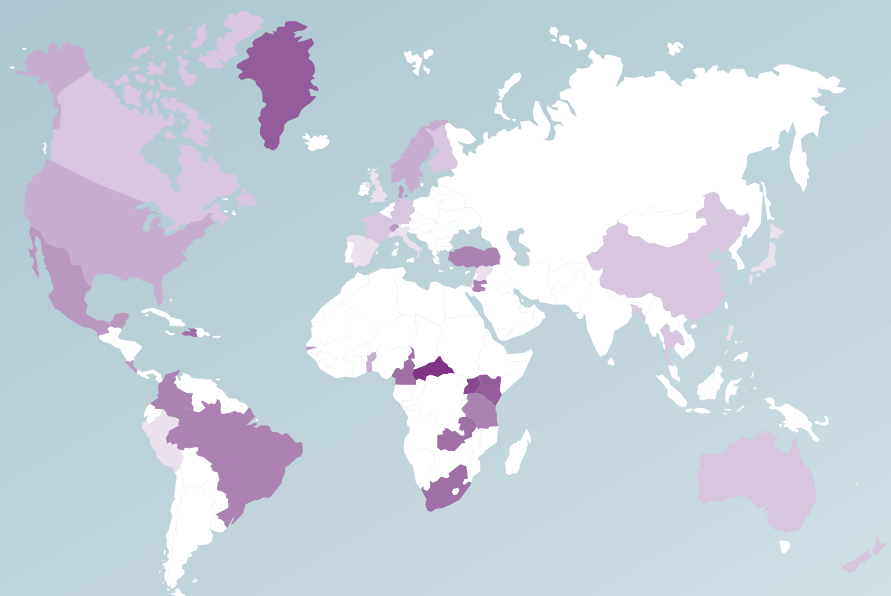
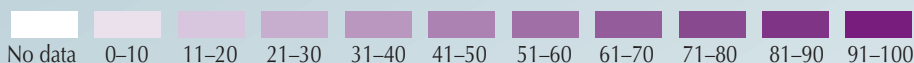


HERPES

THE JOURNAL OF THE IHMF



Non-high-risk female HSV-2 prevalence rate (%)



Global Epidemiology of Genital Herpes and the Interaction of Herpes Simplex Virus with HIV

Recommendations from the *IHMF Management Strategies Workshop* held on 25–26 September 2002 and ratified at the *10th Annual Meeting of the IHMF*, Paris, France, 28 February–2 March 2003

Supplement Editor: Lawrence Corey



IHMF

International
Herpes Management
— Forum —

Indexed in Medline, Index Medicus and Excerpta Medica (EMBASE)

Editors-in-Chief:

Lawrence Stanberry
USA

Antonio Volpi
Italy

Editorial Office:

HERPES journal, Cambridge Medical
Publications, Wicker House, High Street,
Worthing, West Sussex, BN11 1DJ, UK;
Telephone +44 (0)1903 288251;
Telefax +44 (0)1903 288292
E-mail cmp@hbase.com

IHMF website www.ihmf.org

Editorial Board

Jan Andersson
Sweden

Ann Arvin
USA

Laurent Belec
France

Guy Boivin
Canada

David Brown
UK

Lawrence Corey
USA

C Stephen Foster
USA

Paul Griffiths
UK

Robert Johnson
UK

Per Ljungman
Sweden

Jean-Elie Malkin
France

Adrian Mindel
Australia

Tsuneo Morishima
Japan

André Nahmias
USA

Robert Pass
USA

Raj Patel
UK

David Patrick
Canada

Anthony Simmons
USA

Anders Strand
Sweden

Britta Wahren
Sweden

Anna Wald
USA

Richard Whitley
USA

Publishing Information

Scientific Review and Acceptance

Articles printed in this publication are usually by invitation; however, unsolicited manuscripts or photographs are welcomed for consideration by the Editorial Board. All manuscripts submitted for publication are peer reviewed, the most important criterion for acceptance being that the articles address patient management concerns.

Editorial Statement

All reasonable precautions have been taken by the authors, editors and Cambridge Medical Publications to verify drug names and doses, the results of experimental work and the clinical findings published in this journal. Views and factual claims expressed are those of the authors and are not necessarily endorsed by the Editors, Advisors, Publisher, Distributors of the journal nor the Grantor. Readers are advised to consult the full prescribing information before using any medication mentioned in this publication.

The *International Herpes Management Forum* (IHMF) was established to improve the awareness, understanding, counselling and management of infections caused by herpesviruses. Steered by Professor Richard Whitley, Professor Lawrence Corey, Professor Paul Griffiths, Dr Jean-Elie Malkin, Dr Antonio Volpi, Dr Robert Johnson, Dr David Patrick, Dr Lawrence Stanberry and Dr Anders Strand, the IHMF involves international opinion leaders in all aspects of the management of herpesvirus infections.

Subscriptions (2004)

HERPES is available on subscription: for Volume 11, Europe £60.00, rest of the world £65.00. Subscribers will also receive any journal supplements which may be published. Back issues are also available on request and the price for a single issue is £28.50. Cheques, bankers' drafts and money orders should be made payable to PAREXEL MMS Europe Ltd. Payment by Visa, Eurocard or Mastercard is also accepted. For further details please telephone the UK office on +44 (0) 1903 288251.

Distribution

HERPES is distributed throughout the world to Universities, Medical Schools, Medical Libraries, Research Institutes and selected Hospitals in addition to individual subscribers in industry, institutes and private practice.

A mailing list is maintained on computer solely for the purpose of distributing this journal. Personal information contained therein will not be disclosed except with consent of the Data Subject. Objections by Data Subjects to use of this personal data should be addressed to the Publishing Editors.

Publishing Staff

Publisher Robert Kasprowicz

Publishing Editors Linda Edmondson, Rebecca Gardner

Desk Editor Simone Hayes, **Operational Support** Alison Tunks

Art Editor Monica Saunders, **Graphic Artists** Paul Jonas, Gavin Kimber

Publishing Grant

HERPES (ISSN 0969-7667; on-line 1470-1537) is published by Cambridge Medical Publications and supported by an educational grant from GlaxoSmithKline, UK. The terms of the grant are such that GlaxoSmithKline does not influence the content of the journal and can make no restriction on its distribution. The Editorial Board remains free to accept or reject all articles in accordance with normal journal practice. The educational grant is made in order to further the knowledge and understanding of herpesvirus infections and their management.

Paper Quality

This journal is printed on acid-free paper.



Copyright © Cambridge Medical Publications 2004. All rights reserved.

Editorial

Lawrence Corey

Professor of Medicine and Laboratory Medicine, University of Washington, and Head of the Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, WA, USA



Lawrence Corey

THE *International Herpes Management Forum* (IHMF) is delighted to present the first of two supplements of reviews on various aspects of herpes simplex virus (HSV) transmission. We believe that these reviews give a detailed picture of the current understanding of genital herpes transmission.

These publications have been developed from presentations and discussions at the IHMF Annual Meeting held in Paris (February 2003) and IHMF Workshop Meetings held in San Diego (September 2002) and Seattle (May 2003). The IHMF Board would like to thank the presenters and discussants at these meetings for their insightful and knowledgeable contributions.

In this first volume, Drs Jean-Elie Malkin and Helen Weiss provide the most comprehensive coverage yet available of the epidemiology of genital herpes infections in developed and developing countries. The articles detail the global pandemic that has ensued in the past two decades. In many parts of the developing world, the HSV-2 prevalence exceeds 50%. In the developed world, the rates may vary from 10 to 30%. There are several similarities in HSV epidemiology between developed and resource-poor regions. HSV is more prevalent in women and increases with age.

It is now understood that transmission of genital herpes can occur through asymptomatic infection. In fact, the majority of HSV transmissions occur without the

infected individual being aware of their infection. Genital herpes can be caused by both HSV-1 and HSV-2, with HSV-2 the most common cause. Interestingly, HSV-1-mediated disease is increasing, especially in developed countries. This may be due to the lower acquisition rate of HSV-1 in childhood and changes in sexual practices.

The transmission of HSV takes on a particular importance in the developing world, especially in sub-Saharan Africa, due to the increased risk of HIV acquisition in HSV-infected individuals. Dr Connie Celum provides a concise, logical explanation of the interaction between HSV-2 and HIV. This increased risk is thought to be due to HSV-mediated mucosal disruption through which HIV can be transmitted. Activated CD4 cells are also recruited into the lesion, which are targets for HIV infection. Asymptomatic HSV infection may also increase the risk of HIV acquisition.

This supplement represents the combined experience and knowledge of the many physicians and healthcare professionals involved with the IHMF. The practical implications of this knowledge are emphasized, with each paper stating IHMF best-practice recommendations and suggestions for future research. The information contained within this supplement represents a valuable resource to all healthcare professionals involved in the management of genital herpes.

Epidemiology of Genital Herpes Simplex Virus Infection in Developed Countries

Jean-Elie Malkin, Centre Médical de l'Institut Pasteur, Paris, France

KEY WORDS

■ **EPIDEMIOLOGY** ■ **HSV** ■ **PREVALENCE** ■ **GENITAL HERPES**
■ **INCIDENCE** ■ **DEVELOPED COUNTRIES** ■ **ASYMPTOMATIC**
INFECTIONS ■ **PRIMARY INFECTION** ■ **TYPE-SPECIFIC** ■ **TESTS**
■ **PREVENTION**

SUMMARY

Comparisons of the seroepidemiology of genital herpes simplex virus (HSV) infection within and between countries are hampered by variations in tests, methods and populations sampled. Differences in seroprevalence may partly reflect variability in diagnostic efforts and healthcare awareness, expectations and utilization. To allow comparison between surveys and to improve their performance, seroepidemiological studies should use validated HSV type-specific tests, report age-specific or age-adjusted prevalence and define the period of time over which samples were collected. Despite the difficulty of comparing studies, the prevalence of HSV-2 infection varies between developed countries. Among healthy adult populations, HSV-2 seroprevalence is higher in the USA than in Europe. Furthermore, HSV-2 seroprevalence varies widely among European countries. For example, in 1989 HSV-2 seroprevalence among pregnant women was reported to be 33% in Sweden compared with 8.3% in Germany. In some, but not all, countries, HSV-2 seroprevalence appears to be increasing. In the USA, the National Health and Nutrition Examination Surveys found that HSV-2 seroprevalence increased by almost one third from 16.4% to 21.8% from 1976 to 1994 in people over 12 years old. The incidence of HSV infection is a measure of primary infection. HSV incidence is difficult to quantify, partly due to unrecognized or asymptomatic infections. However, estimates of incidence in North American and European populations range from 5 to 24 per 100 people per year. Prevention programmes should recognize that HSV-2 seroprevalence increases rapidly in early adult life. The proportion of genital herpes infections caused by HSV-1 is increasing in the developed world, possibly due to changes in oral-genital sexual behaviour and lower rates of HSV-1 acquisition in childhood.

Introduction

SEROEPIDEMIOLOGICAL SURVEYS HAVE yielded valuable information on the prevalence and incidence of herpes simplex virus (HSV)-2 infection in general and selected populations. Many of these studies identify risk factors associated with HSV-2 infection, while others allow assessment of the impact of prevention strategies. This paper summarizes many of the studies conducted in industrialized countries, where the prevalence of HSV-2 infection is generally lower than in the developing world. For each country, representative studies are discussed and summaries of studies provided in accompanying tables. This paper also considers the increasing contribution of genital HSV-1 infection to the overall burden of genital herpes.

Factors Limiting the Validity of Direct Comparison of Study Findings

- ◆ Standardized epidemiological surveys can contribute to improved knowledge of the genital herpes epidemic and provide information on prevention strategies and prevention-orientated research (research need recommendation)
- ◆ Seroepidemiological studies must use validated type-specific tests (research need recommendation)
- ◆ Seroepidemiological studies must report age-specific or age-adjusted prevalence and the period over which the samples were collected should be stated (research need recommendation)

Serological studies can be compared, providing general differences in seroprevalence and seroincidence. However, a caveat must be applied to such comparisons as the surveys may have used different tests, employed different study designs or sampled different populations. Tests can differ markedly with respect to their sensitivity, specificity and positive predictive value. For example, many of the older serological tests had relatively low sensitivity and specificity compared with more modern tests.^{1,2} Western blot is the gold standard serological test but is only available in research laboratories due to its complexity.³ Other accepted standards, such as validated type-specific serological assays measuring antibodies to glycoprotein (g)G-1 and/or gG-2 are available⁴⁻⁶ and have been used to improve understanding of the natural history and epidemiology of infection. A study can be cross-sectional, cohort or case-control in design according to the purpose of the study and hypotheses tested. As the population characteristics will reflect the study design, any comparison between studies should consider this.

One of the most important variables to be considered is the population studied, as demographic differences between studies can render comparisons meaningless. One type of group studied is a population selected without prior bias, which may be truly representative of the national population (e.g. as in the National Health and Nutrition Examination Survey [NHANES] conducted in the USA), or may be less representative (e.g. blood donors). Other studies may examine selected populations whose demographic sexual behaviour variables put them at higher risk of acquisition of HSV-2 infection than the population at large. Therefore, comparison between a general and selected population is unwise, as are direct comparisons between different selected populations. As age-specific HSV-2 seroprevalence rates vary, another important factor is the age of the population studied. Single summary estimates of HSV-2 seroprevalence (e.g. mean or median values) can be misleading when age is not specified. Thus, all studies should report age-specific or age-adjusted prevalence. In addition, as rates at which individuals are infected can change with time, the period over which the samples were collected should be stated.

RECOMMENDATIONS AND STATEMENTS

- Prevention programmes should recognize that the seroprevalence of HSV-2 infection increases rapidly in early adult life (category 1 recommendation)
- Standardized epidemiological surveys can contribute to improving knowledge of the genital herpes epidemic and provide information on prevention strategies and prevention-orientated research (research need recommendation)
- Seroepidemiological studies must report age-specific or age-adjusted prevalence and the period over which the samples were collected should be stated (research need recommendation)
- Seroepidemiological studies must use validated type-specific tests (research need recommendation)
- Studies of genital ulcers should use polymerase chain reaction (PCR) as studies consistently show increased sensitivity over HSV culture (research need recommendation)

Prevalence of HSV-2 Infection in the USA

NATIONALLY REPRESENTATIVE POPULATIONS

Two national US surveys have gathered comprehensive data on the seroepidemiology of HSV infection.^{7,8} The surveys used a stratified, multistage, probability design for selecting a sample that was representative of the US population. The first survey, NHANES II, which was conducted from 1976 to 1980, collected serological data on HSV-2 from 28 000 individuals.⁷ The second, NHANES III, took place between 1988 and 1994. It differed from NHANES II in that it had a larger sample size (over 40 000 for HSV-2) and included information on behavioural risk factors for HSV-2 infection. The serum samples in both studies were tested for HSV-2 antibodies with the same type-specific immunodot test that used purified HSV-2 gG as the antigen. The sensitivity of the test for culture-proven, recurrent genital HSV-2 infection is over 98% and the specificity is greater than 99%.⁹

In NHANES III, the overall prevalence of HSV-2 antibody among study participants aged 12 years or older was 21.9% (Table 1).¹⁰ This corresponded to a HSV-2 seroprevalence of 45 million people in the general US population. The seroprevalence was higher among women (25.6%) than men (17.8%) and higher among blacks (45.9%) versus whites (17.6%). The seroprevalence in Mexican-Americans was 22.3%. The overall HSV-2 seroprevalence rose rapidly in the younger age groups and then remained stable among people older than 30 years of age, in the range 24% to 28%.

