Eur J Epidemiol (2007) 22:937–944
DOI 10.1007/s10654-007-9178-2

INFECTIOUS DISEASES

Rise in seroprevalence of herpes simplex virus type 1 among highly sexual active homosexual men and an increasing association between herpes simplex virus type 2 and HIV over time (1984–2003)

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Received: 18 January 2007 / Accepted: 23 August 2007 / Published online: 10 October 2007

Abstract *Objectives* Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) are both highly prevalent. The rate of genital HSV-1 transmission is reportedly increasing over time. HSV-2 is considered to be an important risk factor for HIV transmission. We therefore studied changes in the HSV-1 and HSV-2 prevalence in a large cohort of men who have sex with men (MSM) over a 20-year time period. *Methods* Among 1847 HIV-infected and HIV-uninfected MSM participating in the Amsterdam Cohort Studies, seroprevalence of HSV-1 and HSV-2 was determined and prevalence rate ratios (PRR) and 95% confidence intervals were calculated. *Results* Between 1984 and 2003 the HSV-1 and HSV-2 prevalence decreased among HIV-uninfected MSM ($P < 0.001$), but remained stable among HIV-infected MSM. HSV-1 prevalence increased among men with at least 200 sexual partners over lifetime (PRR: 1.49, $P < 0.001$). The association between HIV infection and HSV-2 became stronger over time (PRR: 3.45, $P < 0.001$). *Conclusions* Seroprevalence of HSV-1 and HSV-2 remained high among HIV infected MSM from 1984 to 2003. The association of HIV and HSV-2 increased during the HIV epidemic. Since the proportion of sexual transmission of HSV-1 is rising, it is important to study the potential role of HSV-1 as risk factor for HIV acquisition.

Keywords HSV-1 · HSV-2 · HIV · MSM · Prevalence

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Introduction

Herpes simplex virus type 1 (HSV-1) is widespread in the general population, while herpes simplex virus type 2 (HSV-2) is more restricted to risk groups such as men who have sex with men (MSM). HSV-1 prevalence is around 70% in the general population [1, 2]. Transmission usually occurs during childhood through oral contact and normally causes oropharyngeal infection. Childhood HSV-1 transmission has declined in industrialised countries, resulting in a lower prevalence of HSV-1 and leaving a larger population of adolescents at risk for sexual transmission of HSV-1. Earlier studies have reported sexually related risk factors for HSV-1 infection in women [3]. Among those persons attending the STD clinic and blood donors, HSV-1 infection is associated with younger age of first intercourse [4]. However, less is known about sexually related risk

factors for HSV-1 infection among MSM [5]. HSV-2 infection is usually transmitted sexually and is considered as a marker for sexual risk behaviour in populations [6]. In HIV-infected MSM, the prevalence of HSV-2 is as high as 61% [1], while being 15–25% in the general population [7, 8]. HSV-2 is a risk factor for HIV acquisition, especially in the African setting [9] and in MSM [10]. HSV-2 infected persons are more susceptible for HIV [11, 12]. Moreover, HIV-infected persons are more likely to have subclinical reactivation of HSV-2 and are therefore more likely to transmit the virus [13].

We previously demonstrated a decline in the prevalence of HSV-2 among MSM in Amsterdam between 1984–1997, which could be explained by a decrease in sexual risk behaviour [5]. However, in the second half of the 1990s their sexual risk behaviour increased after effective HIV therapy became generally available. This may have caused an increase in the prevalence of HSV-2 and possibly also in HSV-1 since 1996.

We here studied the trend in HSV-1 and HSV-2 prevalence among homosexual men over a 20-year time period (1984–2003) and whether risk factors for infection changed during this period.

Methods

Study population

In 1984 an open and prospective cohort study on HIV seroconversion and AIDS among sexually active HIV-negative and positive homosexual men was started. The Amsterdam Cohort Study (ACS) is still ongoing, although entry criteria with respect to HIV status and age have changed over time. From 1984 until May 1985, both HIV-positive and HIV-negative men were included. From May 1985 until February 1988, only HIV-negative men were allowed in the study. From February 1988 through 1994, HIV-positive and HIV-negative men could enter the study, but since 1995, they must be ≤30 year of age.

