

# EPIDEMIOLOGY OF HERPES SIMPLEX VIRUS TYPES 2 AND 1 AMONGST MEN WHO HAVE SEX WITH MEN ATTENDING SEXUAL HEALTH CLINICS IN ENGLAND AND WALES: IMPLICATIONS FOR HIV PREVENTION AND MANAGEMENT

C Hill (caterina.hill@hpa.org.uk)<sup>1</sup>, E McKinney<sup>1</sup>, C M Lowndes<sup>1</sup>, H Munro<sup>1</sup>, G Murphy<sup>1</sup>, J V Parry<sup>1</sup>, O N Gill<sup>1</sup>, the GUM Anon Network<sup>2</sup>

1. Health Protection Agency, Centre for Infections, HIV and STI Department, London, United Kingdom

2. Members of the network are listed at the end of the article

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The objective was to investigate herpes simplex virus (HSV) epidemiology amongst HIV-positive and HIV-negative men who have sex with men (MSM) in England and Wales. Unlinked anonymous sera from 3,968 MSM attending 12 sexual health clinics in 2003 were tested for HIV, HSV-2 and HSV-1 antibodies. Fifty-five percent of HIV-positive MSM were HSV-2-seropositive, compared to 17% of HIV-negative MSM (Adj RR: 2.14 [CI: 1.92-2.37]). Amongst HIV-positive individuals, there was no significant difference in HSV-2 seroprevalence by knowledge of HIV status or whether the HIV infection was recently acquired (determined through STARHS). HIV infection was also independently associated with HSV-1 serostatus (Adj RR 1.19 [CI: 1.14-1.24]). Four of the twelve attendees who received a diagnosis of recurrent anogenital herpes at the clinic visit were HSV-1-seropositive but not HSV-2-seropositive at the time, although no cultures or PCR results were available to type the cause of the ano-genital presenting disease. It is of concern that one in two HIV-positive MSM and one in six HIV-negative MSM may be infected with HSV-2, given increasing evidence of its impact on HIV progression, onward transmission and acquisition. To date results have been disappointing from trials aimed at reducing HIV onward transmission and HIV acquisition using HSV antiviral medication. However, recent research in an African context demonstrates the efficacy of HSV antivirals in delaying HIV progression. The high prevalence of HSV-2 amongst HIV-positive MSM suggests that an increased focus on HSV control in the management of HIV amongst MSM in the United Kingdom (UK) may be warranted. Given this and existing research on the high prevalence of genitally acquired HSV-1 amongst MSM in the UK, further research is also warranted into the role of HSV-1 in the HIV epidemic in this context.

### Introduction

Genital herpes is caused by infection with herpes simplex types 2 and 1 (HSV-2 and HSV-1). There is increasing evidence from biological and epidemiological studies of the link between HSV-2 and the HIV epidemic. Research has shown that for HIV-positive individuals, frequent asymptomatic HSV-2 reactivations are associated with increased HIV viral load and genital shedding. In addition, HSV-2 suppression using antivirals reduces HIV viral load and genital shedding [1-3]. Whilst trials to date have

failed to find evidence that HSV antivirals can reduce onward HIV transmission [1,2,4], the recent Partners In Prevention (PIP) trial has demonstrated that HSV antivirals can significantly reduce HIV progression according to key indicators amongst HIV-positive HSV-2-positive African men and women [4]. For HIV-negative individuals, HSV-2 infection increases the risk of HIV acquisition more than two-fold [1,3,5,6], although trials to date have failed to show an impact of HSV medication on HIV acquisition [1-3]. The impact of HSV-1 on HIV is less researched, possibly as it causes genital herpes with less severe symptoms and less frequent recurrences [7] and because it is primarily acquired orally early on in childhood in most countries with a high HIV incidence [7,8]. However, 50% of diagnoses of first attacks of ano-genital herpes amongst MSM in the United Kingdom (UK) are now caused by HSV-1 [5,7,9,10].