HSV-2 seroprevalence was 23% among 500 randomly selected patients attending a family medicine clinic in Seattle, WA, USA.¹¹ The prevalence of HSV-2 antibodies in this small study, which was conducted from 1991 to 1992, is similar to that recorded in NHANES III (conducted from 1988 to 1994). The patients were visiting the clinic for a variety of complaints. Women comprised 63% of the study population. The majority of patients were white (85%), followed by black patients (9%) and Asians (7%), with the remaining 3% defining themselves as other races. As in NHANES III, women were more likely than men to be HSV-2 seropositive, and the majority of blacks had serological evidence of HSV-2 infection. In common with the national survey, the prevalence of HSV-2 increased with age, in this case by 1.6-fold per decade. Despite nearly one quarter of patients being HSV-2 seropositive, only a minority (27%) had a clinical history of genital herpes. The frequency of unrecognized or asymptomatic infection

- Additional studies on the temporal changes in the incidence of HSV-2 infection are required (research need recommendation)

RECOMMENDATION AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

did not differ by any demographic characteristic. There is, therefore, a large reservoir of potentially contagious patients unaware that they are infected.

TEENAGERS AND YOUNG ADULTS

Two studies of US teenagers and young adults recorded an HSV-2 seroprevalence of 12%.^{22,31} In the first study, published in 1996, HSV-2 seroprevalence was determined in a cohort of 399 subjects aged 12 to 22 years, at high risk of a sexually transmitted infection (STI).³¹ The mean age for the entire cohort was 17.1 years; 78% were African-American and 22% were Caucasian. When seroprevalence was considered by gender, 8% of the boys and 14% of the girls were HSV-2 seropositive, a difference that approached statistical significance. The study found that girls acquired HSV-2 infection at young ages, with a HSV-2 seroprevalence among girls younger than 16 years of 16%. In comparison, the youngest male with antibody to HSV-2 was 17 years old. African-American adolescents were more likely to be HSV-2 seropositive than Caucasian adolescents ($P=0.02$; odds ratio [OR], 3.3; 95% confidence interval [CI], 1.14–9.44).

In the second study, 381 adolescents (aged 14–19 years) were recruited from an urban sexually transmitted disease (STD) clinic, an urban, low-income patient population, a juvenile detention facility, an outreach programme and a family planning clinic. The mean age was 17.4 years and 64% were girls, 47% were white and 27% were African-American. Overall, 12% had HSV-2 antibodies and, as in the other US adolescent study, the HSV-2 seroprevalence was higher in girls (17%) than boys (4%; $P<0.001$). This difference was particularly marked among the adolescents younger than 16 years of age; none of the 20 boys were seropositive compared with 16 (18%) of the 87 girls. More African-Americans (18%) than whites (11%; $P=0.09$) had HSV-2 antibodies.

The HSV-2 seroprevalence in the adolescents in these studies is higher than that in NHANES III but similar to other studies of adolescents at high risk of an STI³⁸ and slightly lower than estimates from a juvenile detention health clinic.³⁰ The finding from both these studies that HSV-2 was more prevalent in females than males in this young age group is consistent with other studies, many of which involved older individuals.^{7,39} The two studies documented that girls acquired HSV-2 infection at young ages; the HSV-2 seroprevalence among girls younger than 16 years of age was 16–19%. The difference may be partly attributable to partner selection as adolescent girls are more likely to have older partners who have a higher chance of being infected with HSV-2.⁸

Table 1: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in the USA¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
National (1988–1994) ⁸	TS immunodot assay	Random sample of non-institutionalized civilians, NHANES III	F/M	12–≥70	6687/6407	26/18
			F+M	12–≥70	13094	22
				12–19	2396	5.6
				20–29	2750	17
				30–39	2567	28
				40–49	2061	27
				50–59	884	25
				60–69	1069	24
		≥70	1367	28		
California Los Angeles (1985–1989) ¹²	Western blot	Women in obstetrical care with no history of genital herpes	F	32	613	32
California Northern California: Alameda, Contra Costa, San Francisco, San Joaquin, San Mateo counties ¹³	TS immunoblot (Chiron)	Random sample of households with median income	F	18–29	1663	33
California San Francisco (1996–1998) ¹⁴	TS immunoblot assay (Chiron)	Population-based sample of women in low-income neighbourhoods	F	18–29	1635	35
				18–21		28
				22–25		32
				26–29		46
Georgia Atlanta (1991–1993) ¹⁵	TS immunoblot test	Health clinics	F	16 (14–19)	589	14
New Mexico Albuquerque (1989–1992) ^{16,17}	TS glycoprotein G assay	Women with normal pap smears	F	18–40	333	29
				18–21	82	16
				22–25	78	24
				26–29	80	35
				30–40	93	41
New York Brooklyn (1994–1995) ¹⁸	Western blot	Population-based sample of primarily low-income Latinos and blacks	F/M	18–21	50/52	64/37
Ohio Cincinnati (pre-1999) ¹⁹	Screened with type common ELISA (SmithKline Beecham), followed by TS ELISA	Black college women	F	18–24	88	30
Oregon Large city ²⁰	TS immunoblot assay	Homeless adolescents	F+M	18/19	217/319	12/5.5
Texas Houston (pre-1984) ²¹	TS solid-phase microradio-immunoassay	Participants in diethylstilbestrol adenosis study	F	21	230	12
				≤19		6.0~
				20–22		9.0~
				≥23		19~
Washington Seattle (1994–1996) ²²	Western blot	Sexually active adolescents	F/M	17	379	17/4
Washington Seattle (1989–1995) ²³	Western blot	Women at delivery	F	25	8408	32
Washington Seattle (1991–1993) ²⁴	Western blot	Adults attending family medicine clinic	F/M	33	610/351	29/13
Washington Seattle (1989–1993) ²⁵	Western blot	Pre-natal patients	F	25	8538	28
Washington Seattle (1991–1992) ²⁵	Western blot	Patients attending family medical centre	F/M	33 (18–45)	315/185	27/15
			F+M	18–25		22/4.0~
				26–35		24/10~
				36–45		37/20~
Washington Seattle (1984–1986) ²⁶	Western blot	Attendees of University of Washington student health clinic	F	24	636	8.8
Washington Washington State (1985–1989) ²⁷	Western blot study	Controls in oral cancer study	M	52~ (18–65)	92	15

Table 1: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in the USA¹⁰ (cont.)

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)	
High-risk populations							
Cities of Miami, New York, San Francisco (1991–1992) ²⁸	Western blot	Women recruited in areas where illicit drug use is common	F	25	1104	59	
Alabama Birmingham (pre-1999) ²⁹	TS assay	STD clinic attendees	F+M	18–34	1103	64	
				18–19	126	45	
				20–22	280	58	
				23–26	272	62	
				27–29	201	74	
30–34	224	79					
California Santa Clara (1994–1995) ³⁰	TS in-house assay, borderline results confirmed with Western blot	Adolescents at juvenile detention facility	F/M	16 (13–18)	41/94	20/15	
Ohio Cincinnati (1996) ³¹	TS ELISA	Urban adolescents with STD or attendees of adolescent clinic	F/M	17/18	237/129	14/7.8	
Pennsylvania Pittsburgh (1984–1985) ³²	TS immunoblot	Homosexuals	M	33~	98	43	
Washington Seattle (1998) ³³	TS ELISA (Gull-Meridian) with Western blot for repeatedly equivocal samples	STD clinic attendees without a history of genital herpes	F+M	≤19–>40	756	30	
				≤19	29	24	
				20–29	292	17	
				30–39	172	34	
				>40	93	33	
Washington Seattle (1995) ³⁴	Western blot	HIV-negative men who have sex with men	M	32 (18–71)	572	26	
Washington Seattle (1989–1995) ²³	Western blot	HIV-infected women	F	27	60	75	
Washington Seattle (1988–1990) ³⁵	Western blot	Intravenous drug users	F/M	39	62/151	50	
Washington Seattle (1984–1986) ³⁶	Western blot	Randomly selected STD clinic attendees	F	26 (16–50)	213	43	
Washington Seattle (1984–1986) ²⁶	Western blot	STD clinic attendees	F	24	776	43	
Washington Seattle (1983–1986) ³⁷	Western blot	Homosexual STD clinic attendees, HIV-negative:	M				
				HIV-positive:	25	85	36
					28	100	66

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; ~, estimated from graph or table or age range inferred from text; F, female; M, male.
Adapted from Smith JS *et al.*¹⁰

The two studies differed in the relationship between sexual history variables and the likelihood of HSV-2 infection. In the first study, HSV-2 seropositivity was associated with the number of STD episodes for boys and the number of lifetime sexual partners for girls. Sexual history variables, such as multiple sexual partners, early age of first sexual intercourse and a history of an STD, are associated with HSV-2 infection in other studies.^{40–42} The relationship between these behavioural variables and HSV-2 infection suggests that a sexual history for adolescents should always include information about previous STDs and the number of lifetime sexual partners. However, the second study indicates that demographic rather than behavioural risk factors predict HSV-2 infection in sexually active adolescents.²² Sexual history variables in the second study (e.g. number of sexual partners in the last 2 months; condom use during last sexual intercourse; number of prior non-HSV STDs) were not associated with HSV-2 seropositivity. In multivariate analysis only female gender and African–American ethnic origin remained significant predictors of HSV-2 infection.

Other studies of adolescents and adults have also found no correlation between sexual activity and risk of HSV-2 infection.^{11,15,30}

STD CLINIC ADULT ATTENDEES

A cross-sectional study among STD clinic attendees in Seattle documented an overall HSV-2 seroprevalence of 25.9% in persons with no history of genital herpes (Table 1).³³ The HSV-2 seroprevalence was higher than that in the general population, which reflects the STD population being at higher risk of acquiring HSV-2 infection, but the same correlates of HSV-2 infection were found. HSV-2 seroprevalence was higher in women than men, and greatest in people aged 30 years or older ($P < 0.01$ for both comparisons, Table 1). HSV-2 infection was also higher in blacks (44.8%) than whites (20.6%; $P < 0.01$). There was no significant difference in HSV-2 seropositivity by sexual orientation among men, median number of sexual partners in the past 2 or 12 months, or a diagnosis of another STD.

Women attending an STD clinic in Atlanta, GA, USA had a higher HSV-2 seroprevalence (64%) than the STD

clinical attendees in Seattle.²⁹ The study included 1103 women aged between 18 and 35 years, 89% of whom were African-Americans. The prevalence of HSV-2 antibodies was related to age ($P < 0.001$ for trend) and was higher among African-Americans (66%) than whites (55%). HSV-2 seroprevalence rose with the number of lifetime sexual partners, an early age of first sexual intercourse, a history of syphilis and HSV-1 seronegativity. The higher odds of HSV-2 seropositivity among African-Americans was also confirmed by NHANES III, as was increasing seroprevalence with age.⁸ In this STD clinic population, the high prevalence of HSV-2 infection by 20 years of age suggests that most women were infected during the first years after sexual debut. The association between early age at first intercourse and HSV-2 seropositivity could indicate that younger women are more exposed to HSV-2 or that they are more susceptible because of their lack of HSV-1 antibodies. However, the cross-protection offered between HSV-1 and HSV-2 infections has not been confirmed by all studies.²⁵ An important finding of the study was that only 5% of HSV-2 seropositive women displayed symptoms of genital herpes at examination, and a lower proportion of African-Americans than whites had symptoms of the disease. Therefore, in common with other studies, genital HSV-2 infection was most often asymptomatic.

The seroprevalence of HSV-2 infection was 40.8% among 4128 patients from five STD clinics enrolled in Project RESPECT, a randomized controlled trial of HIV and STD counselling efficacy (Figure 1).⁴³ HSV-2 seroprevalence was higher in women than in men (52.0% versus 32.4%; $P < 0.0001$) and higher in blacks than in whites, Hispanics and other ethnic groups (48.1% versus 29.6%; $P < 0.0001$). Among 14–19-year-old patients, 36.8% of black women and 25.8% of non-black women were infected with HSV-2. For both sexes, past sexual behaviour and history of an STD were predictors of HSV-2 infection, particularly the number of lifetime sexual partners and a prior history of gonorrhoea or syphilis. Overall, 84.7% of patients had never been given a diagnosis of genital herpes by a physician either before the study or at the enrolment visit.

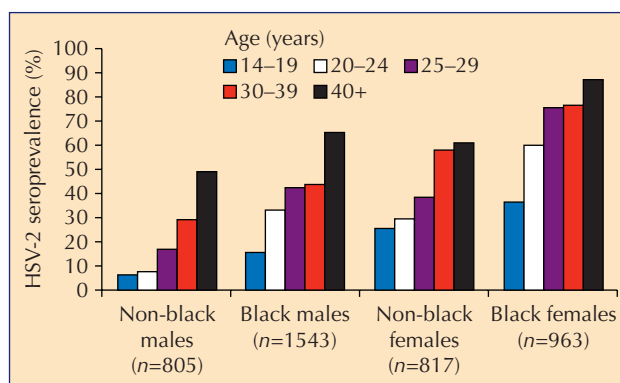


Figure 1: HSV-2 seroprevalence according to age, race and sex in five STD clinics in the USA.⁴³ Reproduced with permission from Gottlieb SL, Douglas Jr, JM, Schmid DS et al. *Seroprevalence and correlates of herpes simplex virus type 2 infection in five sexually transmitted disease clinics.* *J Infect Dis* 2002;186:1381–1389. University of Chicago. © 2002 by the Infectious Diseases Society of America. All rights reserved.

Trends in HSV-2 Seroprevalence and Seroincidence in the USA

The age-adjusted seroprevalence in the USA rose from 16% in NHANES II to 20.8% in NHANES III, a relative increase of 30%. The relative increase was similar among men and women but differed by ethnic group.

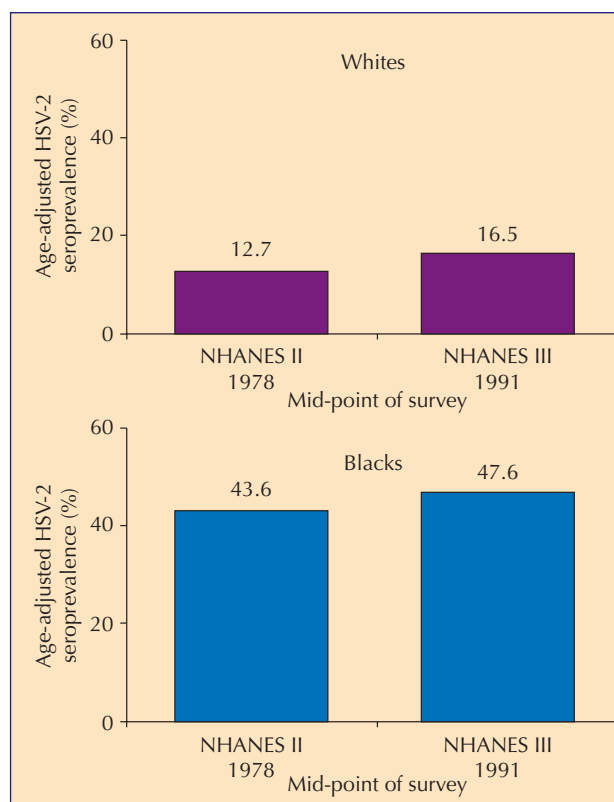


Figure 2: HSV-2 seroprevalence in NHANES II and NHANES III.⁴⁴

The absolute increase in HSV-2 seroprevalence was similar among whites and blacks but the relative increase among whites was greater because of the lower baseline seroprevalence in this group (Figure 2).⁴⁴

The increases in the prevalence of HSV-2 antibodies were concentrated in the younger age groups (i.e. those aged 12–39 years). The change in prevalence of HSV-2 between the two studies was particularly marked among whites aged 12–19 years and in 20–29 year olds, in whom it increased from 0.96% to 4.5%, and from 7.7% to 14.7%, respectively. Among older whites and among blacks of all ages, relative increases were much smaller.

The national studies of HSV-2 seroprevalence in the USA have important findings. The overall seroprevalence in the early 1990s was 21.9%. With age adjustment, this was an increase of 30% since the 1970s, and this increase was particularly apparent among young whites. An important factor that may have contributed to this increase was the low level of recognition of genital herpes. In fact, of all persons in NHANES III with antibody to HSV-2, only 9.2% reported 'ever having had genital herpes'. The great majority of people who were seropositive for HSV-2 had no history of genital herpes. Some of these individuals have truly asymptomatic infection, in which virus is shed in the absence of any signs or symptoms.^{45,46} Others may have symptoms, such as itching or discharge, that are due to HSV-2 but may not be recognized as an infection⁴⁷ and, thus, may unknowingly be contributing to the spread of the infection.