At an ACS visit, a standardised questionnaire is administered regarding demographics, sexual behaviour, and medical history for sexually transmitted infections (STI). Blood samples are collected for immunologic and virologic testing and for storage. For this study, stored sera (collected at the first cohort visit) taken from ACS participants with at least two cohort visits (1847/2100 (88%)) were tested for HSV-1 and HSV-2.

Laboratory methods

Sensitive and specific FDA approved serological assay for HSV-1&2 was used (HerpeSelect by FOCUS technologies, USA). Its manufacturer recommends an index value > 1.1 as positive. However, there is evidence that using this cut-off value in HSV-2 studies yields a high rate of false positive results in populations with multiple infections, such as those in Africa [14]. Raising the positive cut-off will increase the specificity [14]. Since the optimal cut-off for our target population has not been established, 100 samples with results in the range of 0.9 and 3.5 were re-tested with a highly specific Western blot. HSV-2 ELISA and Western blot results were concordant for 80/100 samples. The proportion of samples that were positive with both ELISA and Western blot increased with increasing index value (Fig. 1). Based on these results, we consider a cut-off value of ≥2.1 as being positive and an index value <2.1 is classified as negative. The HSV-2 index value <2.1 had 36% concordance with Western blot results, while the HSV-2 index value of ≥2.1 showed 93% concordance. There were no differences in Western blot outcomes between HIV-infected and HIV uninfected MSM.

Blood samples were tested for HSV-1 and HSV-2 at the Public Health Laboratory of the Health Service of Amsterdam. The Western blot was conducted at the Institute for Pathology and Medical Research (ICPMR) in Sydney, Australia. Blood samples are also tested for HIV antibodies by enzyme linked immunosorbent assay (ELISA) (Abbot Laboratories, North Chicago, Illinois, USA; Vironostika, Organon, Teknika, Boxtel, the Netherlands), and when positive, are confirmed by Western blot.

Variables and statistical analyses

The statistical analyses were based on the data collected at entry of the cohort. Variables used in this study were calendar year of ACS entry, HIV-status, age, nationality, education, age of first homosexual contact, lifetime sexual

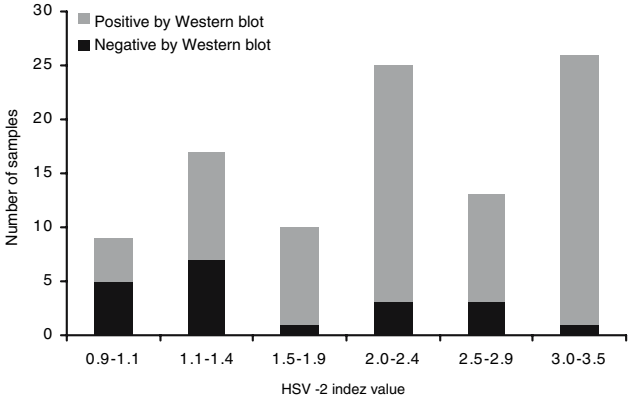

Fig. 1 Comparison of HSV-2 serology by ELISA and Western blot. 100 samples were tested with HSV-2 ELISA and re-tested with the Western blot to identify discrepancies between the two assays

partners, and self-reported history of syphilis and gonorrhoea in the past 5 years.

Variables concerning sexual practices included orogenital, anogenital and oroanal contact in the prior 6 months. Some changes in the questions were made in the questionnaires between 1984 and 2003 regarding the sexual practices. Oro-anal contact was not asked for from 1889 to 1994, resulting in approximately 25% missing values on this variable. From 1995 onward, the most important difference was that orogenital contact with ejaculation was asked, while in the previous years orogenital contact in general was asked. The percentage of participants not having orogenital contact was somewhat higher for the years 1995 and 1996.

The prevalence of HSV-1 and 2 at the ACS entry was determined and risk factors for HSV-1 and 2 were assessed by calculating prevalence rate ratios (PRR), with their 95% confidence interval (CI). Odds ratios could not be interpret as relative risks, since the rare event assumption was not reached. Therefore PRR's were directly estimated, using a modified Poisson regression approach [15]. This approach provided a correctly estimated standard error for the estimated relative risk. Since inclusion criteria with respect to age and HIV-status changed over time, all risk factor analyses were adjusted for age and HIV-status. Variables that were statistically significant were included in the multivariate model, using a stepwise forward approach forcing age and HIV-status in the model.