The prevalence of HSV type 2 and 1 varies widely between and within countries [8,11]. In the UK as elsewhere in Western Europe, there are high rates of sexually transmitted infections (STI) (other than HSV) amongst MSM, particularly HIV-positive MSM [12,13], and there have been increasing diagnoses of anogenital herpes reported by sexual health clinics [9]. However, information on the prevalence of HSV amongst HIV-positive and HIV-negative MSM in the UK is not available: the infection is primarily asymptomatic or unrecognised and serological screening is not routinely performed [3,5]. Furthermore, mandatory reports from STI clinics do not currently include the HIV status of the person diagnosed. Previous prevalence surveys in the UK included small numbers of MSM [14] or combined HIV-positive and HIV-negative MSM [15]. This study was carried out to measure the seroprevalence of HSV amongst HIV-positive and HIV-negative MSM in England and Wales to inform our understanding of the role of HSV in the HIV epidemic amongst MSM in the UK and the potential of HSV interventions to contribute to HIV prevention and management in this context.

### Methods

Samples were drawn from the National Unlinked Anonymous Survey of Genito-Urinary Medicine Clinic Attendees (GUM Anon) [16] serum archive, which includes unlinked anonymous

residual blood specimens collected for routine syphilis serology at representative sentinel sexual health clinics across England and Wales. For each serum limited information was available, including prevention group, prior knowledge of HIV status and diagnoses received at the visit. All specimens were screened for anti-HIV-1/2 antibodies using an immunometric ('third generation') enzyme immunoassay (Murex HIV-1.2.O EIA (GE95), Abbott Diagnostics) [17]; reactive specimens were further examined to establish their true HIV status by a 2nd generation indirect EIA based on oligopeptide antigens (Clonesystems HIV-1/HIV-2 EIA (851403), BioChem ImmunoSystems Inc)[17] and by an in-house IgG class-specific capture assay which distinguishes HIV-1 from HIV-2 infection (GACPAT HIV 1+2) [18]. Specimens whose HIV status was still ambiguous were also examined by Western Blot. Sera from individuals with a previously undiagnosed HIV infection were further examined by the Serological Testing Algorithm for Recent HIV Seroconversion (STARHS) using the 'detuned' Vironostika HIV-1 microelisa test (bioMérieux). The mean time since seroconversion for sera testing positive for recently acquired HIV infection by the detuned test is six months [19].

The study included a randomised age-stratified sample of 3,968 specimens from a total of 8,463 specimens obtained from MSM attending twelve sentinel sexual health clinics (seven in London and five elsewhere across England and Wales) during 2003. All sera were tested for HSV-2 and HSV-1 antibodies using a pair of enzyme immunoassays that distinguish the type-specific antibody response against HSV-2 and HSV-1 [20]. They utilise type-specific murine monoclonal antibodies whose binding to the homologous HSV antigen is blocked when the specimen under test also contains the homologous antibody type. Specimens that inhibit the binding of the monoclonal antibody by  $\geq 50\%$  are considered to be positive for that HSV type-specific antibody. The performance of these assays has been established and validated against independent typing methods [21,22].

Point prevalence estimates of HSV-2 and HSV-1 serostatus were calculated. These were weighted to adjust for age-group stratification. Associations of HSV serostatus with HIV infection and other risk factors were analysed using prevalence risk ratios (RR) at the univariate and multivariate level, through applying

**TABLE 1**

**Seroprevalence of herpes simplex virus type 2 (HSV-2) and prevalence risk ratios amongst men who have sex with men (MSM) attending sentinel sexual health clinics in England and Wales, by selected clinical and demographic characteristics, 2003**