ESTIMATED INCIDENCE OF HSV-2 INFECTION IN THE USA

Although the two NHANES surveys documented an increase in HSV-2 seroprevalence, there are no national data on its incidence in the USA. The incidence of HSV infection is the proportion of susceptible individuals who acquire HSV in a given time period. Thus, it represents acute disease and for this reason is clinically important. Primary infection with HSV is generally more severe than a recurrence and can have important sequelae. For example, HSV infection in late pregnancy increases the risk of neonatal herpes, a devastating

disease with a high rate of mortality if untreated and severe neurological impairment among survivors.^{48,49} Infection in immunosuppressed hosts may result in severe local disease and, occasionally, disseminated disease.

A study to determine seroconversion rates in a cohort would be possible but costly. Moreover, it is difficult to determine the incidence of genital herpes in the USA partly because it is not reportable, and because infection can be asymptomatic or unrecognized.³⁹ Some information on the number of initial visits to physicians, which probably represent first episode genital herpes, is available. It documents an increase from 20 000 visits in the mid-1960s to 150 000 in the mid-1990s (Figure 3).⁴⁴ These data may be unrepresentative as the visits may reflect more severe cases or visits from those with a greater awareness of and concern about genital herpes. Nevertheless, the number of consultations appeared to increase from 1970.

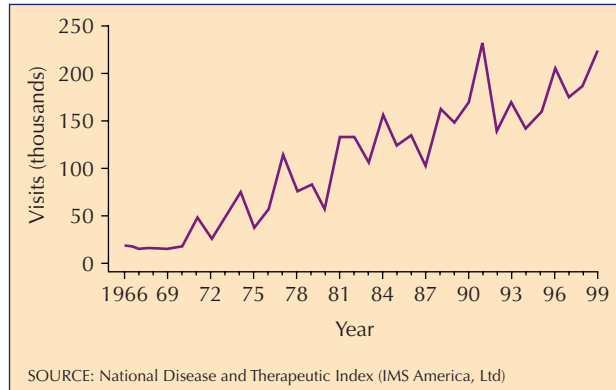


Figure 3: Initial visits to physicians' offices in the USA for genital HSV infections.

The incidence of infection can be estimated by comparing studies performed at different time periods. This method is fraught with difficulties, even using surveys conducted with identical methods. In a single survey, different age groups may have acquired HSV at different times and, unless it was a cohort study, the individuals from whom samples were taken will not be the same ones in both surveys. An approach to overcome this problem is catalytic modelling. This technique relates incidence to prevalence, given several data points of the latter, under the assumption of an exponential increase in incidence (the exponential curve being called 'catalytic' at the time the model was first developed). The model allows the overall incidence to increase linearly with time but assumes the exponential shape of the age-specific incidence curve remains constant. In doing so, it modelled what incidences could have led to observed rises in prevalence.

Catalytic modelling was applied to data from the NHANES II and NHANES III surveys to estimate annual incidences of infection until 1985.⁴⁴ The model made assumptions about the underlying process, the first being that incidence increased by the same proportion in all age groups. The second assumption was that incidence was constant for many years and then began rising linearly with time from 'year zero (y_{r_0})'. The values for y_{r_0} and the rate of increase were determined empirically by fitting the modelled prevalence to the actual prevalence.

The estimated annual incidence of infection varied according to the identity of y_{r_0} . Age-specific estimates of the force of infection were least dependent on y_{r_0} if it was before the 1970s (4–5 per 1000) or after the mid-1980s (8–9 per 1000). The estimated force of infection in the late 1970s and in the 1990s was much more dependent on the choice of y_{r_0} . Sensitivity analyses with the model indicate that best fit for y_{r_0} was when it fell between 1970 and 1980. As published data show that outpatient visits began to rise in about 1970

(Figure 3), this year was chosen as y_{r_0} in the model. The best fit for the model was when the annual rates of increase in the force of infection were 7% for whites, 2% for blacks and 9% for others.

Between 1970 and 1985, the estimated annual force of infection increased from 4.6 per 1000 to 8.4 per 1000, a relative increase of 82%. During this time, the increase in prevalence would have lagged behind this increase in incidence; in the overall population (i.e. aged 12 years or older) the prevalence would have increased by 15% (i.e. from 13.6% to 15.7%). The implication for prevention of infection is that changes in prevalence may not accurately reflect alterations in incidence. The lag between incidence and prevalence could allow seroprevalence to rise while incidence is stabilizing or even decreasing.

The results of the model are consistent with other published estimates of incidence in North American and European populations, in which the annual rates of HSV seroconversion ranged from 5 to 24 seroconversions per 1000 people per year.^{25,44,50–52} In a prospective cohort of Swedish girls in 1958 and 1969, the annual HSV-2 seroconversion rates per 1000 people were 5, 24 and 23 for those aged 13–18, 17–22 and 21–29 years, respectively.⁵⁰ In a cohort of university students in the USA in the mid-1980s, the annual seroconversion rate was 20 per 1000.⁴¹ In pregnant women in Washington State and Alabama, the respective seroconversion rates were 16 and 20 per 1000 seronegative women.^{25,51} In two HSV-2 vaccine trials, rates of seroconversion of men and women at increased risk of infection were 44 and 68 per 1000, respectively.⁵²

The age-specific force of infection in 1985 in the model was higher in blacks than whites and in women than men (Figure 4). The increase with age peaked in men and women aged 20–29 years. This peak is consistent with findings from other studies in the USA and in the UK, which show that outpatient visits for genital herpes peak in this age group.^{53,54} This is older than the peak age for acquisition of gonorrhoea and chlamydia, which are most frequently reported in women in their late teens and men in their early twenties.⁴⁴ This underscores the need for prevention campaigns to consider older age groups as well as teenagers.

The model was not robust enough to extrapolate results beyond the mid-1980s, as the estimates of incidence beyond this time point depended greatly on the year chosen for y_{r_0} . In addition, the model only contained data from two points, and assumed that the increase in infection was linear. In reality, the increase was almost certainly non-linear and probably varied by age group. Moreover, the incidence of other STIs has decreased since the mid-1990s,^{55–57} making it uncertain whether or not HSV-2 incidence is continuing to increase. The next NHANES survey is underway and will provide new estimates on the seroprevalence of HSV-2 in the USA.

Prevalence of HSV-2 Infection in Canada

There are no serological surveys for HSV-2 among the general population in Canada but a recent study documented an age-adjusted HSV-2 seroprevalence of 17.3% among Canadian women attending an antenatal clinic. The study collected samples in 1999 from 1215 women from pregnant women aged 15–44 years from major metropolitan regions and less urbanized areas.

As the women in this study were pregnant, they would have been sexually active and likely not making consistent use of barrier contraception. This may explain why the younger women in this study (i.e. aged 15–19 years) had a higher HSV-2 seroprevalence than those of similar age in the NHANES III study. The age-specific seroprevalence did not increase markedly among women between the ages of 15 and 24 years; greater increases occurred in older subjects (Figure 5).⁵⁸

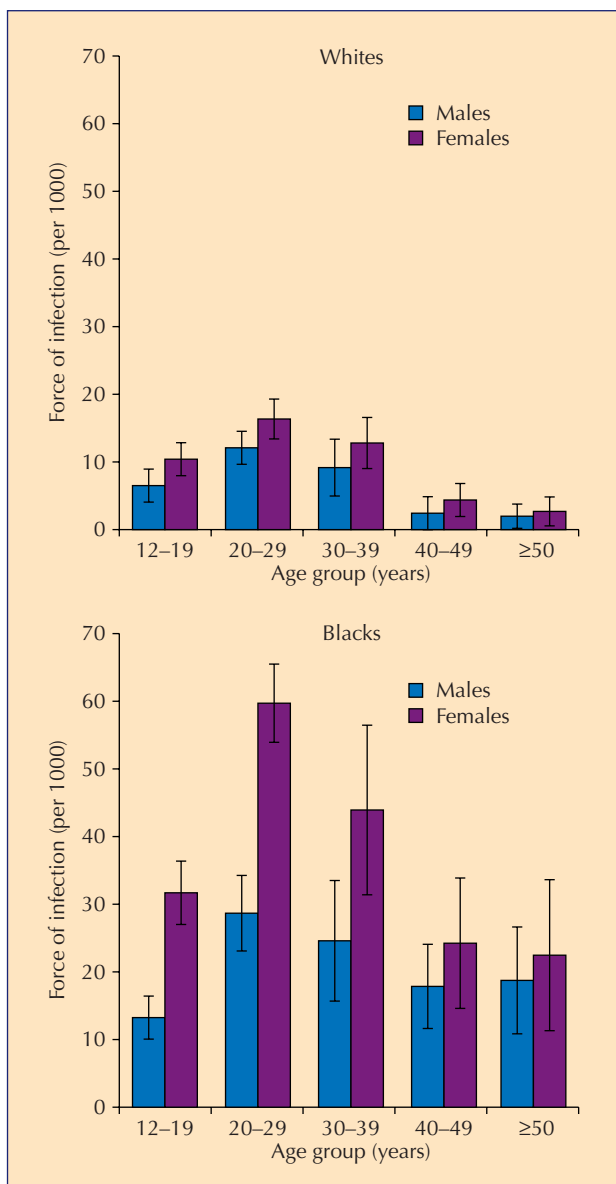


Figure 4: Force of infection of HSV-2 in blacks and whites by age and gender in 1985. Armstrong GL, Schillinger J, Markowitz L et al. Incidence of herpes simplex virus type 2 infection in the United States. *Am J Epidemiol* 2001;153:912-920, by permission of Oxford University Press.

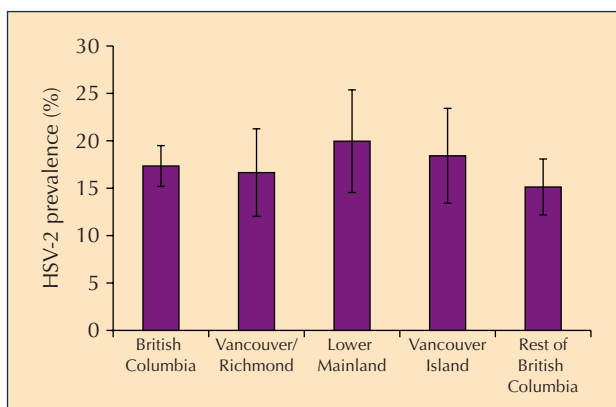


Figure 5: Age-specific seroprevalence of HSV-2 among Canadian women attending an antenatal clinic.⁵⁸ Reproduced with permission from Patrick DM, Dawar M, Cook DA, Kraiden M, Ng HC, Rekart ML. Antenatal seroprevalence of herpes simplex virus type 2 (HSV-2) in Canadian women: HSV-2 prevalence increases throughout the reproductive years. *Sex Transm Dis* 2001;28:424-428. © Lippincott, Williams & Wilkins.

This observation may also be explained by the likelihood that the younger girls would carry a higher burden of HSV-2 because of their behavioural attributes, which would blunt the ability to detect an apparent increase. An alternative explanation for the higher prevalence of HSV-2 infection in older women is that their sexual experiences began during the sexual revolution of the 1960s and before intensive condom promotion, which may have led to greater cumulative exposure.⁵⁸

In samples randomly selected from public health laboratories in Ontario, Canada, the overall age- and gender-standardized seroprevalence of HSV-2 was 9.1% (95% CI, 8.6-9.7).⁵⁹ The specimens were from subjects aged 15-44 years, including men ($n=979$), women not under prenatal care ($n=638$), and women under prenatal care ($n=701$). The seroprevalence of HSV-2 increased from 3.8% to 21.3% in men aged 15-16 and 40-44 years of age, from 0% to 18.9% in women not under prenatal care, and from 3.4% to 23.1% in women under prenatal care. HSV-2 antibodies appeared to be acquired earlier among women under prenatal care than among men and women not under prenatal care.

Prevalence of HSV-2 Infection in Sweden

HSV-2 seroprevalence studies in Sweden have only been undertaken in females, with no studies among the general population. The prevalence of HSV-2 antibodies has generally been high (Table 2), although in a survey carried out from September 1989 to September 1990 in girls attending an upper secondary school, only 1.0% (1/98) of 16-year-old girls were HSV-2 seropositive.⁶⁰ During a 2-year follow-up, only one girl seroconverted to HSV-2. This low prevalence was similar to the 0.4% reported in another study of 839 girls aged 14-15 years in 1972.⁵⁰

The age-adjusted seroprevalence of HSV-2 in pregnant Swedish women increased from 19% in 1969 to 33% in 1989.⁶¹ The study took samples from three separate cohorts of women in 1969 ($n=941$), 1983 ($n=1759$) and 1989 ($n=1000$). An increase in HSV-2 seropositivity with age was similar and slight in 1969 and 1989 but was much steeper in 1983, indicating a shift in sexual behaviour.⁶¹ That HSV-2 seroprevalence increased was based on the assumption that the behavioural and demographical characteristics of the women were similar in each cohort. All the women came from the same catchment area in Stockholm, which led the authors to assume that their socioeconomic background was similar. However, there are inherent difficulties in making a comparison between the groups. For example, the country of origin of the women in the first two surveys was unknown, yet immigration into Sweden over the period of the study increased considerably, especially from countries outside Europe where HSV-2 seroprevalence could be different.⁶¹

An increase in HSV-2 seroprevalence has been reported in another Swedish study of pregnant women. An 11% increase in HSV-2 seroprevalence occurred between 1973 (12.8%; 38/297) and 1989 (23.7%; 70/295).⁶² An increase is not reported in all studies; an age-matched comparison of HSV-2 antibody rates in two populations of Swedish women suggests a lower incidence of HSV-2 infection in women younger than 20 years in the early 1990s compared with those of similar age in the early 1970s.⁶³

The increases in seroprevalence, and the rise in HSV-2 seroprevalence with age, can be explained by a sexual lifestyle pattern in which young adults have a few short-term monogamous relationships before they enter into a longer-term monogamous relationship. It need not be due to higher rates of partner change, although such behaviour probably contributed to the increase.