We tested whether risk factors changed over time by testing for interaction between variables under investigation and calendar time in the multivariate model. Calendar time therefore was categorised as 1984–1986, 1987–1991, 1992–1996, 1997–2003.

Confounding was defined to be present when the included variable caused a change of the prevalence ratio by more than 10%. Interaction was defined to be present when the addition of an interaction term improved the original model and the *P*-value was <10%. Statistical significance was defined as a *P*-value <0.05. To reduce residual confounding when measuring the association between HSV and sexual practices, three variables measuring sexual practices over the prior 6 months were included in the model at the same time, together with the lifetime sexual partners. We modelled time trends in the HSV-1 and 2 prevalence with calendar time as a continuous variable using restricted cubic splines with four knots, resulting in a smoothly varying curve.

For 77 MSM the HSV-1 index value was missing and 91 MSM had a missing HSV-2 index value. Participants with a missing index value for both HSV-infections were not included in the analyses. MSM with a missing index value for one HSV-infection, but with a known HSV status of the other HSV-infection were included in the analyses for the known HSV serostatus.

Finally, sensitivity analyses for HSV-2 were conducted by using the cut-off value of 1.1, as recommended by the manufacturer and by using the cut-off value of 3.5, excluding those with an index value in the grey area (between 0.9–1.1 and 0.9–3.5). However, time trends in prevalence and risk factors found were comparable to when 2.1 was the cut-off value (data not shown).

Results

General characteristics

Between 1984 and 2003, a total of 1847 MSM had at least two visits. General characteristics of the total study group are presented in Table 1. Of the 1847, 1207(65%) MSM were HSV-1 antibody positive, while 759/1847(41%) of the men were HSV-2 antibody positive. Of the total group, 558(30%) were positive for both. Participants were predominantly of Dutch nationality (86%) and had a median age of 29 years (interquartile range: 25–36).

Prevalence of HSV-1 and HSV-2 over time

There was an overall decline in the prevalence of both HSV-1 and 2 between 1984 and 2003 (Tables 1, 2). To investigate time trends in HSV seroprevalence we included an interaction term between time and HIV-status (Fig. 2a, b). Among HIV-negative MSM, the HSV-1 prevalence decreased significantly over time, $P < 0.001$ (Fig. 2a). Among HIV-positive MSM, the HSV-1 prevalence remained stable over time, $P = 0.35$(Fig. 2a).

The HSV-2 prevalence significantly decreased among HIV-negative men, $P < 0.001$(Fig. 2b). Results from the regression models showed that, after adjustment for changes in age, nationality, education and changes in sexual risk behaviour, the decline in HSV-2 prevalence among HIV negative MSM remained significant (PRR adjusted 0.92, $P < 0.001$). In contrast, the HSV-2 prevalence remained stable over time for men infected with HIV ($P = 0.12$). Again, this result was observed after controlling for age, demographic characteristics and sexual behaviour.

Risk factors

Risk factors for HSV-1 and HSV-2 infection, adjusted for age and HIV-status, are presented in Table 1.

In the final model calendar year, HIV-status, nationality, and number of lifetime sexual partners remained independent predictors for HSV-1 infection (Table 2). For HSV-2 infection, earlier year of study entry, positive HIV-status, HSV-1 co-infection, a history of syphilis and sexual behaviour remained independent predictors (Table 2).

Table 1 Demographic and sexual characteristics of 1847 homosexual men, for the total study group, and for HSV-1-infected participants and HSV-2-infected participants separately, between 1984 and 2003, with the prevalence ratios for HSV-1 and HSV-2 with their 95% confidence intervals[a]

