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Clinician and Patient Recognition of Anogenital Herpes Disease in HIV Positive Men Who Have Sex with Men

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Abstract

Anogenital ulcers caused by HSV-2 are associated with an increased risk of HIV transmission. When compared to clinician examination, HIV/HSV-2 coinfecting men who have sex with men are frequently unaware of anogenital ulcers. These data underscore the importance of condom use and the need for new HSV-2 prevention strategies.

Keywords

Genital herpes; HIV; men who have sex with men

Herpes simplex virus type 2 (HSV-2) infection is one of the most prevalent sexually transmitted diseases (STD)^{1, 2}. HIV-infected men who have sex with men (MSM) are at increased risk for HSV-2 infection compared to the general population, with 27% seroprevalence in HIV-negative MSM³ and 80% seroprevalence in HIV-positive MSM⁴. HSV-2 infection is an important risk factor for the acquisition of HIV^{5, 6}, and the probability of HIV transmission per coital act is increased four-fold in the presence of genital ulcers in the HIV-positive partner⁷. High quantities of HIV RNA are found in most HSV-2 genital ulcers in HIV-infected men, suggesting a mechanism for this finding⁸. HSV-2/HIV co-infected MSM are also more likely to have HSV-2 detected on the genital skin or mucosa (“shedding”) than HSV-2 seropositive, HIV-seronegative MSM⁹, increasing the possibility

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of HSV-2 transmission. The risk of both HSV-2 related genital ulcers and HSV-2 shedding increases as CD4+ T cell counts fall^{9, 10}.

The 2010 Centers for Disease Control STD Treatment Guidelines recommend that persons with genital herpes avoid sexual activity when lesions or prodromal symptoms are present¹¹. In HIV-1 seropositive persons this advice is even more pertinent given the potential to transmit both HIV and HSV-2. To determine the ability of patients to accurately recognize genital herpes recurrences, we compared participant recognition of genital symptoms or lesions with clinician identification of HSV-2 genital ulcers and HSV-2 detection in HIV-1/HSV-2 co-infected MSM with a history of symptomatic genital herpes.

Ten HIV-1 and HSV-2 seropositive MSM were enrolled in a study conducted in Seattle, Washington from June-September 1995. This study was approved by the University of Washington Human-Subjects Review Committee. All participants gave written informed consent. HIV-1 seropositivity was confirmed by commercial enzyme immuno-assay (EIA) and Western blot. Serologic testing for antibodies to HSV-1 and HSV-2 was done by Western blot¹²

At study entry, each participant received genital herpes education, including review of symptoms and techniques for self-examination. Each day, participants used a diary to record the presence or absence of symptoms (itching, redness, skin splits) and lesions (ulcers, sores) in the penile and perianal ("anogenital") region, identified using self-examination¹³ and performed a single swab from the entire genital area. Participants were seen by a clinician daily (Monday through Friday) over an 8 week period to assess for anogenital lesions and to obtain penile and perianal swabs. Additional samples were collected from the buttocks when signs or symptoms of HSV-2 recurrences were present. Swabs were placed in 1ml vials containing 1X PCR buffer and placed at -20°C. HSV DNA was quantitated using liquid hybridization polymerase chain reaction (PCR), with a positive result defined as detection of more than 500 copies HSV DNA per ml of PCR buffer¹⁴.

Herpes lesions were defined as blisters, ulcers, sores or crusts on the penile, perianal, or buttock region as reported by the clinician. HSV swabs were considered positive for a given day if either the participant or clinician collected swab had HSV detected. HSV detection rates in the presence and absence of lesions, and overall, were calculated by determining the number of days with HSV detected over the total number of days with swabs collected, per anatomic site. A generalized estimating equation (GEE) Poisson model with an exchangeable correlation structure and robust covariance estimator for correlated data was used to determine the probability that participants reported symptoms on days when clinicians observed lesions or when HSV was detected. A two-sided P-value <0.05 was considered statistically significant. Data were analyzed using Stata 10.0.