Table 2: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Sweden¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Karlstad (1989–1990) ⁶⁰	TS ELISA	Secondary school girls	F	16 (15–17)	98	1.0
Malmö (1990–1993) ⁶³	TS ELISA	Antenatal patients	F	15–≥36	1190	21
				15–20	45	4.4
				21–25	283	12
				26–30	436	15
				31–35	284	31
Stockholm (1989) ⁶¹	TS ELISA	Pregnant women	F	≥36	142	37
				30	1000	33
				≤25		32
				26–30		30
Urban area (1987) ⁵⁰	Crude ELISA used to screen, followed by TS ELISA	School girls	F	31–35		39
				≥36		31
				14–15	739	0.4
High-risk populations						
Göteborg (1989) ⁶²	Screened with type common ELISA, confirmed with TS ELISA	STD clinic attendees	F/M	<21 21–25 26–30 >30	295	13~/2.0~ 21~/9.0~ 32~/11~ 58~/26~

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; ~, estimated from graph or table or age range inferred from text; F, female; M, male.
Adapted from Smith JS *et al.*¹⁰

Prevalence of HSV-2 Infection in Finland

Three HSV seroprevalence studies have been undertaken in Finland (Table 3). In the Helsinki area, the seroprevalence of HSV-2 among pregnant women in their first trimester was 15.7%.⁶⁴ The prevalence increased with age, from 13.8% (5/36) in women aged less than 20 years to 22.2% (4/18) in those older than 40 years. The samples analysed were collected from 997 women from January 1988 to May 1989. The seroprevalence among this population was similar to that noted in US and Swedish populations of pregnant women.^{51,61,62}

Prevalence of HSV-2 Infection in Norway

In Norway, the prevalence of HSV-2 antibodies was similar among women in two studies conducted at similar times involving non-high-risk populations (Table 4).^{67,68} In a random sample of 961 women drawn from a study population of 35 940 pregnant women during 1992–1994, 26.6% (256/961) had antibodies to HSV-2. The prevalence increased with age, from 17% in 20–24 year olds to 34% in those aged 35 years or older. The presence of antibodies varied geographically, from 18% in the south to 39% in the north of Norway. Among women with repeated anti-HSV-2 tests during pregnancy, 2.6% of the seronegative women seroconverted (16/623). The HSV-2 seroprevalence was 25% in the second study, which comprised controls from a population-based study of cervical intraepithelial neoplasia that took place in Oslo.⁶⁸

Prevalence of HSV-2 Infection in The Netherlands

Four HSV-2 seroprevalence studies have been undertaken in The Netherlands (Table 5). The overall HSV-2 seroprevalence among STD clinic attendees in Amsterdam was 32.3%.⁶⁹ In total, 1798 serum samples were collected from 1986 to 1988. The prevalence of HSV-2 antibodies was significantly higher among women, 47.2% (274/580) and homosexual men, 40.5% (87/215) than among heterosexual men, 23.6% (208/883). HSV-2 seroprevalence increased consistently with age for men while there was a similar but less clear trend for women and homosexual men. The presence of HSV-2 antibodies was strongly associated with past sexual behaviour,⁶⁹ with the following behavioural risk factors being important: homosexual orientation, increasing number of years of sexual activity, increasing number of lifetime partners, number of past STD infections and having receptive anal and (or) vaginal contact. There was no association with age at first intercourse.⁶⁹ At the time the serum samples were collected, gonorrhoea rates among homosexual men were declining, suggesting that behavioural changes in response to AIDS had already occurred.⁷⁰

Similar findings for HSV-2 seroprevalence were documented for a study in which samples were collected in 1993 and 1998 from randomly selected STD attendees in Rotterdam.⁷³ The HSV-2 seroprevalence decreased from 30% in 1993 to 22% in 1998 ($P<0.001$). Although it is likely that different individuals would have been sampled at the two periods, the prevalence of HSV-2 infection apparently fell among STD clinic attendees in Rotterdam. In both time periods, HSV-2

Table 3: Prevalence of HSV-2 infection among non-high-risk populations in Finland¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Helsinki (1988–1989) ⁶⁴	TS ELISA	Pregnant women	F	30	997	16
				<20	36	14
				21–25	181	16
				26–30	344	17
				31–35	297	16
				36–≥41	139	12
National (1966–1972) ⁶⁵	TS ELISA	Population-based, random sample from Finnish social insurance institution	F	39 (15–83)	143	26
National registry (1966–1972) ⁶⁶	TS ELISA	Control patients in cervical neoplasia study, matched by sex, age and time of diagnosis	F	44~	64	31

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; ~, estimated from graph or table or age range inferred from text; F, female. Adapted from Smith JS *et al.*¹⁰

Table 4: Prevalence of HSV-2 infection among non-high-risk populations in Norway¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Multi-site (1992–1994) ⁶⁷	TS ELISA	Pregnant women	F	<20–>34	961	27
				<20		24
				20–24		17
				25–29		27
				30–34		28
				>34		35
Oslo (1991–1992) ⁶⁸	TS indirect blocking ELISA	Random sample	F	32 (20–44)	216	25

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; F, female. Adapted from Smith JS *et al.*¹⁰

seropositivity was significantly associated with age and ethnicity, and HSV-2 seropositivity was more prevalent in females and related to sexual lifestyle variables. A study in Groningen among STD attendees found a lower HSV-2 seroprevalence (22%) in 1998 using a different type-specific enzyme-linked immunosorbent assay (ELISA).⁷⁴ Although the HSV-2 seroprevalence in the study in Groningen is similar to that reported for the same time period in Rotterdam, it does not necessarily support a decline as there may be geographical differences in HSV-2 prevalence.

Genital HSV infection was largely unrecognized by both physicians and patients in a study at the STD clinic in Rotterdam.⁶⁹ Over 80% of HSV-2 seropositive individuals did not have a history of genital herpes and 95% had no current clinical signs of infection.⁶⁹ Thus, non-serological methods, such as a reported history of genital herpes or clinical diagnoses, are revealed to be poor predictors of HSV infection – findings that have also been reported elsewhere.⁴⁵

Prevalence of HSV-2 Infection in Switzerland

In a Swiss study of non-high-risk patients (Table 6), HSV-2 seroprevalence was 14.6% for women ($n=89$) and 8.1% for men ($n=62$).⁷⁵ The study was conducted in 1997 and involved 151 adult volunteers from the region of Basel. They had no history of genital herpes or any other STD, and 87% were between 20 and 49 years of age.

The annual seroconversion rate was estimated to be 0.61% (95% CI: 0.14–1.4) for women and 0.49% (95% CI: 0.09–1.4) for men. This is lower than that estimated in other studies.^{25,41,50–52} The survey took place after the widespread promotion of safer sex and condoms but, as the study was not longitudinal, it is not possible to assess the impact of this educational initiative nor to attribute the lower annual incidence of HSV-2 infection in Switzerland to this initiative. In a large

Table 5: Prevalence of HSV-2 infection among high-risk populations in The Netherlands¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Amsterdam (1995–1997) ⁷¹	TS immunoblot (Chiron)	Homosexual men	M	26 (23–28)	300	19
Amsterdam (1986–1988) ⁶⁹	TS monoclonal antibody blocking ELISA	Heterosexual STD clinic attendees	F/M	<20–≥45	580/883	43/24 30~/4.0~ 21~/13~ 39~/18~ 53~/27~ 67~/33~ 56~/37~
		Homosexual STD clinic attendees	M	<20–≥45 <24 25–29 30–34 35–44 ≥45	215	41 33~ 26~ 58~ 51~ 55~
Amsterdam (1984) ⁷²	TS ELISA	Homosexual men	M	35	107	49
Rotterdam (1998) ⁷³	TS HSV ELISA (Gull)	STD clinic attendees	F+M	13–71	653	22
				13–24	209	8.0
				25–29	140	25
				30–34	102	26
				35–39	78	31
		40–71	124	31		
Females	F	27 (13–60)	292	27		
Heterosexual males	M	31 (16–71)	307	18		
Homosexual males	M	31 (18–60)	55	15		

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; ~, estimated from graph or table or age range inferred from text; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

Table 6: Prevalence of HSV-2 infection among non-high-risk populations in Switzerland¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Basel (1997) ⁷⁵	TS ELISA (SmithKline Beecham)	Adult volunteers from population with no history of STDs	F/M	20–29	39/27	5.1/3.7
				30–≥50	50/35	22/11

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

population-based sample in Switzerland, 18.9% (588/3110) of individuals were HSV-2 seropositive, while the prevalence of HSV-1 seropositivity was 80.5%.⁷⁶ As in other studies, HSV-2 infection was associated with female sex (adjusted OR 1.26; $P=0.017$) and with various indirect indicators of sexual activity or STD risk (e.g. marital status, with those being divorced (adjusted OR, 2.04; $P<0.001$) or divorced/separated (OR, 1.9; $P=0.004$) being at higher risk of infection than married or single persons). There was a negative association of HSV-2 infection with HSV-1 seropositivity (OR 0.71, $P=0.046$).

Prevalence of HSV-2 Infection in France

A national serological survey found an overall HSV-2 seroprevalence of 17.2% among older adults from the general French population (Table 7).⁷⁷ The prevalence of HSV-2 infection was higher in females than males (17.9% versus 13.7%, respectively; $P<0.001$). There was a slight but not significant increase in HSV-2 seroprevalence with age, which may be because the samples were taken from individuals who were 35 years of age or older. In the NHANES III survey, HSV-2 seroprevalence remained stable in people aged over

Table 7: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in France¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
National (1996) ⁷⁷	Gull HSV gG-EIA	Randomly selected from cancer and cardiovascular disease study	M/F	35–40	2934/1478	13.7/17.9
				41–45		-/15.7
				46–50		-/18.8
				51–55		12.5/18.1
				≥55		14.2/17.0
Paris (1994) ⁷⁸	TS gG2 EIA (SmithKline Beecham Biologicals)	STD clinic attendees	M/F	31/37	223/264	45/67
				18–24		53
				25–34		66
				≥35		80

TS, type specific; HSV-2, herpes simplex virus type 2; gG, glycoprotein G; EIA, enzyme immunoassays; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

30 years.⁸ Thus, this suggests that HSV-2 infection is largely acquired in the first three decades of life.

The prevalence of HSV-2 antibodies was higher in people living alone (single, widowed, separated or divorced) compared with those who were married (>20% versus 15%; $P < 0.001$). While other studies confirm a higher HSV-2 seroprevalence in widowed, separated and divorced people, they reported a lower seroprevalence in single individuals than in those who were married.^{8,79} Once again, this discrepancy can be explained by the age structure of the population surveyed, as older individuals would have had a greater mean lifetime sexual activity than younger persons, thereby lessening the effect of domiciliary status. The HSV-2 prevalence was higher in the south of France and in Paris. This disparity with the rest of France could be due to variations in sexual behaviour, which could, in turn, be related to cultural diversity and/or the level of urbanization.

In common with studies in other countries, a study in Paris documented that HSV-2 seroprevalence was higher among STD clinic attendees than in the general population (Tables 7 and 8).⁷⁸ Of 487 patients attending an STD clinic, 55% were HSV-2 seropositive (44.7% of men and 67.3% of women). A number of factors were predictive of HSV-2 seropositivity in this study (Table 8). As in other studies,^{8,24,31,40,79} age and gender were predictors of HSV-2 infection. The importance of country of origin as a predictive factor in this French study should be confirmed in future studies but is supported by studies in the developing world, which show a high HSV-2 seroprevalence. However, there was no correlation between sexual behaviour (i.e. number of sexual partners in the previous 6 months, age at first intercourse, condom use or previous STDs) and the probability of HSV-2 seropositivity. This may be because the population had a high background prevalence of STIs or because the population sampled differed from that in other surveys.

Prevalence of HSV-2 Infection in Germany

Three studies have looked at HSV-2 seroprevalence in Germany (Table 9). A serological survey analysed 2999 samples collected from pregnant women from Stuttgart over three time periods and found no change in HSV-2 seropositivity: 8.3% (34/408) in 1988–1989; 6.3% (37/592) in 1990–1991; and 8.9% (179/1999) in 1996–1997.⁸⁰ In another German study, HSV-2 seroprevalence was 15.1% among females aged 20–29 years but this higher prevalence must be interpreted in the context of differing backgrounds and

serological testing.⁸¹ The HSV-2 seroprevalence in this population was also much lower than that in pregnant women in Scandinavia and the USA.^{51,61,62}

The same authors also determined the prevalence of HSV-2 antibodies in sera submitted for routine diagnostics in 1996–1997. HSV-2 antibodies were detected in 4.5% of newborn sera; these are likely to be of maternal origin as HSV-2 antibody was absent in children aged 6–9 years. HSV-2 infection largely occurred with the onset of sexual activity; the seroprevalence in men and women aged 15–40 years was 8.8% and 10%, respectively. The similar HSV-2 prevalence in the genders ($P = 0.91$) contrasts with the higher prevalence of HSV-2 infection in women than men in another study in Germany⁸¹ and to studies in other countries. In this study the seroprevalence of HSV-2 was determined in blood donors, hospital patients and HIV-seropositive individuals.⁸¹ The prevalence of HSV-2 antibodies was higher in HIV-seropositive individuals than among hospital patients and blood donors. Consistent with other studies, serological evidence of HSV-2 infection was more common in HIV-infected individuals than among non-high-risk groups.^{82,83} HSV-2 seroprevalence was higher among German blood donors than British donors (14.9% versus 7.5%, respectively), although such comparisons should be made cautiously because of the likely differences between the populations; blood donors in one country do not necessarily share characteristics with those from another, even though each may be considered somewhat representative of a general population.

Antibodies to HSV-2 were strongly associated with increasing age. Among blood donors and hospital patients (considered to be ‘non-high-risk’), HSV-2

Table 8: Factors predictive of HSV-2 seropositivity in Paris, France⁷⁸

Factor	OR
Female	3.37
Age	1.04
Country of origin:	
Central Africa	3.52
North Africa	1.36
History of genital herpes	10.97
Hepatitis B virus markers	1.92
Hepatitis C virus markers	3.96

OR, odds ratio. Reproduced from Javier M *et al.*⁷⁸

Table 9: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Germany¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Urban and rural area from non-specified district (1996–1997) ⁸¹	Screened with TS ELISA (Gull) and immunoblot; equivocal ELISA or positive immunoblot confirmed with in-house Western blot	Blood donors and hospital patients	F/M	1–≥70	2591/2467	15/11
				1–5		2.0~/1.0~
				6–11		4.0~/1.0~
				12–16		7.0~/7.0~
				17–19		5.0~/5.0~
				20–29		15~/10~
				30–39		21~/13~
				40–49		19~/13~
				50–59		21~/15~
				60–69		25~/28~
≥70	25~/28~					
Stuttgart (1996–1997) ⁸⁰	TS EIA (Cobas)	Routine diagnosis of:				
		Women	F	15–40	797	10
		Men	M	15–40	68	8.8
		Children	F/M	6–9	31	0.0
High-risk populations						
One district (1996–1997) ⁸¹	TS ELISA (Gull); immunoblot with in-house Western blot	HIV-infected individuals	F/M	20–39	110/272	66/40

TS, type specific; HSV-2, herpes simplex virus type 2; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ~, estimated from graph or table or age range inferred from text; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

seroprevalence increased from a low level before the onset of sexual activity to the highest level in the third decade of life. For HIV-positive individuals, the HSV-2 seroprevalence rate increased with age but was significantly higher than among the non-high-risk group; the highest HSV-2 seroprevalence was 71.4% in women 30–39 years of age. These age distributions are consistent with the acquisition of HSV-2 subsequent to sexual debut.

Prevalence of HSV-2 Infection in Italy

Several HSV-2 seroprevalence studies have been undertaken in Italy (Table 10). A study among various non-high-risk populations in Rome recorded an overall HSV-2 seroprevalence of 5.5%.⁸⁴ The seroprevalence of HSV-2 was similar among men (4.9%) and women (6.7%), and there was no increase in the prevalence of HSV-2 infection with age. The highest prevalence of HSV-2 seropositivity in any of the groups tested was 7.6%, in pregnant women. This figure is similar to the 8.4% seroprevalence reported in a similar setting in northern Italy in samples collected before 1990.⁵¹ The HSV-2 seroprevalence of 3.8% among military recruits was much higher than the 0.086% seroprevalence recorded in another study among Italian military recruits that used blood samples drawn in 1981.⁸⁵ However, the two studies used different serological tests and the older test may have had a lower sensitivity.

