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BRIEF REPORT

Correlates of bacterial ulcers and acute HSV-2 infection among men with genital ulcer disease in South Africa: age, recent sexual behaviours, and HIV[i,ii]

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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 ulcers) and acute HSV-2 ulcers (HSV-2 positive ulcer specimen, HSV-2 sero-negative, and negative for bacterial pathogens) versus recurrent HSV-2 ulcers (sero-positive), separately. Men with bacterial ulcers had larger ulcers compared to men with recurrent HSV-2 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; however, this difference was not statistically significant.

Keywords: acute HIV, acute HSV-2, bacterial ulcers, genital ulcer disease, 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 behaviours 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 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 counselling 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 STI prevention efforts.

Thus, we compared demographics and recent sexual behaviours 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 a larger randomised 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 versus recurrent HSV-2 ulcers. The RCT was approved by US Centers for Disease Control and Prevention and University of Witwatersrand ethics review boards. RCT 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, USA) and Capillus (Trinity Biotech PLC, Ireland] were used to screen patients at the clinic; discordant results were further tested in the laboratory using three enzyme-linked immunosorbent assays (Bio-Rad, USA; Abbott Murex, UK; and bioMérieux, France). Blood serum from antibody negative participants, who consented to storage of their specimens 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., USA) and the *Treponema pallidum* particle-agglutination (Fujirebio Inc., Japan) assays and HSV-2 IgG (Kalon Biological, UK).[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 a 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. Men with acute HSV-2, but did not have a bacterial ulcer, were compared to men with recurrent HSV-2 ulcers. Analyses were conducted for each ulcer outcome measures, separately. Correlates examined included demographics, recent sexual behaviours and HIV test results (HIV sero-positivity or acute HIV). In the absence of anti-HIV antibodies at baseline levels, acute HIV was defined by either detection of HIV RNA at the baseline level 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 $p < 0.10$ 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 categorised 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 = 0.02), 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 = 0.01). There were no differences between the groups for other sexual behaviours, 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 ($p < 0.0001$); and, fewer were HIV-positive (24/48; 50.0% vs. 237/308; 77.0%, $p < 0.0001$). There was no difference in the prevalence of acute HIV between the two groups. In adjusted analyses, men with a bacterial ulcers 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 versus recurrent HSV-2 ulcers, in bivariate analyses, men with acute HSV-2 were younger ($p < 0.0001$) (Table 2). Conversely, as compared to men with recurrent HSV-2, there were fewer reports of men with acute HSV-2 that had multiple regular sex partners ($p < 0.01$), but also a lower incidence of consistent condom usage with these partners (p = 0.09), although this difference was not significant. Note, however, the majority (>75%) of men in both groups reported multiple regular sex partners in the past 3 months and consistent condom use was remained 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 = 0.01). Fewer men with acute HSV-2 tested positive for HIV infection (55/136; 40.4% vs. 237/308; 77.0%, $p < 0.0001$). 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 = 0.22). 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 levels (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 emphasise the importance of testing all men with GUD with a rapid and sensitive HIV screening assay 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, 5 January 2015).

Recent sexual behaviours 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 behavioural 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 STI/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

Our findings emphasise 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 diagnoses among HIV-negative young adult men can be sentinel for public health opportunities to engage this high risk group in STI/HIV

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)			0.02	
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			0.04	
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			0.52	
South African	38 (79.2%)	229 (74.8%)		–
Other	10 (20.8%)	77 (25.2%)		–
Recent Sexual Behaviours				
Had multiple regular sex partners, last 3 months			0.36	
No	9 (19.2%)	43 (14.1%)		–
Yes	38 (80.9%)	263 (86.0%)		–
Condom use with regular partners[b]			0.11	
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			0.01	
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]			0.95	
Never	12 (52.2%)	42 (50.6%)		–
Inconsistently	7 (30.4%)	24 (28.9%)		–
Always	4 (17.4%)	17 (20.5%)		–
STI/HI				
Mean time to seek care, days (SD)	8.3 (5.0)	7.1 (5.3)	0.16	–
Ulcer size			<0.0001	
50 mm or smaller	13 (27.1%)	209 (67.9%)		Ref
>50 mm	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)	0.27	–
HIV results			<0.0001	
HIV-negative	24 (50.0%)	71 (23.1%)		Ref
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%)	0.42	–
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).

prevention counselling or education. It is important that men are equipped with the appropriate knowledge and skills to either prevent, or to seek early treatment for, STIs including GUD. Furthermore, given the high levels of risk behaviour we observed, it is also important for prevention messages to be disseminated to all men including those with recurrent HSV-2 infections.

Table 2: Characteristics of men with acute and recurrent HSV-2 ulcers, South African, 2006–07

Correlate	HSV-2 Ulcers			
	Bivariate Analyses			Adjusted Model (*n*=389) AOR (95%CI)
	Acute HSV-2 (*n*=136) *n* (%)	Recurrent HSV-2 (*n*=308) *n* (%)	*P* value	
Demographics				
Age (years)			<0.0001	
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			0.12	
Married	29 (21.3%)	90 (29.2%)		–
Cohabitating	17 (12.5%)	46 (14.9%)		–
Currently single[a]	90 (66.2%)	172 (55.8%)		–
Nativity			0.27	
South African	95 (69.9%)	229 (74.8%)		–
Other	41 (30.2%)	77 (25.2%)		–
Recent Sexual Behaviours				
Had multiple regular sex partners, last 3 months			<0.01	
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]			0.07	
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			0.61	
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]			0.67	
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)	0.01	0.94 (0.88–1.00)
Ulcer size			0.97	
50 mm or smaller	92 (67.7%)	209 (67.9%)		–
>50 mm	44 (32.3%)	99 (32.1%)		–
Number of ulcers – mean (SD)	2.9 (1.9)	2.5 (2.3)	0.09	1.05 (0.95–1.16)
HIV results			<0.0001	
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]			0.22	
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).

Conflict of interest – None

Notes

i. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

ii. A portion of these findings were presented at the 19th meeting of the International Society for Sexually Transmitted Disease Research (12/7/2011 in Québec City, Canada).

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