Study Population

Ten HIV-1 and HSV-2 co-infected MSM were enrolled. The median age was 44 years (range 38–57); 9 were Caucasian, one was African-American. All participants were HSV-2 seropositive; 7 were also HSV-1 seropositive. Education level was available for 4 participants; 2 had completed high school and 2 were college graduates. The median time from genital herpes diagnosis to study enrollment was 8.1 years (range 2 to 15 years). At study entry, the median CD4 count was 236 (range 64–541), and the median log₁₀ plasma HIV RNA level/ml was 4.2 (range 3.5–5.0).

Follow up was performed for a median of 55 days per participant (range 35–57 days), for a total of 529 days of observation. Swabs were obtained from the genital, perianal and buttock

region for PCR on 520 (98%) of 529 possible days. Overall, 1069 anogenital swabs were collected.

Participant and Clinician Recognition of Genital Ulcers and HSV shedding

Nine (90%) participants reported penile, perianal or buttock symptoms or lesions during the study. Lesions or symptoms were reported on 158 of 529 days (30%); on the penis on 17 (3%) days, the perianal area on 106 (20%) days and buttocks on 45 (9%) days. Eight (80%) participants had typical herpes ulcers reported by clinicians during the study. Clinicians reported a total of 192 (36%) days with lesions, with penile lesions noted on 22 (4%) days, perianal lesions on 127 (24%) days and buttock lesions on 54 (10%) days (Table 1). Participants had a 51% probability of reporting penile or perianal symptoms on days that a clinician reported an anogenital lesion (probability=0.51, 95% CI=0.28–0.92, $p=0.02$, for the test that agreement=100%). In a sensitivity analysis in which only anogenital ulcers reported in the presence of HSV detection were included, participants had only a 75% probability of noting symptoms in the presence of an ulcer (data not shown).

Eight (80%) participants had HSV detected from the penile, perianal or buttock region during the study period. HSV was detected from the penile or perianal area on 165 (35%) of 520 days and from 222 (21%) of 1069 swabs (Table 2a). Careful examination by a clinician identified genital lesions on 84 (51%) days. Participants reported penile or perianal symptoms or lesions on only 72 (44%) days with HSV detected (Table 2b). Participants were unlikely to report penile or perianal symptoms or lesions on days when HSV was detected at these sites (probability of reporting symptoms=0.34, 95% CI=0.19–0.76, $p=0.006$).

The relationship between anogenital HSV shedding, clinician reported anogenital lesions, and participant reported anogenital symptoms or lesions is shown in Figure 1. Of 165 days with HSV detected, only 67 (41%) were days in which participants had symptoms of a clinical recurrence in the presence of a lesion. On 33 (20%) days with HSV shedding, a lesion was noted by a clinician in the absence of symptoms, and on 57 (34%) days HSV shedding was noted in the absence of lesions and participant symptoms. On 8 (5%) days with HSV shedding, symptoms were reported by the participant, in the absence of clinician reported lesions.

Our objective was to rigorously determine how frequently MSM who have both HIV and HSV-2 infections recognized genital herpes recurrences in the presence of a documented anogenital ulcer. We found that men in our cohort were frequently unaware of the presence of anogenital ulcers, with only a 51% probability of describing symptoms or lesions in the presence of an ulcer. As HIV transmission occurs more frequently in the presence of genital ulcers⁷, and genital ulcers harbor HIV RNA⁸, the inability to recognize lesions may have significant consequences for both HIV and HSV-2 transmission¹¹.

With careful, daily examination, it is possible that genital ulcers were overestimated by the clinician. In systematically training our participants in self-examination and the manifestations of genital herpes, we increased the likelihood that participants would detect signs and symptoms of anogenital herpes recurrences. As most individuals with HSV-2 are unaware of their infection¹⁵, it is likely that the inability to recognize a genital herpes recurrence would be even more profound in the general population. This study was conducted with a PCR assay which used a higher cutoff and thus was less sensitive than our currently used PCR assays¹⁶, suggesting that HSV shedding, both in the presence and absence of a lesion, was underestimated in this study. Due to the intensive nature of this study, we were restricted to a small sample size.

Although this study was performed in the pre-HAART era these data remain relevant for HIV-infected persons today. While some studies have shown that HAART decreases the risk of genital ulcers¹⁷, others have shown no difference in genital ulcer frequency during HAART as compared to pre-HAART¹⁸. In addition, HSV-2 genital ulcers are a leading cause of the immune reconstitution inflammatory syndrome¹⁹.