Characteristics	Total	HSV-1-infection	PRR (95% CI)	Overall *P*-value	HSV-2-infection	PRR (95% CI)	Overall *P*-value
Total	1847	1207 (65)			759 (41)		
Year of study entry				<0.0001			<0.0001
1984–1986	943	675 (72)	1		461 (49)	1	
1987–1991	165	113 (68)	0.87 (0.78–0.97)		92 (56)	0.84 (0.72–0.98)	
1992–1996	222	138 (43)	0.88 (0.79–0.96)		80 (36)	0.66 (0.56–0.77)	
>1997	517	281 (54)	0.76 (0.70–0.84)		126 (24)	0.47 (0.40–0.55)	
Index value							
<0.9	–	535			853		
0.9–1.1	–	29			32		
1.1–2.1	–	100			112		
≥2.1	–	1107			759		
Missing		77			91		
Age				<0.0001			<0.0001
<30 years	1002	570	1		252	1	
≥30 years	845	637	1.20 (1.13–1.29)		507	1.98 (1.75–2.23)	
Nationality:				0.006			0.62
Dutch	1586	947 (60)	1		615 (39)	1	
Northern/central Europe	116	72 (62)	1.04 (0.92–1.18)		54 (47)	1.08 (0.90–1.38)	
Non-European	145	117 (81)	1.17(1.07–1.28)		75 (52)	1.04 (0.91–1.23)	
Education				0.005			0.007
Low	96	77 (80)	1		57 (59)	1	
Middle	669	408 (61)	0.85 (0.76–0.95)		239 (36)	0.72 (0.59–0.87)	
High	971	574 (59)	0.81 (0.73–0.81)		387 (40)	0.79 (0.66–0.94)	
Missing	115	77 (67)			54 (47)		
Sexual partners in lifetime							
1–20	860	497 (58)	1	<0.0001	277 (32)	1	0.51
21–200	531	360 (68)	1.12 (1.04–1.22)		212 (40)	2.30 (0.93–1.21)	
>200	443	339 (77)	1.24 (1.15–1.34)		262 (59)	1.07 (0.95–1.20)	
Age of first homosexual contact (median, IQR)	18 (15–20)	17 (15–20)	1.01(1.01–1.02)^	<0.0001	17 (15–20)	0.99 (0.99–1.01)[c]	0.32
HSV co-infection	568	568	1.29 (1.14–1.47)	<0.0001	568	1.167 (1.08–1.24)	<0.0001
HIV infection (%)	513	367 (72)	1.11 (1.03–1.18)	0.007	312 (61)	1.12 (1.00–1.24)	0.05
History of gonorrhoea in the past 5 years	1053	666 (63)	0.88 (0.83–0.93)	0.0005	424 (40)	0.88 (0.79–0.97)	0.02
History of syphilis in the past 5 years	278	219 (79)	1.15 (1.07–1.24)	0.001	197 (71)	1.51 (1.36–1.69)	<0.0001
Orogenital contact in the past 6 months[b]	1363	892 (65)	0.99 (0.82–1.22)	0.46	565 (41)	0.69 (0.55–0.87)	0.01
Anogenital contact in the past 6 months[b]	1222	819 (67)	1.11 (1.14–1.60)	0.002	551 (45)	1.36 (1.16–1.60)	0.0002
Oroanal in the past 6 months[b]	1081	700 (65)	1.00 (0.91–1.09)	0.99	438 (41)	0.98 (0.85–1.12)	0.80

[a] Since ACS inclusion criteria have changed over times all analyses were adjusted for age (per 10-year increase) and HIV status at cohort entry

[b] Analyses are also adjusted for the sexual techniques and number of partners to exclude residual confounding

[c] Per 10 year of increase

Changing risk factors over time

Different interaction terms were included in the model. It appeared that the effect of calendar year differed between HIV-infected and HIV-uninfected MSM for both HSV-1 and HSV-2.

As shown in Fig. 2a, the association between HIV and HSV-1 became stronger over time. This was due to the