In contrast to the relatively low HSV-2 seroprevalence in groups representative of the general population (i.e. military recruits, vaccinees, blood donors and pregnant women), the prevalence of HSV-2 infection was much higher in Italian STD clinic attendees.⁸⁸ The HSV-2 seroprevalence was 24.6% among 919 patients attending an STD clinic in northern

Italy, and HSV-2 infection was equally prevalent in men (24.5%) and women (24.8%). However, in common with other serological surveys, seroprevalence increased with age, ranging from 14.2% among those aged 25 years or younger to 37.5% among those older than 35 years of age. There was also an increase in seroprevalence with the number of sexual partners in the last year. The prevalence of HSV-2 infection in the Italian STD clinic attendees is lower than that reported in an earlier study, in which 69.0% (109/158) of men who have sex with men (MSM) and 35.0% (274/783) of heterosexual men were HSV-2 seropositive but, again, this may be due to differences in performance of the tests used.⁸⁹ It is also lower than that in STD clinic attendees in the USA⁹⁰ and Australia,⁴² but similar to that reported in the UK⁷⁹ and New Zealand.⁹¹

Prevalence of HSV-2 Infection in Spain

Since 1985, four HSV seroprevalence studies have been carried out in non-high-risk populations, and one in a high-risk population (Table 11). The HSV-2 seroprevalence in the Spanish general population was reported to be 3.6%⁹² using samples from a study on heart disease, which was designed to be a representative cross-sectional survey of the Spanish population. In total, 3974 sera from individuals aged 5–59 years were assayed. The prevalence of HSV-2 antibodies was similar in males and females (3.7% versus 3.6%, respectively). There was no significant difference between age groups with respect to HSV-2 seroprevalence. Children aged 5–12 years of age had a similar seroprevalence (4.1%) to the other age groups, which the authors of the study suggested was due to acquisition of HSV-2 during the perinatal period.⁹² They further suggested that, because age-specific seroprevalence remains stable, HSV-2 is not circulating

Table 10: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Italy¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
National (1981) ^{85,86}	TS ELISA	Male military draftees	M	18–25	1169	0.1
Central Italy (1985) ^{85,86}	TS ELISA	Health personnel	F/M	30 (16–64)	246/165	4.8
Naples (1988) ⁸⁷	TS ELISA	Patients in hepatitis B immunization centre	F/M	26 (18–42)	86/2	1.1
High-risk populations						
Northern Italy (1997–1998) ⁸⁸	TS ELISA (Gull/Meridian)	STD clinic attendees	F	27 (16–65)	258	25
			M	32 (18–75)	661	25
			F/M	≤25		11/16~
				26–35		27/20~
			>35			50/35~
Naples (1988) ⁸⁷	TS ELISA	Drug addicts	F/M	26 (18–42)	88	9.1
Rome (1984) ⁸⁵	TS ELISA	Homosexuals	M	30 (20–50)	397	55
Rome (1986) ⁸⁹	TS ELISA	STD clinic attendees	F/M	18–≥53	941	41
		Heterosexual STD clinic attendees		18–≥53	783	35
				18–27	302	25
		Homosexual STD clinic attendees		28–42	302	35
				43–52	97	42
			≥53	82	62	
			18–≥53	158	69	
	18–27	41	51			
	28–42	82	71			
	43–≥53	35	86			

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; ~, estimated from graph or table or age range inferred from text; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

among the general population but is restricted to populations at high risk of virus transmission.

A similar overall HSV-2 seroprevalence of 3.5% was documented for pregnant women in the autonomous region of Madrid.⁹⁴ However, the HSV-2 seroprevalence in pregnant women from Madrid aged 15–24 years was 1.7%, which was lower than the 3.1–3.4% reported for women of similar age in the Spanish general population study. Unlike the cross-sectional survey of the Spanish population,⁹² the study in pregnant women found that the prevalence of HSV-2 antibodies increased with age.⁹⁴ In this respect, this sexually active population is similar to populations in the USA and other parts of Europe for which HSV-2 seroprevalence increases with age.^{8,79,97} This difference between the studies may be real or an artefact due to differing performance of the tests used, but, nevertheless, the study of pregnant women suggests that HSV-2 is being transmitted sexually in the general population.

The HSV-2 seroprevalences in these two studies were lower than those reported in studies in Spain published from 1987 to 1994.^{51,92,94,98} The seroprevalence rates in the earlier studies varied according to the population studied and the serological test used: 10% and 7% in pregnant women and their partners from Seville using a purified gG-2 ELISA,⁵¹ 9% in pregnant women from Madrid using an ELISA with a whole cell lysate as antigen;⁹² and 11–12% in women who were controls in a study on the relationship between cervical cancer and

STIs.⁹⁸ The higher prevalence of HSV-2 infection in the earlier studies may be attributable to the lower specificity of the tests used, which would have overestimated the cases of HSV-2 infection.⁹⁴

Among 374 STD clinic attendees in Madrid, Gijon and Malaga, 25% were seropositive for HSV-2.⁹⁶ More women than men were HSV-2 seropositive (30% versus 12%, respectively, $P < 0.001$) and the risk of being HSV-2 seropositive was related to the number of sexual partners in the last 5 years. As in other studies, only a minority of patients (30% in this study) reported a history of genital herpes; in a study published in 1990 among STD clinic attendees in Seville, HSV-2 seroprevalence was 13% in men and 30% in women.⁵¹ Therefore, the HSV-2 seroprevalence is higher among those who have more risk factors for HSV-2 infection, which suggests that HSV-2 is circulating in Spain via sexual transmission. The study also followed a prospective cohort of HSV-2 seronegative individuals for 6–18 months. It recorded a 4% annual rate of seroconversion but this figure should be considered cautiously as the characteristics of the population did not remain constant during the follow-up period.

Prevalence of HSV-2 Infection in the UK

Prevalence studies of HSV-2 infection are outlined in Table 12. In the only serological survey conducted to date in the general population of England and Wales,

Table 11. Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Spain¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Eight regions (1992–1993) ⁹²	TS indirect EIA	Representative sample of eight geographical regions	F/M	5–59	2052/1922	3.6/3.6
				5–12	306/328	2.6/5.5
				13–19	350/332	3.4/3.9
				20–29	422/372	3.6/2.7
				30–39	338/326	2.7/1.5
				40–49	329/302	3.0/4.0
				50–59	307/262	6.2/4.6
Barcelona (1985–1987) ⁹³	TS ELISA (gC2)	Random sample from general population	F	36	242	11
				53	238	12
Autonomous region of Madrid (1993–1994) ⁹⁴	TS recombinant ELISA (Biokit)	Population-based sample	F	15–45	692	3.5
				15–24	303	1.7
				25–34	239	4.2
				35–45	150	6.0
Madrid (1993) ⁹⁵	ELISA (Menarini Diagnostics)	Representative sample of adolescents	F/M	15 (14–17)	1191	4.8
High-risk populations						
Gijón, Madrid, Málaga (1996–1997) ⁹⁶	TS indirect ELISA (Captia Select, Centocor) with Western blot confirmation of positive and equivocal sera	STD clinic attendees	F/M	32 (18–65)	245/129	30/12

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

antibodies to HSV-2 were found in 3.3% of men and 5.1% of women ($P=0.009$).⁹⁹ The sera were collected from 4930 individuals aged 0–69 years between January 1994 and June 1995, and from 500 children aged 10–14 years between November 1986 and December 1987. Ninety-eight per cent of the samples were collected from outside London. In common with other studies, the prevalence of HSV-2 antibodies increased with age (i.e. in males aged 16–60 years [$P=0.006$] and in females aged 16–40 years [$P=0.011$]).

A study among 1347 blood donors in London, found an overall seroprevalence of 7.6%, with a higher seroprevalence among women (12.4%) than men (3.2%).¹⁰⁰ Although blood donors are not truly representative of the general population, they may serve as a guide. In this respect, the seroprevalence among male blood donors¹⁰⁰ is similar to that of men in the general population but the seroprevalence among female blood donors was twice that reported for the general population.⁹⁹ However, direct comparison of the data may not be appropriate because of the different age structures in the two studies. Moreover, the samples collected in the general population survey did not include any from adults in London. As is the case for other STDs, the prevalence of HSV-2 infection may be higher in London than the rest of England and Wales.

The prevalence of HSV-2 antibodies is also high among sexually active adults in urban centres outside London.^{100,101} In an STD clinic in Trafford, Manchester, the HSV-2 seroprevalence among attendees was 14.3%, which comprised 9.9% (24/242) men and 18.7%

(46/246) women.¹⁰¹ In a study among attendees at in STD clinic in London, 17.3% (51/294) of men and 24.5% (85/347) of women were HSV-2 seropositive.¹⁰⁰ In Middlesborough, the HSV-2 seroprevalence among 198 women attending an antenatal class was 8.1%, while it was 21.6% among 269 women attending an STD clinic.¹⁰² In both groups, there was a significant effect of increasing age on HSV-2 seropositivity; the OR was 1.94 (95% CI, 1.32–2.86) for prevalence for each decade increase in age.

Taken together, these studies suggest that the overall prevalence of HSV-2 infection is much lower in England and Wales than in the USA. Yet despite this difference in absolute prevalence, the epidemiology of the disease is similar in that women have a higher prevalence of infection than men, and HSV-2 seroprevalence increases with age.

Prevalence of HSV-2 Infection in New Zealand

HSV-2 seroprevalence increased with age in a cohort of individuals followed as part of a multidisciplinary study in Dunedin (Table 13).¹⁰⁵ The seroprevalence among the 1037 people in the cohort at age 21 years (in 1993–1994) was 3.4% (4.3% in women and 2.7% in men). Of the 869 specimens collected when the subjects were 26 years old, 11% had antibodies for HSV-2, and the HSV-2 seroprevalence was higher among women than men (15.3% versus 7.1%; $P<0.001$). Among those known to be seronegative at age 21 years, the annual

Table 12: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in the UK¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)			
Non-high-risk populations									
England and Wales (2% from London) (1994–1995) ⁹⁹	TS monoclonal antibody blocking ELISA	Immuno-competent	F/M	16–69	3347	5.1/3.3			
				16–19		3.0~/2.0~			
				20–24		4.0~/1.4~			
				25–29		6.6~/4.7~			
				30–34		6.2~/3.3~			
				35–39		8.3~/3.0~			
				40–49		3.2~/4.2~			
				50–59		4.9~/7.2~			
60–69		4.6~/1.3~							
National sample (1984–1988) ¹⁰³	TS ELISA	Controls from cervical cancer study	F	20–44	387	4.7			
				20–29	50	4.0			
				30–34	113	3.5			
				35–39	155	6.5			
				40–44	69	2.9			
Central London (1992) ⁷⁹	Modified Western blot	Blood donors	F/M	30/36 (18–68)	639/708	12.4/3.2			
				18–25		3.0~/2.0~			
				26–30		10~/2.0~			
				31–35		17~/4.0~			
				36–40		20~/7.0~			
				41–45		25~/7.0~			
				46–50		16~/4.0~			
				50–55		16~/2.0~			
				56–60		12~/3.0~			
				61–68		0.0~/0.0~			
London (1981–1982) ¹⁰⁴	ELISA for total HSV antibodies, positives confirmed with TS ELISA	Antenatal patients	F	<20–≥35	3533	10			
				<20	545	4.4			
				20–24	1240	9.5			
				25–29	1027	11			
				30–34	515	14			
				≥35	202	19			
High-risk populations									
Central London (1992) ⁷⁹	Modified Western blot	Heterosexual STD clinic attendees	F M F/M	25 (17–68)	347	25			
				29 (17–69)	294	17			
				17–25		17/0.0~			
				26–30		26/17~			
				31–35		40/27~			
				36–40		36/35~			
				41–45		50/20~			
				46–68/9		–/35~			
				Modified Western blot	Homosexual STD clinic attendees	M	29 (19–69)	192	27
							<25		11
	26–30		15						
					31–35		43		
					36–40		41		
				41–45		52			
				46–69		61			

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; ~, estimated from graph or table or age range inferred from text; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

seroconversion rate was 13.5 cases per 1000, compared with 8.1 cases per 1000 per sexually active year before the age of 21. This increase is not attributable to a higher rate of partner change with age, as the average rate of partner change was lower after the age of 21 years, and was only modestly increased in those who acquired new infections between 21 and 26 years of age. The rise in infection with age may be because partner selection plays a greater role in determining HSV-2 risk than the

number of partners. Alternatively, the force of infection may differ, with the prevalence of HSV-2 infection in the potential partner pool being higher in later life.

The prevalence of HSV-2 antibodies among 300 attendees from four STD clinics in New Zealand was 25.7% (Table 13), which falls within the seroprevalence range reported for STD clinic attendees in other countries.⁹¹ The seroprevalence increased with age up to age 50 years but no specific differences were found for

Table 13: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in New Zealand¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Dunedin (1993–1994) ¹⁰⁶	TS ELISA with Western blot confirmation of positive sera	General population cohort	F/M	21/21	372/407	4.3/2.7
High-risk populations						
Auckland, Christchurch (1991–1992) ⁹¹	Indirect TS ELISA, equivocal typed by Western blot	STD clinic patients	F/M	<20–≥50 <20 20–29 30–39 40–≥50	123/171 63 151 53 27	30/22 14 20 43 50

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

gender or ethnic group (European, Maori or Pacific Island origin). There were significant differences in the prevalence of HSV-2 antibodies from one of the four clinics, which underscores the importance of considering the characteristics of the population studied before assuming the finding is representative of another group.

Prevalence of HSV-2 Infection in Australia

Key findings of Australian HSV-2 seroprevalence studies are outlined in Table 14. The HSV-2 seroprevalence among pregnant women attending antenatal classes in Sydney lies within the range reported for pregnant women in other countries. Overall, 14.5% of 229 women were positive for HSV-2 antibodies.⁴² HSV-2 seroprevalence increased with age, peaking at approximately 30 years.

The seroprevalence of HSV-2 infection was high in homosexual Australian men, with HSV-2 antibodies being prevalent in nearly twice as many HIV-positive men as HIV-negative men (60.9% versus 27.8%; $P < 0.0001$).¹⁰⁷ The HIV-positive men were slightly older (39 versus 36 years; $P = 0.00125$) and also had a higher number of lifetime sexual partners (633 versus 271; $P < 0.0001$). A similarly high HSV-2 seroprevalence (64.7%) was found among 300 heterosexual male patients at an STD clinic in Sydney.¹⁰⁸ This is one of the highest prevalences of HSV-2 infection recorded in heterosexual men in the developed world. In a contemporaneous survey, also among STD clinic attendees in Sydney, the prevalence of HSV-2 antibodies in men was 35% and 55% in women, with an overall seroprevalence of 40%.⁴²

HSV-2 seroprevalences similar to those reported in the study by Cunningham *et al.*⁴² were noted in a serological survey of prisoners from 27 correctional centres across New South Wales. The prevalence of HSV-2 antibodies was 58.3% (77/132) in women, which was higher than in males (21.0%; 138/657).¹¹⁰ HSV-2 prevalence increased with the number of sexual partners. The presence of HSV-2 antibodies was associated with increasing age and aboriginality for men, and a higher reported number of lifetime sexual partners and the presence of hepatitis C antibodies for women.

Prevalence of HSV-2 Infection in Japan

In Japan, HSV-2 seroprevalence was lowest among pregnant women in Tokyo (7%) and highest among

female commercial sex workers in the Osaka area (80%) (Table 15).¹¹¹ The seroprevalence among blood donors, who are often considered to be representative of the general population, was low (0% in women and 2% in men; aged 38.2 ± 9.8 years and 38.8 ± 11.9 years, respectively). However, it is difficult to draw conclusions about the overall prevalence of HSV-2 in Japan because of the different populations sampled. For example, the seroprevalence was higher among pregnant women in Kagoshima (17%) than in pregnant women in Tokyo (7%), despite similar mean ages (29.1 ± 4.1 versus 29.9 ± 4.6 years). In another representative group of healthy women (mean age 48.7 years) attending a clinic in Osaka for regular health checks, 15% of subjects were HSV-2 seropositive.

Clinical Presentation of Genital HSV Infection

A common feature of many of the seroepidemiological studies is that only a minority of patients had ever received a diagnosis of genital herpes. Generally, less than one-fifth of HSV-2 seropositive participants in the surveys had ever received such a diagnosis.¹¹³ Another important factor in this underdiagnosis is the prevalence of atypical lesions. In a study among STD clinic attendees, only two-thirds of women with positive HSV cultures had typical external herpes lesions. In the remaining patients, HSV was isolated from atypical lesions or in the absence of signs and symptoms. This under-recognition is likely contributing to the spread of genital HSV infection.

Genital HSV-1 Infection

- Studies of genital ulcers should use polymerase chain reaction (PCR) as studies consistently show increased sensitivity over HSV culture (research need recommendation)

The rates of HSV-2 infection in the general US population and in many populations in Europe are substantial but are likely to be underestimates of the true prevalence of genital herpes. Seroepidemiological studies that use HSV-2 infection as a surrogate for genital herpes do not quantify the contribution of genital HSV-1 infection. The prevalence of genital HSV-1 infection is increasing in many countries, a change that has implications not only for the epidemiology of the disease but also for management.