	n	HSV-2 seroprevalence# (95% CI)	Univariate risk ratio (95% CI)	Multivariate risk ratio** (95% CI)
<b>Unlinked anonymous HIV serostatus</b>				
HIV-seronegative	3,363	17% (CI: 15%-18%)	1	1
HIV-seropositive	605	55% (CI: 51%-59%)	3.29 (2.94-3.68)*	2.14 (1.92-2.37)*
<b>World region of birth</b>				
United Kingdom	2,416	18% (CI: 16%-19%)	1	1
Other European country or United States	477	31% (CI: 27%-35%)	1.75 (1.48-2.08)*	1.27 (1.08-1.49)*
Caribbean	31	46% (CI: 28%-64%)	2.59 (1.69-3.95)*	1.94 (1.33-2.84)*
Sub-Saharan Africa	102	17% (CI: 10%-26%)	0.94 (0.59-1.51)	0.79 (0.52-1.21)
Central and South America	115	43% (CI: 34%-53%)	2.44 (1.92-3.11)*	1.93 (1.55-2.39)*
Elsewhere	206	16% (CI: 11%-21%)	0.89 (0.64-1.24)	0.97 (0.74-1.27)
Not recorded	621	34% (CI: 30%-38%)	1.93 (1.67-2.24)*	1.13 (1.00-1.29)
<b>Age-group (in years)</b>				
<25	1,283	7% (CI: 5%-8%)	1	1
25-34	889	18% (CI: 16%-21%)	2.71 (2.12-3.47)*	1.92 (1.560-2.45)*
35-44	895	33% (CI: 30%-36%)	4.98 (3.99-6.23)*	3.24 (2.59-4.07)*
$\geq 45$	901	42% (CI: 40%-46%)	6.41 (5.16-7.96)*	4.55 (3.65-5.68)*
<b>Clinic location</b>				
Outside London	1,304	10% (CI: 9%-12%)	1	1
London	2,664	28% (CI: 26%-30%)	2.75 (2.28-3.31)*	1.71 (1.43-2.05)*
<b>Unlinked anonymous HSV-1 serostatus</b>				
HSV-1-seronegative	1,159	17% (CI: 15%-20%)	1	1
HSV-1-seropositive	2,809	25% (CI: 23%-27%)	1.46 (1.26-1.71)*	1.00 (0.88-1.14)
<b>Diagnosis of acute STI at clinic visit \$</b>				
No	2,620	24% (CI: 22%-26%)	1	1
Yes	1,348	20% (CI: 18%-23%)	0.84 (0.74-0.96)*	1.04 (0.93-1.16)
<b>Total</b>	<b>3,968</b>	<b>23% (CI: 21%-24%)</b>	<b>n/a</b>	<b>n/a</b>

# Weighted to adjust for age-group stratification in the sampling

\*Chi-squared test shows this to be a statistically significant difference at the 95% level

\*\*All risk factors included in multivariate analysis

\$ Acute sexually transmitted infection (STI) defined as presenting at the clinic visit with one of the following: infectious syphilis, gonorrhoea, chlamydia, non-specific urethritis (NSU), trichomoniasis, scabies/pediculosis, human papillomavirus (HPV) first attack or molluscum contagiosum. Excludes ano-genital herpes diagnoses.

a modified Poisson Regression method [23]. Risk ratios were used rather than odds ratios, as the seroprevalence of HSV was high. Among HIV-positive individuals, the association of HSV-2 and HSV-1 serostatus with knowledge of HIV serostatus, recently acquired HIV infection (derived through STARHS) and other characteristics was investigated. HSV-2 and HSV-1 serostatus was also determined for individuals who received diagnoses of clinical first attack and recurrent genital herpes at the visit. All confidence intervals (CI) were calculated at the 95% level. STATA 10 was used for analysis.

The legal and ethical basis for unlinked anonymous HIV testing was established before the programme began and is consistent with the Human Tissue Act 2004 and other guidelines [24]. Approval was received from local ethics committees covering each site where

the GUM Anon survey was underway. Approval for HSV testing was also given by a Multi-Centre Research Ethics Committee (REC: 05/MRE02/4).

## Results

### The study population

Sixteen percent (CI: 15%-17%) of the study population were HIV-positive according to unlinked anonymous HIV antibody testing. Of these 83% (CI: 80%-86%) already knew their status on attending the clinic, 8% (CI: 6%-11%) were diagnosed at the visit and 9% (CI: 6%-11%) remained undiagnosed on leaving the clinic. Overall, 59% (CI: 57%-60%) of the study population were UK-born, 59% were under the age of 35 years, and 70% (CI: 69%-71%) attended a clinic in London. Forty-seven individuals (1%, CI: 1%-2%) received an ano-genital herpes diagnosis at

TABLE 2

### Seroprevalence of herpes simplex virus type 2 (HSV-2) amongst HIV-positive and HIV-negative men who have sex with men (MSM) attending sentinel sexual health clinics in England and Wales, by world region of birth and age-group, 2003