Table 2 Multivariate model of risk factors associated with HSV-1 infection

	HSV-1	Overall *P*-value
(a) HSV-1 infection		
Year of study entry		<0.0001
1984–1986	1	
1987–1991	0.91 (0.70–1.18)	
1992–1996	0.83 (0.66–1.02)	
>1997	0.75 (0.63–0.90)	
Age	1.13(1.07–1.18)	<0.0001
HIV serostatus		
Negative	1	0.01
Positive	1.10 (1.02–1.18)	
Nationality		
Dutch	1	0.0006
Northern or Central European	1.05 (0.92–1.20)	
Non European	1.62 (1.12–1.36)	
Education		0.25
Low	1	
Middle	0.90 (0.79–1.00)	
High	0.84 (0.76–1.06)	
Sexual partners in lifetime		
1–20	1	0.003
21–200	1.13 (1.05–1.25)	
>200	1.13 (1.04–1.23)	
History of Gonorrhoea in the past 5 years	0.97 (0.90–1.03)	0.11
History of Syphilis in the past 5 years		
Orogenital contact in the past 6 months	1.12 (0.88–1.43)	0.42
Anogenital contact in the past 6 months	1.08 (0.97–1.20)	0.20
Oroanal contact in the past 6 months	1.02 (0.70–1.13)	0.81
	HSV-2	Overall *P*-value
(b) HSV-2 infection		
Year of study entry		<0.0001
1984–1986	1	
1987–1991	0.86 (0.70–1.06)	
1992–1996	0.58 (0.48–0.71)	
>1997	0.47 (0.39–0.56)	
HIV serostatus		
Negative	1	<0.0001
Positive	1.50 (1.37–1.68)	
HSV coinfection	1.15 (1.02–1.30)	0.02
History of Syphilis in the past 5 years	1.21 (1.08–1.36)	0.001
Orogenital contact in the past 6 months	0.69 (0.56–0.84)	<0.0001
Anogenital contact in the past 6 months	1.20(1.08–1.42)	0.02
Oroanal contact in the past 6 months	1.00(0.87–1.15)	0.72

decline in HSV-1 prevalence over time among HIV-negative MSM but not among HIV-positive MSM (Fig. 2a).

For HSV-2 the association with HIV infection increased with calendar year and was highest after 1996 (Fig. 2b).

For HSV-1, also the effect of calendar time differed with respect to nationality, number of lifetime sexual partners, and with HSV-2 co-infection. As shown by the regression model, a decrease in HSV-1 infection over time was

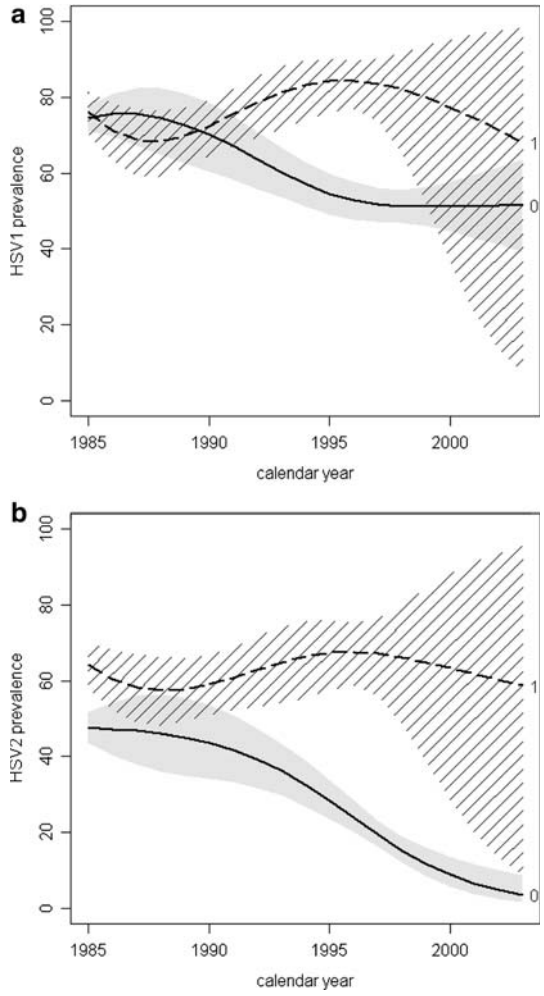

Fig. 2 (**a**) HSV-1 prevalence in the Amsterdam Cohort Study among MSM, according to the HIV status (1 = HIV positive, 0 = HIV negative) and the 95% confidence interval. (**b**) HSV-2 prevalence in the Amsterdam Cohort Study among MSM, according to the HIV status (1 = HIV positive, 0 = HIV negative) and the 95% confidence interval

observed only among MSM with Dutch or Northern/Central-European nationality. The association between HSV-1 and having non-European origin became stronger over time. The adjusted PRR was 1.08 ($P = 0.3$) before 1986 and the adjusted PRR became 1.58 ($P < 0.0001$) for the time period after 1996.

Also the association between HSV-1 and a higher number of lifetime sexual partners became stronger after 1996. Figure 3a shows the prevalence of HSV-1 infection over time according to the number of sexual lifetime partners. A decrease in the HSV-1 prevalence was seen among MSM with fewer than 21 partners ($P < 0.0001$), while among MSM with more than 200 partners, the HSV-1 prevalence increased between 1988 and 2003 ($P = 0.01$).