Our data raise the issue of what therapeutic intervention might be useful for HIV-1-infected MSM with HSV-2 infection. In HSV-2 discordant heterosexual couples without HIV-1 infection, suppressive valacyclovir decreased HSV-2 transmission by only 48%²⁰, and suppressive acyclovir does not prevent heterosexual HIV transmission from an HIV-1/HSV-2 coinfecting partner²¹. While condoms are quite effective for prevention of HIV transmission²², they are only partly effective for HSV-2 transmission²³. More effective strategies for interruption of HSV-2 transmission are needed.

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LC has received consulting fees from AiCuris, which is developing treatments for HSV and cytomegalovirus infections, is listed as a coinventor on several patents describing antigens and epitopes to which T-cell responses to HSV-2 are directed (these proteins have the potential to be used in candidate vaccines against HSV), and has received fees for serving as the head of the scientific advisory board of Immune Design, including equity shares that are less than 1% ownership.

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**Days without any genital symptoms, lesions or HSV detection:
N=286 days (55%)**

Figure 1.

Venn diagram showing interactions between days with **HSV detection, Clinician observed lesions, and Participant signs and symptoms**. Number of days and percentages in each category are shown; the denominator is the total number of days of observation (520 days). Because there are days on which more than one category was present (i.e. HSV detection and clinician lesions), percentages for bolded categories exceed 100%.

Table 1

Days that clinicians reported lesions and participants reported signs or symptoms, by site

Ppt. symptoms	Clinician observed lesion present			Clinician observed lesion absent			Probability of ppt. sx/les on days that clinicians noted lesions (95% CI)	P-value
	Present	Absent	Total	Present	Absent	Total		
Penile	4 (18)	18 (82)	22	13 (3)	494 (97)	507	NC	NC
Perianal	86 (68)	41 (32)	127	20 (5)	382 (95)	402	0.54 (0.31 – 0.96)	0.04
Penile or Perianal	90 (60)	59 (40)	149	31 (8)	349 (92)	380	0.51 (0.28–0.92)	0.02
Buttock	35 (65)	19 (35)	54	10 (2)	465 (98)	475	0.64 (0.34–1.20)	0.16

Ppt=participant, sx/les=symptoms or lesions

Note: All numbers are n (%) unless otherwise indicated

NC = regression model did not converge due to insufficient observations—all 22 genital lesions were observed among one participant

Table 2

a: HSV detection at each anatomical site in the presence and absence of anogenital lesions and overall						
Site	HSV Detection in Presence of Lesion	HSV Detection in Absence of Lesion	Overall Rate of HSV Detection			
Penile	5/43 (12)	38/43 (88)	43/519 (8)			
Perianal	79/152 (52)	73/152 (48)	152/510 (30)			
Penile or perianal	84/165 (51) *	81/165 (49)	165/520 (32) *			
Buttock **	26/27 (96)	1/27 (4)	27/40 (68)			

b: Days on which participants noticed symptoms in the presence and absence of anogenital HSV2 detection						
Ppt. symptoms	Days with HSV Detected		Day with HSV Absent		Probability of ppt. sx/les on days with HSV detected (95% CI)	P-value
	Present	Absent	Present	Absent		
Penile	10 (23)	33 (77)	7 (2)	469 (98)	0.22 (0.08–0.64)	0.005
Perianal	63 (41)	89 (59)	40 (11)	318 (89)	0.31 (0.12–0.81)	0.02
Penile or Perianal	72 (44)	93 (56)	43 (12)	312 (88)	0.38 (0.19 – 0.76)	0.006
Buttock *	23 (85)	4 (15)	9 (69)	4 (31)	0.78 (0.50 – 1.22)	0.28

Note: All numbers represent days with HSV detected/Total days with samples collected (%).

* For all summary variables, days were only included if site of lesion AND site of HSV detection matched

** Buttock swabs collected only in presence of genital ulcers or participant symptoms

Ppt=participant, sx/les=symptoms or lesions

All numbers represent n (%), unless otherwise noted

* Buttock swabs collected only in presence of genital ulcers or participant symptoms