	HIV-positive MSM		HIV-negative MSM	
	n	HSV-2 prevalence# (95% CI)	N	HSV-2 prevalence# (95% CI)
World region of birth				
United Kingdom	257	52% (CI: 45%-58%)	2,159	13% (CI: 12%-15%)
Other European country or United States	104	57% (CI: 47%-66%)	373	23% (CI: 19%-28%)
Caribbean	8	82% (CI: 47%-96%)	23	33% (CI: 16%-56%)
Sub-Saharan Africa	21	28% (CI: 12%-51%)	81	14% (CI: 7%-24%)
Central and South America	23	79% (CI: 56%-92%)	92	33% (CI: 24%-44%)
Elsewhere	23	38% (CI: 20%-59%)	183	13% (CI: 9%-18%)
Not known	160	60% (CI: 52%-68%)	461	25% (CI: 21%-30%)
Age group (in years)				
<25	47	28% (CI: 17%-43%)	1,236	6% (CI: 5%-7%)
25-34	138	39% (CI: 32%-48%)	751	14% (CI: 12%-17%)
35-44	217	65% (CI: 58%-71%)	678	23% (CI: 20%-27%)
>=45	194	70% (CI: 64%-76%)	707	35% (CI: 32%-39%)

# Weighted to adjust for age-group stratification in the sampling

TABLE 3

### Seroprevalence of herpes simplex virus type 2 (HSV-2) amongst men who have sex with men (MSM) attending sentinel sexual health clinics in England and Wales, 2003, by knowledge of HIV status and recently acquired HIV infection

	n	HSV-2 seroprevalence (95% CI)#	Univariate risk ratio (95% CI)	Multivariate risk ratio** (95% CI)
Knowledge of HIV status				
HIV-negative	3,363	17% (CI: 15%-18%)	1	1
Diagnosed HIV-positive at the visit	46	49% (CI: 34%-63%)	2.91 (CI: 2.11-4.02)*	2.57 (CI: 1.92-3.43)*
Remained undiagnosed HIV-positive after visit	46	52% (CI: 37%-66%)	3.12 (CI: 2.31-4.22)*	2.45 (CI: 1.86-3.23)*
Diagnosed HIV-positive before visit	513	56% (CI: 51%-60%)	3.34 (CI: 2.98-3.76)*	2.08 (CI: 1.87-2.32)*
Recently acquired HIV infection (determined through STARHS)^				
HIV-negative	3,363	17% (CI: 15%-18%)		
Recently acquired HIV infection	20	39% (CI: 20%-62%)	2.34 (CI: 1.31-4.18)*	1.95 (CI: 1.16-3.28)*
Non-recently acquired HIV infection	62	53% (CI: 41%-66%)	3.2 (CI: 2.49-4.15)*	2.61 (CI: 2.06-3.32)*

\* Chi-squared test shows this to be a statistically significant difference at the 95% level

\*\* Multivariate analysis is adjusted by world region of birth, age-group, clinic location, HSV-1 serostatus diagnosis with acute STI

^ derived through the Serological Testing Algorithm for Recent HIV Seroconversion (STARHS) which was applied to all 'previously undiagnosed' HIV positive sera. The mean time since seroconversion for those testing positive for recently acquired HIV infection is six months, and diagnosis with acute STI

the visit, including 12 (24% (CI: 13%-39%)) that were recurrent infections. Thirty-four percent of the study population (CI: 33%-36%) received a diagnosis with another 'acute STI' diagnosis at the visit (infectious syphilis, gonorrhoea, chlamydia, non-specific urethritis (NSU), trichomoniasis, scabies/pediculosis, human papilloma virus (HPV) first attack or molluscum contagiosum). Of the 92 sera with a previously undiagnosed HIV infection 82 had STARHS results available. Of these, 23% (CI: 15%-33%) were classified as a 'recent' infection.

#### HSV-2 seroprevalence amongst HIV-positive and HIV-negative MSM

Of HIV-positive men, 55% (CI: 51%-59%) were HSV-2-seropositive, compared to 17% (CI: 15%-18%) of HIV-negative men. The unadjusted risk ratio for HSV-2 infection was 3.29 (CI: 2.94-3.68,  $p < 0.001$ ), over three-fold higher amongst HIV-positive men than HIV-negative men, and this association remained highly significant in multivariate analysis (RR=2.14 [CI: 1.92-2.37],  $p < 0.001$ ) (Table 1).