For HSV-2, the effect of calendar time differed with respect to the number of lifetime sexual partners and with HSV-1 co-infection. A large number of lifetime partners also was strongly associated with HSV-2. However, a decrease in the HSV-2 prevalence was seen among all categories of lifetime sexual partners (Fig. 3b), but this decrease was stronger for MSM with fewer than 21 partners and for those MSM with 21–200 partners.

Discussion

In the present study, we demonstrated an overall decrease in HSV-1 and HSV-2 prevalence among HIV-negative MSM, but not among HIV-positive MSM. In the 1984–2003 period, the association between HSV-2 and HIV among MSM became stronger over time, and HSV-1 prevalence increased in highly sexually active HIV-negative MSM. To our

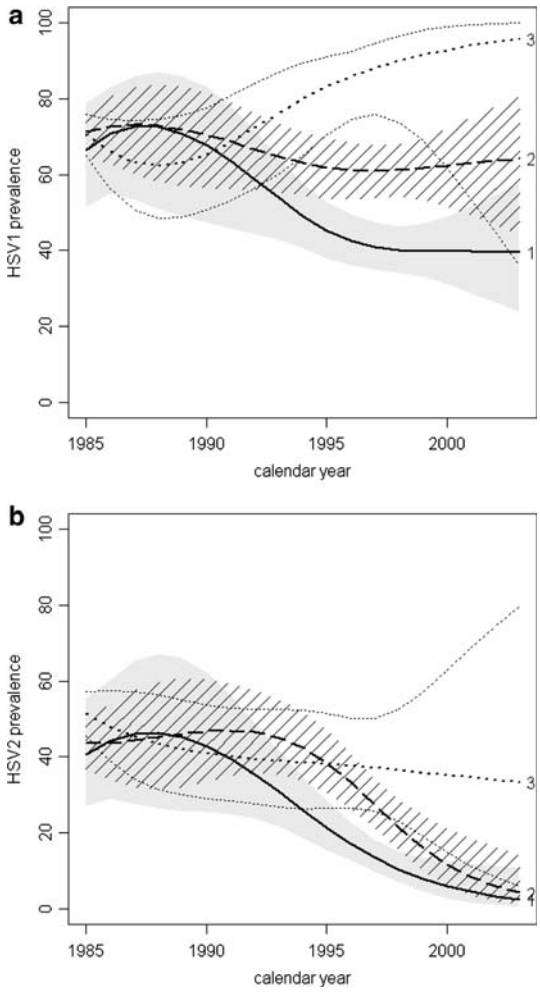

Fig. 3 (a) Prevalence of HSV-1 and the 95% confidence interval over time among HIV negative MSM, according to number of lifetime sexual partners; 1 = 1–20, 2 = 21–200, 3>200 partners. (**b**) Prevalence of HSV-2 and the 95% confidence interval over time among HIV negative MSM, according to number of lifetime sexual partners; 1 = 1–20, 2 = 21–200, 3 > 200 partners

knowledge, this is the first study based on almost 20 years of HSV-1 and HSV-2 prevalence data among MSM.

The decrease seen in the seroprevalence of HSV-1 and HSV-2 over time, could not be explained by changes in demographic characteristics or sexual behaviour. The decrease in HSV-1 is likely to reflect a decrease in childhood transmission by the oropharyngeal contact of HSV-1. Since fewer individuals are infected in childhood with HSV-1, there is a growing population of persons at risk at the time they become sexually active, resulting in a larger proportion of sexual transmission of HSV-1. Two risk factors for HSV-1 infection that could be important in its sexual transmission were identified by this study. First, HIV infection is associated with HSV-1 seropositivity. Second, the prevalence of HSV-1 was higher among highly sexual active MSM (at least 200 lifetime sexual partners). An association also shown earlier by others [3].

HIV infection in this respect may reflect an epidemiological marker for sexual risk behaviour for HSV-1 transmission. HSV-1 prevalence did not decrease in those infected with HIV, and we consider that genital HSV-1 infection has a growing role in the acquisition of HIV.

Likewise, HSV-2 prevalence did not decline over time among those infected with HIV, whereas a decline was noted among HIV uninfected MSM.