Table 14: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Australia¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	<i>n</i>	HSV-2 prevalence (%)
Non-high-risk populations						
Sydney (1995–1998) ¹⁰⁹	TS ELISA	Antenatal patients	F	28	2616	13
Sydney (pre-1992) ⁴²	TS immunodot enzyme assay	Antenatal clinic attendees	F	<20–≥30	229	15
				<20	20	5.0
				20–29	130	16
				≥30	46	17
High-risk populations						
New South Wales (1996) ¹¹⁰	TS indirect immunoassay	Prisoners	F/M	33/34	132/657	58/21
Sydney (1990–1991) ¹⁰⁸	Screen with total HSV antibody by complement fixation, positives tested with indirect IgG EIA with Western blot confirmation	Heterosexual male STD clinic attendees	M	31 (18–69)	300	65
Sydney (pre-1992) ⁴²	Immunodot or indirect ELISA assay	STD clinic attendees	F	32 (<20–≥40)	107	40
				<20–29	66	32
				30–39	24	54
				≥40	17	53

TS, type specific; HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; IgG, immunoglobulin G; EIA, enzyme immunoassay; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

Table 15: Prevalence of HSV-2 infection among non-high-risk and high-risk populations in Japan¹⁰

	Test methodology	Population group	Sex	Mean or median age (range)	<i>n</i>	HSV-2 prevalence (%)
Non-high-risk populations						
Central Japan (1993) ¹¹²	TS gG-capture ELISA	Random population sample in rural towns	F/M	20–49	158/105	1.2/1.8
				20–29	63/30	0.0/2.2
				30–39	54/30	3.6/0.0
				40–49	41/45	0.0/3.3
Kagoshima (1985–1989) ¹¹¹	TS immunodot	Pregnant women	F	29	200	17
Nagoya (1985–1989) ¹¹¹		Blood donors	M	39 (20–59)	41	2.4
				20–39	21	0.0
				40–59	20	5.0
Osaka (1985–1989) ¹¹¹		Women having routine health check	F	49	56	15
Tokyo (1985–1989) ¹¹¹		Pregnant women	F	30	90	6.7
High-risk populations						
Japan, Nagoya area (1985–1989) ¹¹¹	TS immunodot	Homosexuals	M	41 (<20–≥60)	34	24
Japan, Osaka area (1985–1989) ¹¹¹	TS immunodot	CSWs	F	35	70	80
		STD patients	M	45 (<20–≥60)	26	23

TS, type specific; HSV-2, herpes simplex virus type 2; gG, glycoprotein G; ELISA, enzyme-linked immunosorbent assay; CSWs, commercial sex workers; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*¹⁰

SEROPREVALENCE OF HSV-1 INFECTION

In many developing countries, HSV-1 infection is ubiquitous, with as many as 90% of individuals being HSV-1 seropositive by the fourth decade of life. However, there appears to be a decline in the age-specific seroprevalence of HSV-1 infection in industrialized countries. In The Netherlands, HSV prevalence was compared for blood samples drawn from STD clinic patients in 1986 and in 1993–1994.⁷³ The seroprevalence of HSV-1 and HSV-2 decreased by 9% and 8%, respectively ($P < 0.001$). This may reflect a true difference, which may be attributable to the effect of HIV awareness, or could be an artefact due to sampling separate cohorts with different demographic or sexual behaviour variables. In the UK, the prevalence of antibodies to HSV-1 in 10–14 year olds declined from 34% in samples collected in 1986–1987 to 24% in samples collected in 1994–1995 ($P < 0.001$).⁹⁹ Other studies that looked at the prevalence at one time point recorded low age-specific prevalences of HSV-1 infection. In one US study, only 37.2% of first-year college students in 1983 were HSV-1 seropositive.⁴¹ In the UK during the early 1990s, only 44% of blood donors and 59.5% of STD clinic attendees were HSV-1 seropositive.¹⁰⁰

The change in the epidemiology of HSV-1 infection is likely to be due to an improvement in socio-economic conditions. A corollary of the lowering in age-specific rates of infection is that the number of adults susceptible to HSV-1 will increase, many of whom will acquire HSV-1 genitally. Population studies in the USA have found higher rates of HSV-1 infection in black and Hispanic populations than in whites⁸³ but genital HSV-1 infection was four times more prevalent in whites than non-whites among STD clinic attendees in Seattle.¹¹⁴ This finding is consistent with the hypothesis that the low prevalence of genital HSV-1 infection in ethnic minorities in the USA may reflect high levels of acquisition of orofacial HSV-1 infection in childhood.

In the UK, over an 8-year study period, the prevalence of HSV-1 antibodies in cohorts born in 1972–1976 increased from 34% (in 1986–1987) to 41% (in 1994–1995), suggesting that the annual incidence of infection in susceptible adolescents and young adults is 1.3%.⁹⁹ Above the age of 15 years, the prevalence continued to increase, indicating continued transmission among adolescents and adults. The study only reported HSV-2 seroprevalence from samples collected in 1994–1995; HSV-2 antibody was detected in sera from 3.3% of men and 5.1% of women.⁹⁹ A study initiated in 1993 of the efficacy of an HSV-2 glycoprotein subunit vaccine also determined HSV-1 seroconversion rates. In the study, the rate of HSV-1 serological conversion was 1.6 cases per 100 person-years.⁵² The rate of symptomatic genital HSV-1 infection was 0.5 cases per 100 person-years, which was the same as the acquisition rate for oropharyngeal infection.⁵² In comparison, the acquisition rate of HSV-2 infection was higher, at 5.1 cases per 100 person-years.⁵²

CHANGING EPIDEMIOLOGY OF GENITAL HSV-1 INFECTION

USA: HSV-1 is an increasingly important cause of genital herpes in the USA. At a medical centre in Kentucky, 4498 samples collected between 1994 and 1999 were typed for HSV-1 and HSV-2.¹¹⁵ The majority of HSV-2 isolates (91.8%; 437/476) were from anogenital sites, whereas only 36.0% (191/530) of HSV-1 cultures were from this source. Although HSV-2 remained the predominant HSV type isolated from genital specimens, there was an overall increase in the proportion of HSV-1 culture-positive infections with time. In common with other studies, the proportion of cases of genital HSV-1 infection was greater in women than men; for example, in 1999, 43% of female genital isolates and 30% of male genital isolates were HSV-1.

Of 1145 STD clinic patients in Seattle diagnosed with

genital herpes between 1993 and 1997, 17.1% had HSV isolated from their genital ulcer disease (GUD).¹¹⁴ Among those with initial episodes of genital herpes, HSV-1 was isolated more frequently from MSM (46.9%) than from women (21.4%), and was less common among heterosexual men (14.6%). Only 9.9% of isolates from recurrent infections were typed as HSV-1. In the study, there was a positive association between receptive oral sex and a negative association with vaginal sex, suggesting that the partner's mouth, rather than the genital areas, was a source of HSV-1 infection.¹¹⁴

UK: In a study conducted in a genitourinary medicine clinic in Durham, there was a higher proportion of cases of primary genital herpes due to HSV-1 than attributed to HSV-2. In 75% (9/12) of men and 67.6% (25/37) of women, HSV-1 was isolated from primary episodes. A high prevalence of first episode genital HSV-1 infection (71%) was also recorded among patients attending a genitourinary medical (GUM) clinic in Kirkcaldy.¹¹⁶ The proportion of first episode genital herpes due to HSV-1 is increasing in the UK. Among GUM clinic attendees in Scotland, the proportion of cases of genital herpes increased from 20% in 1978 to 41% in 1991.¹¹⁷ At another Scottish GUM clinic, there was a progressive increase in the proportion of HSV-1 first episodes among women from 65% (13/20) in 1995–1996 to 88.2% (15/17) in 1998–1999.¹¹⁶

Northern Ireland: A recent retrospective study analysed laboratory records from six GUM departments over 80 months for recurrent GUD associated with HSV.¹¹⁸ Recurrent infection was considered to be confirmed when HSV was recovered from two or more separate episodes of GUD, at least 12 weeks apart. Sixty-nine patients with recurrent genital herpes infection were identified. Recurrent HSV-1 disease was more common than recurrent HSV-2 disease in women (34 versus 10 cases, respectively) whereas recurrent HSV-2 infection was more common in men (one case of recurrent HSV-1 disease versus 24 cases of HSV-2 disease). The mean age at first diagnosis was 26 years for women and 39 years for men. The authors concluded that HSV-1 was the most common cause of recurrent genital ulceration in women in Northern Ireland, and that women were acquiring infections at an earlier age than men.

Sweden: Of 108 first episodes of genital herpes seen consecutively in a Swedish STD clinic from 1995 to 1999, 44.3% (43/97 typed cultures) of all episodes were due to HSV-1; of these, HSV-1 accounted for 63.5% (33/52) of true primary episodes and for 81.3% (13/16) of the first episodes in women.¹¹⁹ The study found a significant association between oral-genital sex and genital infection with HSV-1, and an association with a history of orofacial herpes. Patients with genital HSV-1 infection were younger (mean age: 27 years) compared with those with HSV-2 infection (31 years; $P = 0.016$), and women with primary HSV-1 infection were younger than men ($P = 0.012$).

Germany: In a study employing PCR, genital swabs were taken from 173 women (average age: 33 years) in a gynaecology surgery in Germany. A total of 26 women were HSV-DNA positive; 38.4% of these HSV-positive genital swabs were HSV-1 positive, while 42% were HSV-2 positive and 19% were not typed.¹²⁰ More patients with HSV-1 positive swabs had 'herpetic symptoms' (54%) than those with HSV-2 positive swabs (15%). As the study did not determine the type of episode, it could not be determined if the episodes of SV-1 shedding were associated with first episodes of the disease.⁵² Approximately two-thirds of newly acquired HSV-1 infections are symptomatic,⁵² which may explain the high proportion of symptomatic HSV-1 infections in the study.

A recent retrospective study in Germany performed virus culture on swab specimens obtained between 1996 and 2002 from 2678 HSV-seropositive patients. HSV-1 was isolated from 20% of genital lesions in men and 25% in women.¹²¹ The proportion of genital infection due to HSV-1 was lower compared with that reported in other studies, which may be attributable to the lower sensitivity of the assay used in this study.

Norway: In a retrospective study at an STD clinic in Bergen, Norway, the proportion of cases of genital herpes due to HSV-1 increased by 42% over a 10-year period.¹²² Primary genital HSV-1 disease increased from 36.0% (45/125) in samples collected from 1987 to 1989 to 50.7% (35/69) for samples collected between 1996 and 1998. The change in the proportion of first episodes of genital disease due to HSV-1 was most marked in women younger than 25 years of age in whom 50–90% of the primary cases were caused by HSV-1 in the 1990s as compared with 30–40% in 1987–1989. There were also more first episodes due to HSV-1 infection in women older than 30 years of age (16% in 1987–1989 to 29–30% in the 1990s) although the increase was not as great as in the younger women. Most cases of recurrent genital herpes were due to HSV-2 but the proportion of recurrences due to HSV-1 also increased from 6.3% (5/80) to 15.0% (21/140) of the total. Twice as many women experienced recurrences of HSV-1 compared with men and, consistent with the first episodes of the disease, the highest proportion of recurrent cases occurred in women aged 24 years or less (e.g. 37% of recurrences occurred in this age group in 1996–1998).

RELATIONSHIP BETWEEN ORAL-GENITAL CONTACT AND GENITAL HSV-1 INFECTION

Many studies document an association between oral-genital contact and genital HSV-1 infection, which suggests that the rise in prevalence of genital herpes due to HSV-1 results from a change in sexual behaviour.^{114,119} In a recent survey of college students in the USA, 59% indicated that they felt that oral-genital contact did not constitute 'having had sex'.¹²³ The benefit of limiting sexual activity to this type of contact may be the preservation of virginity. Other influences on its increased practice may be the perception that it is safe sex, despite the fact that the transmission of several STDs by this route has been documented.^{124,125} Another explanation for the increase in genital HSV-1 infection is that autoinoculation is responsible, but it is unclear how this could explain the observed epidemiology unless personal hygiene practices have changed considerably. Alternatively, if genital HSV-1 infection results mainly from genital contact, then the fall in the incidence of infection in childhood would increase the proportion of adults who are susceptible to genital HSV-1 infection and cause the incidence of genital infection to rise.

ASSESSING THE CONTRIBUTION OF GENITAL HSV-1 INFECTION TO THE OVERALL BURDEN OF GENITAL HERPES

As HSV-2 seroprevalence will not capture the contribution of HSV-1 infection to genital herpes, studies are needed to assess the increasing incidence of genital HSV-1 infection. HSV-1 seroprevalence cannot reflect the epidemiological pattern of genital infection as seropositivity is not solely due to infection at a genital site. Therefore, antigen detection tests (e.g. culture, PCR, ELISA) are required and surveys using these methods could be restricted to targeted populations or encompass the general population.

Conclusions

The prevalence of HSV-2 infection varies throughout the industrialized world. Given the limitations that are imposed on any comparison, HSV-2 seroprevalence is

higher among the general population in the USA than among nationally representative populations in Europe. There are marked variations in HSV-2 seroprevalence in Europe. In general, HSV-2 infection is more prevalent in northern Europe than in southern Europe. For example, in Scandinavia the prevalence of HSV-2 infection ranges from 15% to 35% in women aged 25–35 years. However, in the UK, the HSV-2 prevalence was consistently lower (4.7% among women aged 20–44 years in a national sample) than in other north European countries. In Spain, HSV-2 seroprevalence was low (2–6%) in men and women who were 14–17 years old or 15–45 years of age, although in a study in Barcelona, the seroprevalence among women aged 53 years was 12%. Similar low rates were reported in several studies in Italy (e.g. 0.1% in male draftees aged 18–25; 1.1% in patients with a median age of 26 years who attended a vaccination clinic; 4.8% in healthcare professionals with a median age of 26 years). In the Asia-Pacific region, HSV-2 seroprevalence appears to be lower in Japan (<7% in all age groups) than in Australia (e.g. 11–15% in antenatal patients).

- ◆ Prevention programmes should recognize that the seroprevalence of HSV-2 infection increases rapidly in early adult life (category 1 recommendation)

A number of trends emerge from the seroepidemiological surveys. In general, HSV-2 infection increases rapidly in young men and women (e.g. up to 30 years of age), which should be considered in the development of prevention programmes. In addition, the prevalence of HSV-2 infection is higher among populations with evidence of higher risk sexual behaviour. For example, STD clinic attendees have higher HSV-2 seroprevalences than age-matched non-high-risk groups, and men who have sex with men (MSM) have higher rates of HSV-2 infection than heterosexual men. Irrespective of population studied and geographical location, HSV-2 prevalence increases with age and HSV-2 antibody is found more commonly in women than men.

- ◆ Additional studies on the temporal changes in the incidence of HSV-2 infection are required (research need recommendation)

Data on trends in HSV-2 seroprevalence are extremely limited. When seroprevalence studies have been conducted at different times, HSV-2 seroprevalence has either increased (USA, Sweden), shown no clear trend (Sweden, Denmark) or decreased (Japan). The strongest evidence for a rise in the prevalence comes from the NHANES surveys from the USA. There has been a 30% increase in the overall seroprevalence of HSV-2 in the USA, from 16.4% in the late 1970s to 21.8% in a similar population sample in the early 1990s. This rise was most marked in young white men and women.

In the USA and other countries, HSV-1 is increasingly a cause of first episode genital herpes. The reasons for this change are uncertain but may include changes in oral-genital sexual behaviour and lowered age-specific HSV-1 infection. This change in the aetiology of genital herpes has implications for the management of genital herpes and for estimating the true burden of the disease.

The variations in tests used, methodology and populations sampled limits inter-study comparison. However, differences in the epidemiology of HSV-2 infection between countries may be partly due to variability in healthcare awareness and expectations, in patterns of health service utilization, diagnostic efforts, as well as true differences in prevalence and incidence. To achieve the objective of allowing direct comparison of populations within a country and to compare data between countries, there is a need for standardization of serological assays and of the demographics of the populations studied. Only standardized epidemiological surveys will contribute to a better

knowledge of the genital herpes epidemic and provide relevant information to promote efficient prevention strategies and prevention-oriented research.

Address for correspondence:
Dr Jean-Elie Malkin, Co-ordinator of FSTI,
25-27 rue d'Astorg, Paris 75008, France.