HSV-2 seroprevalence was higher amongst men born outside the UK (28% [CI: 25%-31%], vs 18% [CI: 16%-19%]), even after adjusting for HIV status and other cofactors (adj RR 1.25 [CI: 1.09-1.42]). The prevalence of HSV-2 was particularly high amongst those born in the Caribbean and in Central and South America. There was no statistical difference in HSV-2 seroprevalence between men born in sub-Saharan Africa and those born in the UK, even after adjusting for other variables,  $p = 0.285$ ). HSV-2 seroprevalence increased with age-group (Table 1). These trends were similar for HIV-positive and HIV-negative MSM (Table 2).

Amongst HIV-positive men, there was no statistical evidence for a difference in HSV-2 seroprevalence between those diagnosed with HIV prior to the sexual health clinic attendance, those diagnosed at the visit and those that remained undiagnosed. Prevalence in each of these sub-groups of HIV-positive men was more than two-fold higher than the 17% prevalence (CI: 15%-18%) found amongst HIV-negative men (Table 3).

TABLE 4

#### Seroprevalence of herpes simplex virus type 1 (HSV-1) and prevalence risk ratios amongst men who have sex with men (MSM) attending sentinel sexual health clinics in England and Wales, by selected clinical and demographic characteristics, 2003

	n	Seroprevalence (95% CI) #	Univariate risk ratio (95% CI)	Multivariate risk ratio** (95% CI)
Unlinked anonymous HIV serostatus				
HIV-seronegative	3372	69% (67%-71%)	1	1
HIV-seropositive	596	88% (85%-90%)	1.27 (1.22-1.33)*	1.19 (1.14-1.24)*
World region of birth				
United Kingdom	2,416	68% (66%-70%)	1	1
Other European country or United States	477	77% (73%-81%)	1.14 (1.08-1.21)*	1.09 (1.03-1.16)*
Caribbean	31	81% (61%-92%)	1.21 (1.01-1.44)*	1.22 (1.03-1.45)*
Sub-Saharan Africa	102	79% (70%-89%)	1.20 (1.09-1.33)*	1.19 (1.07-1.32)*
Central and South America	115	89% (81%-93%)	1.33 (1.24-1.43)*	1.30 (1.20-1.41)*
Elsewhere	206	71% (64%-77%)	1.03 (0.94-1.14)	1.03 (0.93-1.13)
Not recorded	621	79% (75%-82%)	1.17 (1.11-1.23)*	1.05 (1.00-1.11)
Age-group (in years)				
<25	1283	56% (53%-59%)	1	1
25-34	889	74% (71%-77%)	1.32 (1.24-1.40)*	1.25 (1.18-1.34)*
35-44	895	81% (78%-83%)	1.44 (1.36-1.52)*	1.37 (1.29-1.46)*
>=45	901	78% (75%-81%)	1.39 (1.31-1.48)*	1.35 (1.27-1.44)*
Clinic location				
Outside London	1304	66% (63%-69%)		
London	2664	75% (73%-76%)	1.13 (1.08-1.19)	0.99 (0.94-1.04)
Unlinked anonymous HSV-2 serostatus				
No	3,034	70% (68%-72%)	1	1
Yes	934	79% (76%-82%)	1.13 (1.08-1.17)*	0.98 (0.94-1.03)*
Diagnosis of STI at clinic visit §				
No	2620	71% (69%-73%)	1	1
Yes	1348	74% (71%-76%)	1.04 (0.99-1.08)	1.06 (1.02-1.11)*
<b>Total</b>	<b>3,968</b>	<b>72% (70%-74%)</b>	<b>n/a</b>	<b>n/a</b>

# Weighted to adjust for age-group stratification in the sampling

\*Chi-squared test shows this to be a statistically significant difference at the 95% level

\*\*All risk factors included in multivariate analysis

§ Acute STI defined as presenting at the clinic visit with one of the following diagnoses: infectious syphilis, gonorrhoea, chlamydia, non-specific urethritis (NSU), trichomoniasis, scabies/pediculosis and human papillomavirus (HPV) first attack or molluscum contagiosum. Excludes ano-genital herpes diagnoses.

Similarly, there was also no statistical evidence for a difference in HSV-2 seroprevalence between MSM with recently acquired HIV infection and those with 'non-recent' HIV infection (p-value=0.269). Both groups had a higher seroprevalence of HSV-2 than HIV-negative men.