Although HSV-2 is sexually transmitted, we did not find an association between a higher number of lifetime partners and HSV-2 infection. HSV-2 was also highly prevalent among MSM with 1–20 lifetime partners. Mainly between 1984 and 1995, there were no major differences in the proportion of MSM infected with HSV-2. This suggests that HSV-2 is highly sexual transmissible and when having a low number of life time partner the risk of receiving a HSV-2 infection is still very high.

The results of this study show a protective effect of orogenital contact for HSV-2 infection, which might be explained by the fact that anogenital contact is a stronger predictor for HSV-2 infection. All variables measuring sexual practices are included in the analyses at the same time. Since most MSM practised all the techniques during the same time period these practices could not be analysed as independent risk factors. The stronger effect of anogenital contact might have overruled the effect of orogenital contact, resulting in a protective effect of orogenital contact.

The overall prevalence of HSV-2 in this study is similar to that among MSM in San Francisco in 1989, but higher than the prevalence found in more recent studies in the US [16–18]. The lower prevalence in those more recent studies probably reflects the decline in HSV-2 prevalence over time, as found in our study.

Russell et al., found high prevalence rates of HSV-2 among HIV-infected MSM in Australia [1]. The HSV-2 seroprevalence was more than twice as high as among HIV-uninfected MSM; there was no significant difference in HSV-1 prevalence between HIV-infected and HIV-uninfected MSM.

Several epidemiological studies have described an association between HIV and HSV-2 [10]. HSV-2 is recognised as a risk factor for HIV acquisition in MSM. In addition, HSV-2 may up-regulate HIV and increase local HIV replication on mucosal surfaces, leading to an increased risk of HIV transmission. Our study is the first to show an increase in the association between HSV-2 and HIV since 1996, suggesting that HSV-2 may play a growing role in driving the HIV epidemic in MSM. If this is the case, prevention of HSV-2 may well contribute to the prevention of HIV among highly sexually active MSM. Although serological screening for HSV-2 among MSM is still under debate, the increasing association between HSV-2 seropositivity and HIV is an argument in its favour. Several reasons against screening have been raised, such as the lack of a reliable serological test. We are aware of the low specificity of the various HSV-2 serological assays. However, these serological assays might be useful as a screening tool, when used with an increased cut-off value less individuals will be classified as false positive. A second argument against serological screening is that HSV-2 infection is largely asymptomatic and condom use appears only partially protective against HSV transmission. These factors complicate the prevention of HSV-2 and genital HSV-1 infection. However, it has been shown that half of the patients, initially unaware of their HSV-2 infection are able to recognise symptoms after being educated to do so [19]. Also, knowledge of the HSV-2 status of a sexual partner has been associated with a reduced risk of HSV-2 transmission [20]. Antiviral drugs used as suppressive therapy will lower the frequency of recurrences by 70–80% [21, 22]. A combined approach of offering serological screening to highly sexual active MSM together with encouraging condom use to reduce the risk of HSV transmission and using suppressive therapy among those with recurrent lesions might eventually play an effective part in controlling the HIV epidemic among MSM.

One limitation of our study is its cross-sectional design. As a consequence, we cannot reveal the relation between HIV and HSV infection, being unable to determine which occurred first. As both HIV and HSV are sexually transmitted diseases, their association may well reflect shared sexual behavioural practices leading to transmission as well as a biological relation. Longitudinal studies, in which incident HIV and HSV cases are captured are therefore needed to give more insight into the relationship between HIV and HSV as affected by changes in sexual risk behaviour.

The results of this study have two implications for HIV and HSV research among highly sexually active MSM.

First, it appears that HSV-2 and HIV are now more strongly related than in the early days of the HIV epidemic. As a vaccine against HSV-2 for MSM is not yet available, a determination of the extent to which the prevention of HSV-2, specially aimed for MSM at high risk for HIV, can contribute to controlling the HIV epidemic is needed. Second, since the extent of sexual transmission of HSV-1 is rising, we need to clarify its potential role as a risk factor for HIV acquisition in longitudinal studies.

Acknowledgments The Amsterdam Cohort Studies on HIV infection and AIDS, a collaboration between the Amsterdam Health Service, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht, are part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment. There are no competing interests to declare.

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