E-mail: jean-elie.malkin@esther.fr

Received for publication: 6 August 2003
Accepted for publication: 19 September 2003

REFERENCES

- Ashley R, Cent A, Maggs V, Nahmias A, Corey L. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus types 1 and 2. *Ann Intern Med* 1991;**115**: 520-526.
- Martins TB, Woolstenhulme RD, Jaskowski TD, Hill HR, Litwin CM. Comparison of four enzyme immunoassays with a western blot assay for the determination of type-specific antibodies to herpes simplex virus. *Am J Clin Pathol* 2001;**115**:272-277.
- Ashley RL. Sorting out the new HSV type specific antibody tests. *Sex Transm Infect* 2001;**77**:232-237.
- Lee FK, Pereira L, Griffin C, Reid E, Nahmias A. A novel glycoprotein for detection of herpes simplex virus type 1-specific antibodies. *J Virol Methods* 1986;**14**: 111-118.
- 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**:71-80.
- Ho DW, Field PR, Irving WL, Packham DR, Cunningham AL. Detection of immunoglobulin M antibodies to glycoprotein G-2 by western blot (immunoblot) for diagnosis of initial herpes simplex virus type 2 genital infections. *J Clin Microbiol* 1993;**31**: 3157-3164.
- Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. *N Engl J Med* 1989;**321**:7-12.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK *et al*. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;**337**: 1105-1111.
- Lee FK, Coleman RM, Pereira L, Bailey PD, Tatsuno M, Nahmias AJ. Detection of herpes simplex virus type 2-specific antibody with glycoprotein G. *J Clin Microbiol* 1985;**22**:641-644.
- 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-S28.
- Oliver L, Wald A, Kim M, Zeh J, Selke S, Ashley R *et al*. Seroprevalence of herpes simplex virus infections in a family medicine clinic. *Arch Fam Med* 1995;**4**: 228-232.
- Frenkel LM, Garratty EM, Shen JP, Wheeler N, Clark O, Bryson YJ. Clinical reactivation of herpes simplex virus type 2 infection in seropositive pregnant women with no history of genital herpes. *Ann Intern Med* 1993;**118**:414-418.
- Ruiz JD, Molitor F, McFarland W, Klausner J, Lemp G, Page-Shafer K *et al*. Prevalence of HIV infection, sexually transmitted diseases, and hepatitis and related risk behavior in young women living in low-income neighborhoods of northern California. *West J Med* 2000;**172**:368-373.
- Buchacz K, McFarland W, Hernandez M, Klausner JD, Page-Shafer K, Padian N *et al*. Prevalence and correlates of herpes simplex virus type 2 infection in a population-based survey of young women in low-income neighborhoods of Northern California. The Young Women's Survey Team. *Sex Transm Dis* 2000;**27**: 393-400.
- Bunnell RE, Dahlberg L, Rolfs R, Ransom R, Gershman K, Farshy C *et al*. High prevalence and incidence of sexually transmitted diseases in urban adolescent females despite moderate risk behaviors. *J Infect Dis* 1999;**180**:1624-1631.
- Becker TM, Wheeler CM, McGough NS, Parmenter CA, Jordan SW, Stidley CA *et al*. Sexually transmitted diseases and other risk factors for cervical dysplasia among southwestern Hispanic and non-Hispanic white women. *JAMA* 1994;**271**:1181-1188.
- Becker TM, Lee F, Daling JR, Nahmias AJ. Seroprevalence of and risk factors for antibodies to herpes simplex viruses, hepatitis B, and hepatitis C among southwestern Hispanic and non-Hispanic white women. *Sex Transm Dis* 1996;**23**: 138-144.
- Friedman SR, Curtis R, Jose B, Neaigus A, Zenilman J, Culpepper-Morgan J *et al*. Sex, drugs, and infections among youth. Parenterally and sexually transmitted diseases in a high-risk neighborhood. *Sex Transm Dis* 1997;**24**:322-326.
- Lewis LM, Bernstein DI, Rosenthal SL, Stanberry LR. Seroprevalence of herpes simplex virus-type 2 in African-American college women. *J Natl Med Assoc* 1999;**91**:210-212.
- Noell J, Rohde P, Ochs L, Yovanoff P, Alter MJ, Schmid S *et al*. Incidence and prevalence of chlamydia, herpes, and viral hepatitis in a homeless adolescent population. *Sex Transm Dis* 2001;**28**:4-10.
- Adler-Storthz K, Dreesman GR, Kaufman RH, Melnick JL, Adam E. A prospective study of herpes simplex virus infection in a defined population in Houston, Texas. *Am J Obstet Gynecol* 1985;**151**:582-586.
- Sucato G, Celum C, Dithmer D, Ashley R, Wald A. Demographic rather than behavioral risk factors predict herpes simplex virus type 2 infection in sexually active adolescents. *Pediatr Infect Dis J* 2001;**20**:422-426.
- Hitti J, Watts DH, Burchett SK, Schacker T, Selke S, Brown ZA *et al*. Herpes simplex virus seropositivity and reactivation at delivery among pregnant women infected with human immunodeficiency virus-1. *Am J Obstet Gynecol* 1997;**177**:450-454.
- Wald A, Koutsky L, Ashley RL, Corey L. Genital herpes in a primary care clinic. Demographic and sexual correlates of herpes simplex type 2 infections. *Sex Transm Dis* 1997;**24**:149-155.
- Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL *et al*. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997;**337**: 509-515.
- Koutsky LA, Ashley RL, Holmes KK, Stevens CE, Critchlow CW, Kiviat N *et al*. The frequency of unrecognized type 2 herpes simplex virus infection among women. Implications for the control of genital herpes. *Sex Transm Dis* 1990;**17**:90-94.
- Maden C, Beckmann AM, Thomas DB, McKnight B, Sherman KJ, Ashley RL *et al*. Human papillomaviruses, herpes simplex viruses, and the risk of oral cancer in men. *Am J Epidemiol* 1992;**135**: 1093-1102.
- Irwin KL, Edlin BR, Wong L, Faruque S, McCoy HV, Word C *et al*. Urban rape survivors: characteristics and prevalence of human immunodeficiency virus and other sexually transmitted infections. Multicenter Crack Cocaine and HIV Infection Study Team. *Obstet Gynecol* 1995;**85**:330-336.
- Austin H, Macaluso M, Nahmias A, Lee FK, Kelaghan J, Fleenor M *et al*. Correlates of herpes simplex virus seroprevalence among women attending a sexually transmitted disease clinic. *Sex Transm Dis* 1999;**26**: 329-334.
- Huerta K, Berkelhamer S, Klein J, Ammerman S, Chang J, Prober CG. Epidemiology of herpes simplex virus type 2 infections in a high-risk adolescent population. *J Adolesc Health* 1996;**18**: 384-386.
- Rosenthal SL, Stanberry LR, Biro FM, Slaoui M, Francotte M, Koutsoukos M *et al*. Seroprevalence of herpes simplex virus types 1 and 2 and cytomegalovirus in adolescents. *Clin Infect Dis* 1997;**24**:135-139.
- Kingsley LA, Armstrong J, Rahman A, Ho M, Rinaldo CR, Jr. No association between herpes simplex virus type-2 seropositivity or anogenital lesions and HIV seroconversion among homosexual men. *J Acquir Immune Defic Syndr* 1990;**3**:773-779.
- Whittington WL, Celum CL, Cent A, Ashley RL. Use of a glycoprotein G-based type-specific assay to detect antibodies to herpes simplex virus type 2 among persons attending sexually transmitted disease clinics. *Sex Transm Dis* 2001;**28**: 99-104.
- Tabet SR, Krone MR, Paradise MA, Corey L, Stamm WE, Celum CL. Incidence of HIV and sexually transmitted diseases (STD) in a cohort of HIV-negative men who have sex with men (MSM). *AIDS* 1998;**12**:2041-2048.
- Schwabke J, Calsyn D, Shriver K, Saxon A, Kleyn J, Oluoch-Mitchell E *et al*. Prevalence and epidemiologic correlates of human T cell lymphotropic virus infection among intravenous drug users. *J Infect Dis* 1994;**169**: 962-967.
- Koutsky LA, Holmes KK, Critchlow CW, Stevens CE, Paavonen J, Beckmann AM *et al*. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;**327**:1272-1278.
- Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *JAMA* 1988;**260**: 1429-1433.
- Boucher FD, Yasukawa LL, Bronzan RN, Hensleigh PA, Arvin AM, Prober CG. A prospective evaluation of primary genital herpes simplex virus type 2 infections acquired during pregnancy. *Pediatr Infect Dis J* 1990;**9**:499-504.
- Mertz GJ, Benedetti J, Ashley R, Selke SA, Corey L. Risk factors for the sexual

- transmission of genital herpes. *Ann Intern Med* 1992;**116**:197–202.
40. Breinig MK, Kingsley LA, Armstrong JA, Freeman DJ, Ho M. Epidemiology of genital herpes in Pittsburgh: serologic, sexual, and racial correlates of apparent and inapparent herpes simplex infections. *J Infect Dis* 1990;**162**:299–305.
 41. Gibson JJ, Hornung CA, Alexander GR, Lee FK, Potts WA, Nahmias AJ. A cross-sectional study of herpes simplex virus types 1 and 2 in college students: occurrence and determinants of infection. *J Infect Dis* 1990;**162**:306–312.
 42. Cunningham AL, Lee FK, Ho DW, Field PR, Law CL, Packham DR *et al*. Herpes simplex virus type 2 antibody in patients attending antenatal or STD clinics. *Med J Aust* 1993;**158**:525–528.
 43. Gottlieb SL, Douglas JM, Jr, Schmid DS, Bolan G, Iatesta M, Malotte CK *et al*. Seroprevalence and correlates of herpes simplex virus type 2 infection in five sexually transmitted-disease clinics. *J Infect Dis* 2002;**186**:1381–1389.
 44. Armstrong GL, Schillinger J, Markowitz L, Nahmias AJ, Johnson RE, McQuillan GM *et al*. Incidence of herpes simplex virus type 2 infection in the United States. *Am J Epidemiol* 2001;**153**:912–920.
 45. Koutsky LA, Stevens CE, Holmes KK, Ashley RL, Kiviat NB, Critchlow CW *et al*. Underdiagnosis of genital herpes by current clinical and viral-isolation procedures. *N Engl J Med* 1992;**326**:1533–1539.
 46. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995;**333**:770–775.
 47. Langenberg A, Benedetti J, Jenkins J, Ashley R, Winter C, Corey L. Development of clinically recognizable genital lesions among women previously identified as having “asymptomatic” herpes simplex virus type 2 infection. *Ann Intern Med* 1989;**110**:882–887.
 48. Whitley RJ, Corey L, Arvin A, Lakeman FD, Sumaya CV, Wright PF *et al*. Changing presentation of herpes simplex virus infection in neonates. *J Infect Dis* 1988;**158**:109–116.
 49. Whitley R, Arvin A, Prober C, Corey L, Burchett S, Plotkin S *et al*. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med* 1991;**324**:450–454.
 50. Christenson B, Bottiger M, Svensson A, Jeansson S. A 15-year surveillance study of antibodies to herpes simplex virus types 1 and 2 in a cohort of young girls. *J Infect Dis* 1992;**25**:147–154.
 51. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;**69**:19–36.
 52. Langenberg AG, Corey L, Ashley RL, Leong WP, Straus SE. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. *N Engl J Med* 1999;**341**:1432–1438.
 53. Becker TM, Blount JH, Guinan ME. Genital herpes infections in private practice in the United States, 1966 to 1981. *JAMA* 1985;**253**:1601–1603.
 54. Kinghorn GR. Epidemiology of genital herpes. *J Int Med Res* 1994;**22**:14A–23A.
 55. Groseclose SL, Zaidi AA, DeLisle SJ, Levine WC, St Louis ME. Estimated incidence and prevalence of genital Chlamydia trachomatis infections in the United States, 1996. *Sex Transm Dis* 1999;**26**:339–344.
 56. Rosenberg PS, Biggar RJ. Trends in HIV incidence among young adults in the United States. *JAMA* 1998;**279**:1894–1899.
 57. Rust KF, Rao JN. Variance estimation for complex surveys using replication techniques. *Stat Methods Med Res* 1996;**5**:283–310.
 58. Patrick DM, Dawar M, Cook DA, Krajden M, Ng HC, Rekart ML. Antenatal seroprevalence of herpes simplex virus type 2 (HSV-2) in Canadian women: HSV-2 prevalence increases throughout the reproductive years. *Sex Transm Dis* 2001;**28**:424–428.
 59. Howard M, Sellors JW, Jang D, Robinson NJ, Fearon M, Kaczorowski J *et al*. Regional distribution of antibodies to herpes simplex virus type 1 (HSV-1) and HSV-2 in men and women in Ontario, Canada. *J Clin Microbiol* 2003;**41**:84–89.
 60. Andersson-Ellstrom A, Svennerholm B, Forssman L. Prevalence of antibodies to herpes simplex virus types 1 and 2, Epstein-Barr virus and cytomegalovirus in teenage girls. *Scand J Infect Dis* 1995;**27**:315–318.
 61. Forsgren M, Skoog E, Jeansson S, Olofsson S, Giesecke J. Prevalence of antibodies to herpes simplex virus in pregnant women in Stockholm in 1969, 1983 and 1989: implications for STD epidemiology. *Int J STD AIDS* 1994;**5**:113–116.
 62. Lowhagen GB, Jansen E, Nordenfelt E, Lycke E. Epidemiology of genital herpes infections in Sweden. *Acta Derm Venereol* 1990;**70**:330–334.
 63. Persson K, Mansson A, Jonsson E, Nordenfelt E. Decline of herpes simplex virus type 2 and Chlamydia trachomatis infections from 1970 to 1993 indicated by a similar change in antibody pattern. *Scand J Infect Dis* 1995;**27**:195–199.
 64. Arvaja M, Lehtinen M, Koskela P, Lappalainen M, Paavonen J, Vesikari T. Serological evaluation of herpes simplex virus type 1 and type 2 infections in pregnancy. *Sex Transm Infect* 1999;**75**:168–171.
 65. Lehtinen M, Dillner J, Knekt P, Luostarinen T, Aromaa A, Kirnbauer R *et al*. Serologically diagnosed infection with human papillomavirus type 16 and risk for subsequent development of cervical carcinoma: nested case-control study. *BMJ* 1996;**312**:537–539.
 66. Hakama M, Lehtinen M, Knekt P, Aromaa A, Leinikki P, Miettinen A *et al*. Serum antibodies and subsequent cervical neoplasms: a prospective study with 12 years of follow-up. *Am J Epidemiol* 1993;**137**:166–170.
 67. Eskild A, Jeansson S, Jennum PA. [Antibodies against Herpes simplex virus type 2 among pregnant women in Norway]. *Tidsskr Nor Laegeforen* 1999;**119**:2323–2326.
 68. Olsen AO, Orstavik I, Dillner J, Vestergaard BF, Magnus P. Herpes simplex virus and human papillomavirus in a population-based case-control study of cervical intraepithelial neoplasia grade II-III. *Apmis* 1998;**106**:417–424.
 69. van de Laar MJ, Vermorshuizen F, Slomka MJ, van Doornum GJ, Ossewaarde JM, Brown DW *et al*. Prevalence and correlates of herpes simplex virus type 2 infection: evaluation of behavioural risk factors. *Int J Epidemiol* 1998;**27**:127–134.
 70. van de Laar MJ, Pickering J, van den Hoek JA, van Griensven GJ, Coutinho RA, van de Water HP. Declining gonorrhoea rates in The Netherlands, 1976-88: consequences for the AIDS epidemic. *Genitourin Med* 1990;**66**:148–155.
 71. Dukers NH, Bruisten SM, van den Hoek JA, de Wit JB, van Doornum GJ, Coutinho RA. Strong decline in herpes simplex virus antibodies over time among young homosexual men is associated with changing sexual behavior. *Am J Epidemiol* 2000;**152**:666–673.
 72. Keet IP, Lee FK, van Griensven GJ, Lange JM, Nahmias A, Coutinho RA. Herpes simplex virus type 2 and other genital ulcerative infections as a risk factor for HIV-1 acquisition. *Genitourin Med* 1990;**66**:330–333.
 73. Roest RW, van der Meijden WI, van Dijk G, Groen J, Mulder PG, Verjans GM *et al*. Prevalence and association between herpes simplex virus types 1 and 2-specific antibodies in attendees at a sexually transmitted disease clinic. *Int J Epidemiol* 2001;**30**:580–588.
 74. Oda-Ikoma M, Glazenburg K, Benne C, Schroder F, Welling-Wester S, Van-Vorst Vader P. HSV-1 and HSV-2 seroprevalence among STC clinic attendees in Groningen, The Netherlands. *Acta Microbiol Immunol Hungarica* 1999;**46**:409.
 75. Laubereau B, Zwahlen M, Neunschwander B, Heininger U, Schaad UB, Desgrandchamps D. [Herpes simplex virus type 1 and 2 in Switzerland]. *Schweiz Med Wochenschr* 2000;**130**:143–150.
 76. Bünzli D, Wietlisbach V, Jeannin A. Epidemiology of herpes simplex virus type 1 and 2 in Switzerland: a population-based study. *42nd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy*, San Diego, California, 27–30 September, 2002; Abstract L-774.
 77. Malkin JE, Morand P, Malvy D, Ly TD, Chanzy B, de Labareyre C *et al*. Seroprevalence of HSV-1 and HSV-2 infection in the general French population. *Sex Transm Infect* 2002;**78**:201–203.
 78. Janier M, Lassau F, Bloch J, Spindler E, Morel P, Gerard P *et al*. Seroprevalence of herpes simplex virus type 2 antibodies in an STD clinic in Paris. *Int J STD AIDS* 1999;**10**:522–526.
 79. 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**:1325–1329.
 80. Enders G, Risse B, Zauke M, Bolley I, Knotek F. Seroprevalence study of herpes simplex virus type 2 among pregnant women in Germany using a type-specific enzyme immunoassay. *Eur J Clin Microbiol Infect Dis* 1998;**17**:870–872.
 81. Wutzler P, Doerr HW, Farber I, Eichhorn U, Helbig B, Sauerbrei A *et al*. Seroprevalence of herpes simplex virus type 1 and type 2 in selected German populations-relevance for the incidence of genital herpes. *J Med Virol* 2000;**61**:201–207.
 82. Hook EW, 3rd, Cannon RO, Nahmias AJ, Lee FF, Campbell CH, Jr, Glasser D *et al*. Herpes simplex virus infection as a risk factor for human immunodeficiency virus infection in heterosexuals. *J Infect Dis* 1992;**165**:251–255.
 83. Siegel D, Golden E, Washington AE, Morse SA, Fullilove MT, Catania JA *et al*. Prevalence and correlates of herpes simplex infections. The population-based AIDS in Multiethnic Neighborhoods Study. *JAMA* 1992;**268**:1702–1708.
 84. Suligoi B, Cusan M, Santopadre P, Palu G, Catania S, Girelli G *et al*. HSV-2 specific seroprevalence among various populations in Rome, Italy. The Italian Herpes Management Forum. *Sex Transm Infect* 2000;**76**:213–214.
 85. Pasquini P, Mele A, Franco E, Ippolito G, Svennerholm B. Prevalence of herpes simplex virus type 2 antibodies in selected population groups in Italy. *Eur J Clin Microbiol Infect Dis* 1988;**7**:54–56.
 86. Franco E, Caprilli F, Zaratti L, Pasquini P. Prevalence of antibodies to herpes simplex virus type 1 in different population groups in Italy. *Eur J Clin Microbiol* 1987;**6**:322.