### HSV-1 seroprevalence

Overall, seven in 10 men were HSV-1 seropositive. As with HSV-2, HSV-1 seroprevalence was higher amongst HIV-positive men (88% [CI: 85%-90%]) than HIV-negative men (69% [CI: 67%-71%]), although the risk ratio was smaller than for HSV-2 (Adj RR: 1.19 [CI: 1.14-1.24]) (Table 4). As with HSV-2, the seroprevalence of HSV-1 increased with age, although it was much higher in the youngest age-group than the seroprevalence of HSV-2 (56% [CI: 53%-59%]) vs 7% [CI: 5%-8%]).

There were 47 (1%, CI: 1%-2%) episodes of ano-genital herpes diagnosed clinically among the 3,968 attendees. Of the 35 diagnoses of first attack ano-genital herpes, 15 (43%) were HSV-1 seropositive and HSV-2 seronegative at the time of clinical diagnosis. The same was true for four (33%) of the 12 diagnoses with recurrent ano-genital herpes (Figure).

### Discussion

To our knowledge this is the first published study of the seroprevalence of HSV-2 and HSV-1 amongst MSM in the UK where it has been possible to differentiate between HIV-positive and HIV-negative MSM. More than one in two HIV-positive MSM and nearly one in six HIV-negative MSM attending sexual health clinics in 2003 were HSV-2-seropositive. This is of concern, given

the increasing evidence for the role of HSV-2 in HIV progression, onward transmission and acquisition [1-3]. The prevalence rates may be an underestimate of current rates amongst MSM attending sexual health clinics, as the annual number of ano-genital herpes diagnoses in sexual health clinics and the prevalence of HIV and other STI have increased since 2003 [9]. It should be borne in mind that in general prevalence rates of STI amongst MSM attending sexual health services are likely to be higher than amongst other MSM.

The prevalence of HSV-2 in this study is similar or lower than those found amongst HIV-positive and HIV-negative MSM in studies elsewhere in Europe, the Americas and Australia [8]. This is consistent with the global epidemiology: whilst there is considerable variation in HSV-2 prevalence worldwide, in general, HSV-2 prevalence is lower in Europe than in Africa and the Americas [8,11]. In our study, the prevalence of HSV-2 amongst MSM born in sub-Saharan Africa was not different to that amongst UK-born MSM, even after adjusting for age and other factors. Additional information such as ethnicity and sexual behaviour would be needed to understand how MSM born in sub-Saharan Africa attending sexual health clinics in England and Wales differ from the overall population in their region of birth. As would be expected, the prevalence of HSV-2 increased with age [8,15]. Whether or not the men knew their HIV status and whether or not they had been recently infected with HIV made little difference to the prevalence of HSV-2 amongst HIV-positive MSM. It was not possible with this study design to identify whether the HSV-2 infection took place before, after or concurrently with the HIV infection.

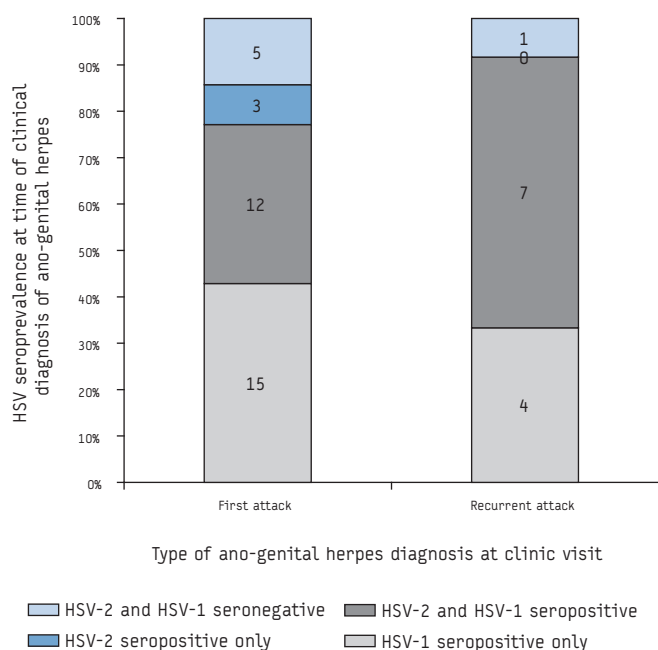
This study also showed that seven in 10 MSM were HSV-1-positive, a rate similar to that found in other high-risk groups in Europe [8]. As with HSV-2, the prevalence was disproportionately high amongst HIV-positive MSM and this association remained significant at the multivariate level. In our study, almost one in two men diagnosed clinically with a first attack of ano-genital herpes and one in three men diagnosed with a recurrent attack of ano-genital herpes had only HSV-1 antibodies at the time of the clinical diagnosis. Unfortunately, no culture or PCR result was available from the genital ulcers to determine the type causing the presenting ano-genital disease. Most of those diagnosed with a first attack of ano-genital herpes who were HSV-1 seropositive only may have been infected with HSV-2 as well but had not yet seroconverted. However, the high proportion of those with a clinical diagnosis of a recurrent attack who were HSV-1 seropositive only is in line with existing data showing that HSV-1 is increasingly acquired genitally in many developed countries. HSV-1 now accounts for approximately half of first episodes of ano-genital herpes amongst MSM in the UK [5,7]. Given this and the association between HSV-1 serostatus and HIV, more research is merited on the role of HSV-1 in the HIV epidemic among MSM in England and Wales.

