3%)		1.06 (0.33–3.41)
25–34	24 (50.0%)	173 (56.2%)		0.99 (0.42–2.32)
35 and older	11 (22.9%)	97 (31.5%)		Ref
Marital status			.04	
Married	7 (14.6%)	90 (29.2%)		Ref
Cohabitating	5 (10.4%)	46 (14.9%)		1.29 (0.36–4.61)
Currently single[a]	36 (75.0%)	172 (55.8%)		2.57 (0.98–6.72)
Nativity			.52	
South African	38 (79.2%)	229 (74.8%)		–
Other	10 (20.8%)	77 (25.2%)		–
Recent Sexual Behaviors				
Had multiple regular sex partners, last 3 months			.36	
No	9 (19.2%)	43 (14.1%)		–
Yes	38 (80.9%)	263 (86.0%)		–
Condom use with regular partners[b]			.11	
Never	20 (48.8%)	152 (55.3%)		–
Inconsistently	18 (43.9%)	80 (29.9%)		–
Always	3 (7.3%)	43 (15.6%)		–
Casual sex partners, last 3 months			.01	
0	25 (52.1%)	219 (71.6%)		Ref
1	12 (25.0%)	57 (18.6%)		1.29 (0.55–3.00)
2 or more	11 (22.9%)	30 (9.8%)		2.10 (0.81–5.41)
Condom use with casual partners[c]			.95	
Never	12 (52.2%)	42 (50.6%)		–
Inconsistently	7 (30.4%)	24 (28.9%)		–
Always	4 (17.4%)	17 (20.5%)		–
STI/HIV				
Mean time to seek care, days (SD)	8.3 (5.0)	7.1 (5.3)	.16	–
Ulcer size			<.0001	
50mm or smaller	13 (27.1%)	209 (67.9%)		Ref
>50mm	35 (72.9%)	99 (32.1%)		6.82 (3.26–14.29)
Number of ulcers – mean (SD)	2.9 (2.3)	2.5 (2.3)	.27	–
HIV results			<.0001	
HIV-negative	24 (50.0%)	71 (23.1%)		Ref

Correlate	Bivariate Analyses			Adjusted Model (n=354) AOR (95%CI)
	Bacterial ulcer (n=48) n (%)	Recurrent HSV-2 (n=308) n (%)	Unadjusted P value	
HIV-positive	24 (50.0%)	237 (77.0%)		0.26 (0.12–0.55)
Detection of acute HIV infection in men testing HIV-negative at baseline[d]				
No	23 (95.8%)	70 (98.6%)	.42	–
Yes	1 (4.2%)	1 (1.4%)		–

SD=standard deviation. Ns are for adjusted analyses. For adjusted analyses, reference group is “recurrent HSV-2”.

[a] includes divorced men who are currently single.

[b] of those who had a regular partner in the past 3 months.

[c] of those who had a casual partner in the past 3 months (n=106).

[d] acute HIV infection – HIV antibody negative test and HIV RNA positive test at baseline or HIV seroconversion (baseline antibody negative, follow-up antibody positive).

Table 2

Characteristics of Men with Acute and Recurrent HSV-2 Ulcers, South African, 2006–07

Correlate	HSV-2 Ulcers			
	Bivariate Analyses			
	Acute HSV-2 (n=136) n (%)	Recurrent HSV-2 (n=308) n (%)	P value	Adjusted Model (n=389) AOR (95%CI)
Demographics				
Age (years)			<.0001	
18–24	51 (37.5%)	38 (12.3%)		6.34 (2.83–14.22)
25–34	72 (52.9%)	173 (56.2%)		2.37 (1.17–4.80)
35 and older	13 (9.6%)	97 (31.5%)		Ref
Marital status			.12	
Married	29 (21.3%)	90 (29.2%)		–
Cohabitating	17 (12.5%)	46 (14.9%)		–
Currently single[a]	90 (66.2%)	172 (55.8%)		–
Nativity			.27	
South African	95 (69.9%)	229 (74.8%)		–
Other	41 (30.2%)	77 (25.2%)		–
Recent Sexual Behaviors				
Had multiple regular sex partners, last 3 months			<.01	
No	33 (24.3%)	43 (14.1%)		Ref
Yes	103 (75.7%)	263 (86.0%)		0.53 (0.30–0.96)
Condom use with regular partners[b]			.07	
Never	74 (60.2%)	152 (55.3%)		Ref
Inconsistently	40 (32.5%)	80 (29.1%)		0.86 (0.50–1.48)
Always	9 (7.3%)	43 (15.6%)		0.56 (0.24–1.32)
Casual sex partners, last 3 months			.61	
0	91 (66.9%)	219 (71.6%)		–
1	30 (22.1%)	57 (18.6%)		–
2 or more	15 (11.0%)	30 (9.8%)		–
Condom use with casual partners[c]			.67	
Never	21 (47.7%)	42 (50.6%)		–
Inconsistently	11 (25.0%)	24 (28.9%)		–
Always	12 (27.3%)	17 (20.5%)		–
STI/HIV				
Mean time to seek care, days (SD)	5.8 (3.6)	7.1 (5.3)	.01	0.94 (0.88–1.00)
Ulcer size			.97	
50mm or smaller	92 (67.7%)	209 (67.9%)		–
>50mm	44 (32.3%)	99 (32.1%)		–
Number of ulcers – mean (SD)	2.9 (1.9)	2.5 (2.3)	.09	1.05 (0.95–1.16)
HIV results			<.0001	

Correlate	HSV-2 Ulcers			
	Bivariate Analyses			
	Acute HSV-2 (n=136) n (%)	Recurrent HSV-2 (n=308) n (%)	P value	Adjusted Model (n=389) AOR (95%CI)
HIV-negative	81 (59.6%)	71 (23.1%)		Ref
HIV-positive	55 (40.4%)	237 (77.0%)		0.31 (0.19–0.50)
Detection of acute HIV infection in men testing HIV-negative at baseline[d]			.22	
No	76 (93.8%)	70 (98.6%)		–
Yes	5 (6.2%)	1 (1.4%)		–

SD=standard deviation. Ns are for adjusted analyses. For adjusted analyses, reference group is “recurrent HSV-2”.

[a] includes divorced men who are currently single.

[b] of those who had a regular partner in the past 3 months.

[c] of those who had a casual partner in the past 3 months (n=129).

[d] acute HIV infection – HIV antibody negative test and HIV RNA positive test at baseline or HIV seroconversion (baseline antibody negative, follow-up antibody positive).