### Implications for HIV prevention and management

Despite several trials demonstrating that HSV antivirals can reduce HIV viral load and viral shedding [25,27], no trials to date have demonstrated the efficacy of HSV antivirals in reducing HIV onward transmission [1,2,4]. Similarly, despite trials showing that HSV-2-seropositive individuals are more than twice as likely to acquire HIV, no trials have demonstrated that antivirals can reduce HIV acquisition [1-3]. Research is ongoing as to whether different antivirals, or an HSV vaccine or other interventions, may yet prove to be successful at using HSV control for HIV prevention (2).

### FIGURE

**Herpes simplex virus type 2 and 1 (HSV-2 and HSV-1) serostatus of patients at time of receiving clinical diagnosis of ano-genital herpes, men who have sex with men (MSM) attending sentinel sexual health clinics in England and Wales, 2003 (n=47)**



Note: No data from culture or PCR from the genital area was available



Results have been more promising in terms of HSV control in the context of HIV management. The recent Partners in Prevention trial showed that HSV antivirals significantly slowed the rate of HIV progression to a CD4 cells count <200 mm<sup>3</sup>, need for antiviral treatment and death amongst dually infected African men and women [4]. This is supported by pre-HAART trials showing that HSV antivirals offered a significant survival benefit for HIV-positive individuals [28]. Currently, clinics in England and Wales do not routinely carry out asymptomatic serological screening for HSV amongst HIV-positive MSM, although they do administer antivirals to symptomatic herpes patients [1]. While the UK context is very different to many African countries, these recent PIP trial results together with the high prevalence of HSV-2 amongst HIV-positive MSM in England and Wales suggest a review of HSV control in the management of HIV amongst MSM is warranted.

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### References

- Barton S, Celum C, Shacker TW. The role of anti-HSV therapeutics in the HIV-infected host and in controlling the HIV epidemic. *Herpes*. 2005;12(1):15-22.
- Padian NS, Buve A, Balkus J, Serwadda D, Cates W Jr. Biomedical interventions to prevent HIV infection: evidence, challenges, and way forward. *Lancet*. 2008;372(9638):585-99.
- Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004;35(5):435-45.
- Lingappa JR, Baeten JM, Wald A, et al. Daily acyclovir delays HIV-1 disease progression among HIV-1/HSV-2 dually-infected persons: a randomized trial. 5th IAS conference on HIV pathogenesis, treatment and prevention (IAS 2009), 19 July 2009.
- Gupta R, Warren T, Wald A. Genital herpes. *Lancet*. 2007;370(9605):2127-37.
- Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *AIDS*. 2006;20(1):73-83.
- Engelberg R, Carrell D, Krantz E, Corey L, Wald A. Natural history of genital herpes simplex virus type 1 infection. *Sex Transm Dis*. 2003;30(2):174-7.
- Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. *J Infect Dis*. 2002;186 Suppl 1:S3-28.
- Health Protection Agency (HPA). Annual STI data. London: HPA. [Accessed 24 Nov 2009]. Available from: [http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb\\_C/1203348026613](http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203348026613)
- Health Protection Agency (HPA). The UK Collaborative Group for HIV and STI Surveillance. Testing Times. HIV and other Sexually Transmitted Infections in the United Kingdom: 2007. London: HPA. Centre for Infections. 2007. Available from: [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1203496897276](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1203496897276)
- Malkin JE. Epidemiology of genital herpes simplex virus infection in developed countries. *Herpes*. 2004;11 Suppl 1:2A-23A.
- Health Protection Agency (HPA). Sexually Transmitted Infections and Men who have Sex with Men in the UK: 2008 Report. London: HPA. 2008. Available from: [http://www.hpa.org.uk/web/HPAwebFile/HPAweb\\_C/1227515298225](http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1227515298225)
- Dougan S, Evans BG, Elford J. Sexually transmitted infections in Western Europe among HIV-positive men who have sex with men. *Sex Transm Dis*. 2007;34(10):783-90.
- Narouz N, Allan PS, Wade AH, Wagstaffe S. Genital herpes serotyping: a study of the epidemiology and patients' knowledge and attitude among STD clinic attenders in Coventry, UK. *Sex Transm Infect*. 2003;79(1):35-41.
- Cowan FM, Johnson AM, Ashley R, Corey L, Mindel A. Antibody to herpes simplex virus type 2 as serological marker of sexual lifestyle in populations. *BMJ*. 1994;309(6965):1325-9.
- Nicoll A, Gill ON, Peckham CS, Ades AE, Parry J, Mortimer P, et al. The public health applications of unlinked anonymous seroprevalence monitoring for HIV in the United Kingdom. *Int J Epidemiol*. 2000;29(1):1-10.
- Perry KR, Ramskill S, Eglin RP, Barbara JA, Parry JV. Improvement in the performance of HIV screening kits. *Transfus Med*. 2008;18(4):228-40.
- Parry JV, Connell JA, Reinbott P, Garcia AB, Avillez F, Mortimer PP. GACPAT HIV 1 + 2: a simple, inexpensive assay to screen for, and discriminate between, anti-HIV 1 and anti-HIV 2. *J Med Virol*. 1995;45(1):10-6.
- Murphy G, Charlett A, Jordan LF, Osner N, Gill ON, Parry JV. HIV incidence appears constant in men who have sex with men despite widespread use of effective antiretroviral therapy. *AIDS*. 2004;18(2):265-72.
- Slomka MJ, Ashley RL, Cowan FM, Cross A, Brown DW. Monoclonal antibody blocking tests for the detection of HSV-1- and HSV-2-specific humoral responses: comparison with western blot assay. *J Virol Methods*. 1995;55(1):27-35.
- Van Dyck E, Buve A, Weiss HA, Glynn JR, Brown DW, Deken B, et al. Performance of Commercially Available Enzyme Immunoassays for Detection of Antibodies against Herpes Simplex Virus Type 2 in African Populations. *J Clin Microbiol*. 2004;42(7):2961-5.
- Gopal R, Gibbs T, Slomka MJ, Whitworth J, Carpenter LM, Vyse A, et al. A monoclonal blocking EIA for herpes simplex virus type 2 antibody: validation for seroepidemiological studies in Africa. *J Virol Methods*. 2000;87(1-2):71-80.
- Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-6.
- Medical Research Council (MRC). Human tissue and biological samples for use in research: Operational and ethical guidelines. London: MRC. 2001. Available from: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002420>
- Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss HA, Vergne L, et al. Reduction of HIV-1 RNA levels with therapy to suppress herpes simplex virus. *N Engl J Med*. 2007;356(8):790-9.
- Zuckerman RA, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, Zuniga R, et al. Herpes simplex virus (HSV) suppression with valacyclovir reduces rectal and blood plasma HIV-1 levels in HIV-1/HSV-2-seropositive men: a randomized, double-blind, placebo-controlled crossover trial. *J Infect Dis*. 2007;196(10):1500-8.
- Delany S, Mlaba N, Clayton T, Akpomiemie G, Capovilla A, Legoff J, et al. Impact of aciclovir on genital and plasma HIV-1 RNA in HSV-2/HIV-1 co-infected women: a randomized placebo-controlled trial in South Africa. *AIDS*. 2009;23(4):461-9.
- Ioannidis JP, Collier AC, Cooper DA, Corey L, Fiddian AP, Gazzard BG, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis*. 1998;178(2):349-59.