87. Sagnelli E, Filippini P, Guarino M, Borrelli G, Aprea L, Malafrente G *et al*. [Epidemiological evaluations of human immunodeficiency virus, herpes simplex virus type 1 and 2 and cytomegalovirus infections in drug addicts]. *Ann Ital Med Int* 1989;**4**:98–104.
88. Cusini M, Cusan M, Parolin C, Cioccati L, Decleva I, Mengoli C *et al*. Seroprevalence of herpes simplex virus type 2 infection among attendees of a sexually transmitted disease clinic in Italy. *Italian Herpes Forum. Sex Transm Dis* 2000;**27**: 292–295.
89. Mele A, Franco E, Caprilli F, Gentili G, Capitanio B, Crescimbeni E *et al*. Genital herpes infection in outpatients attending a sexually transmitted disease clinic in Italy. *Eur J Epidemiol* 1988;**4**:386–388.
90. Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev* 1999;**12**:1–8.
91. Perkins NL, Coughlan EP, Franklin RA, Reid MR, Taylor J. Seroprevalence of herpes simplex virus type 2 antibodies in New Zealand sexual health clinic patients. *N Z Med J* 1996;**109**:402–405.
92. Garcia-Corbeira P, Dal-Re R, Aguilar L, Granizo JJ, Garcia-de-Lomas J. Is sexual transmission an important pattern for herpes simplex type 2 virus seroconversion in the Spanish general population? *J Med Virol* 1999;**59**:194–197.
93. de Sanjose S, Munoz N, Bosch FX, Reimann K, Pedersen NS, Orfila J *et al*. Sexually transmitted agents and cervical neoplasia in Colombia and Spain. *Int J Cancer* 1994;**56**:358–363.
94. de Ory F, Pachon I, Echevarria JM, Ramirez R. Seroepidemiological study of herpes simplex virus in the female population in the autonomous region of Madrid, Spain. *Eur J Clin Microbiol Infect Dis* 1999;**18**: 678–680.
95. Gil A, Gonzalez A, Dal-Re R, Ortega P, Dominguez V. Prevalence of antibodies against varicella zoster, herpes simplex (types 1 and 2), hepatitis B and hepatitis A viruses among Spanish adolescents. *J Infect* 1998;**36**: 53–56.
96. Varela JA, Garcia-Corbeira P, Aguanell MV, Boceta R, Ballesteros J, Aguilar L *et al*. Herpes simplex virus type 2 seroepidemiology in Spain: prevalence and seroconversion rate among sexually transmitted disease clinic attendees. *Sex Transm Dis* 2001;**28**:47–50.
97. Kjaer SK, Engholm G, Teisen C, Haugaard BJ, Lyngge E, Christensen RB *et al*. Risk factors for cervical human papillomavirus and herpes simplex virus infections in Greenland and Denmark: a population-based study. *Am J Epidemiol* 1990;**131**:669–682.
98. de Sanjose S, Munoz N, Bosch FX, Reimann K, Pedersen NS, Orfila J *et al*. Sexually transmitted agents and cervical neoplasia in Colombia and Spain. *Int J Cancer* 1994;**56**:358–363.
99. Vyse AJ, Gay NJ, Slomka MJ, Gopal R, Gibbs T, Morgan-Capner P *et al*. The burden of infection with HSV-1 and HSV-2 in England and Wales: implications for the changing epidemiology of genital herpes. *Sex Transm Infect* 2000;**76**:183–187.
100. Cowan FM, Johnson AM, Ashley R, Corey L, Mindel A. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* 1996;**174**:470–475.
101. Woolley PD, Chandio S, Pumphrey J, Sharratt S, Shanley L, Bennett S. Serological prevalence of herpes simplex virus type 2 amongst GUM clinic attenders in a district general hospital setting. *Int J STD AIDS* 2000;**11**:379–382.
102. Opaneye AA, Bashford J. Seroprevalence of antibodies to herpes simplex virus types 1 and 2 among two sexually active female populations in Middlesbrough, England. *J R Soc Health* 2002;**122**: 108–111.
103. Jha PK, Beral V, Peto J, Hack S, Hermon C, Deacon J *et al*. Antibodies to human papillomavirus and to other genital infectious agents and invasive cervical cancer risk. *Lancet* 1993;**341**:1116–1118.
104. Ades AE, Peckham CS, Dale GE, Best JM, Jeansson S. Prevalence of antibodies to herpes simplex virus types 1 and 2 in pregnant women, and estimated rates of infection. *J Epidemiol Community Health* 1989;**43**: 53–60.
105. Eberhart-Phillips JE, Dickson NP, Paul C, Herbison GP, Taylor J, Cunningham AL. Rising incidence and prevalence of herpes simplex type 2 infection in a cohort of 26 year old New Zealanders. *Sex Transm Infect* 2001;**77**: 353–357.
106. Eberhart-Phillips J, Dickson NP, Paul C, Fawcett JP, Holland D, Taylor J *et al*. Herpes simplex type 2 infection in a cohort aged 21 years. *Sex Transm Infect* 1998;**74**:216–218.
107. Russell DB, Tabrizi SN, Russell JM, Garland SM. Seroprevalence of herpes simplex virus types 1 and 2 in HIV-infected and uninfected homosexual men in a primary care setting. *J Clin Virol* 2001;**22**:305–313.
108. Bassett I, Donovan B, Bodsworth NJ, Field PR, Ho DW, Jeansson S *et al*. Herpes simplex virus type 2 infection of heterosexual men attending a sexual health centre. *Med J Aust* 1994;**160**: 697–700.
109. Mindel A, Taylor J, Tideman RL, Seifert C, Berry G, Wagner K *et al*. Neonatal herpes prevention: a minor public health problem in some communities. *Sex Transm Infect* 2000;**76**: 287–291.
110. Butler T, Donovan B, Taylor J, Cunningham AL, Mindel A, Levy M *et al*. Herpes simplex virus type 2 in prisoners, New South Wales, Australia. *Int J STD AIDS* 2000;**11**: 743–747.
111. Hashido M, Lee FK, Nahmias AJ, Tsugami H, Isomura S, Nagata Y *et al*. An epidemiologic study of herpes simplex virus type 1 and 2 infection in Japan based on type-specific serological assays. *Epidemiol Infect* 1998;**120**:179–186.
112. Hashido M, Kawana T, Matsunaga Y, Inouye S. Changes in prevalence of herpes simplex virus type 1 and 2 antibodies from 1973 to 1993 in the rural districts of Japan. *Microbiol Immunol* 1999;**43**:177–180.
113. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;**98**:958–972.
114. Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000;**181**:1454–1457.
115. Ribes JA, Steele AD, Seabolt JP, Baker DJ. Six-year study of the incidence of herpes in genital and nongenital cultures in a central Kentucky medical center patient population. *J Clin Microbiol* 2001;**39**: 3321–3325.
116. Thompson C. Genital herpes simplex typing in genitourinary medicine: 1995–1999. *Int J STD AIDS* 2000;**11**:501–502.
117. Ross JD, Smith IW, Elton RA. The epidemiology of herpes simplex types 1 and 2 infection of the genital tract in Edinburgh 1978–1991. *Genitourin Med* 1993;**69**: 381–383.
118. Coyle PV, O'Neill HJ, Wyatt DE, McCaughey C, Quah S, McBride MO. Emergence of herpes simplex type 1 as the main cause of recurrent genital ulcerative disease in women in Northern Ireland. *J Clin Virol* 2003;**27**:22–29.
119. Lowhagen GB, Tunback P, Andersson K, Bergstrom T, Johannisson G. First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by the use of herpes simplex virus (HSV) typing and specific serology. *Sex Transm Infect* 2000;**76**: 179–182.
120. Wolff MH, Schmitt J, Rahaus M, Dudda H, Hatzmann W. Clinical and subclinical reactivation of genital herpes virus. *Intervirology* 2002;**45**: 20–23.
121. Buxbaum S, Geers M, Gross G, Schofer H, Rabenau HF, Doerr HW. Epidemiology of herpes simplex virus types 1 and 2 in Germany: what has changed? *Med Microbiol Immunol* 2003;**22**:22.
122. Nilsen A, Myrmed H. Changing trends in genital herpes simplex virus infection in Bergen, Norway. *Acta Obstet Gynecol Scand* 2000;**79**:693–696.
123. Sanders SA, Reinisch JM. Would you say you 'had sex' if...? *JAMA* 1999;**281**: 275–277.
124. Edwards S, Carne C. Oral sex and the transmission of viral STIs. *Sex Transm Infect* 1998;**74**:6–10.
125. Stephenson J. HIV risk from oral sex higher than many realize. *JAMA* 2000;**283**:1279.

Epidemiology of Herpes Simplex Virus Type 2 Infection in the Developing World

Helen Weiss, London School of Hygiene and Tropical Medicine, London, UK.

KEY WORDS

■ HSV-2 ■ DEVELOPING WORLD ■ GENITAL HERPES ■ PREVALENCE
■ INCIDENCE ■ SEROPOSITIVITY ■ TYPE-SPECIFIC ■ TESTS ■ GENITAL
ULCER DISEASE ■ HIV ■ STI

SUMMARY

Herpes simplex virus type 2 (HSV-2) is a common infection in many countries, with prevalence in some regions, such as sub-Saharan Africa, higher than in the USA. Prevalence in adult general populations in sub-Saharan Africa ranges from 30% to 80% in women, and from 10% to 50% in men. Most data from Central and South America are from women, in whom HSV-2 prevalence ranges from about 20% to 40%. Prevalence in the general population in developing Asian countries appears to be lower (10–30%). In common with the developed world, HSV-2 seropositivity is uniformly higher in women than in men and increases with age. In general, HSV-2 seroprevalence is high in populations whose behaviour leads to a high risk of acquiring other sexually transmitted infections (STIs), such as STI clinic attendees and sex workers (SWs), with some African studies reporting greater than 80% HSV seropositivity in SWs. New infections are most common among young adults, a fact that should be considered when proposing and implementing measures to reduce HSV, and possibly HIV, transmission. Currently, comparison between studies is hampered by the lack of a validated type-specific serological assay that has a similar performance across a range of populations. HSV-2 is a major cause of genital ulcer disease (GUD) in the developing world. Genital herpes is a cause of morbidity and increases the risk of HIV acquisition, due to disruption of mucosal membranes. Where possible, the aetiology of GUD should be evaluated using polymerase chain reaction (PCR), while recognizing that co-pathogens can exist in a lesion. GUD management should incorporate HIV testing and antiherpetic treatment.

Introduction

THE PREVALENCE OF HERPES simplex virus type 2 (HSV-2) infection is high in the developing world, especially in sub-Saharan Africa. Epidemiological and biological studies demonstrate an interaction between HIV and HSV-2. This interaction is bi-directional, such that HSV increases the risk of acquisition and, likely, transmission of HIV, while HIV increases the clinical expression of HSV-2 (see *Interaction Between HSV and HIV* in this supplement). Genital herpes is also a major cause of genital ulcer disease (GUD), a known risk factor for HIV. Furthermore, as the importance of bacterial sexually transmitted infections (STIs) decreases when HIV infection spreads from high-risk groups to the general population (i.e. when the epidemic matures), HSV-2 is likely to become more important. This is because at high levels of HSV-2 seroprevalence, the virus is not restricted to 'high-risk' groups (e.g. those with high rates of partner exchange, to be discussed in a future supplement). Therefore, HSV-2 control should be a public health priority and reliable seroepidemiological data are needed to inform any control programmes. This supplement reviews the seroprevalence and seroincidence of HSV-2 infection in the developing world.

HSV-2 Seroprevalence in Africa

HSV-2 SEROPREVALENCE IN NON-HIGH-RISK POPULATIONS IN AFRICA

Most data on HSV-2 prevalence in Africa are from sub-Saharan countries including the Central African Republic,¹ The Gambia,² Tanzania,³ Uganda,^{4–6} South Africa⁷ and Zimbabwe (Table 1).^{8–10} The majority of these studies were of men and women aged 15–54 years, as the data on HSV-2 infection were gathered as part of epidemiological studies of HIV infection. Sub-Saharan Africa is the region most affected by HIV; at least 15% of adults are infected in eight of the countries.

In rural communities in Mwanza region, Tanzania, 43.5% (161/370) of women and 23.7% (70/295) of men had antibodies for HSV-2 in 1994.¹¹ HSV-2 seroprevalence increased rapidly with age, until around age 30, reaching a plateau of about 50% in men and 75% in women. Very similar rates were seen in rural Uganda, where data from 1994 to 1996 showed prevalence of 45% in men aged 25–29 and 74% in women of this age group.¹²

Cross-sectional surveys of four African urban populations found similar high prevalences of HSV-2 infection in three of the towns.¹³ HSV-2 seroprevalence was over 50% among women and over 25% among men in Yaoundé (Cameroon), Kisumu (Kenya) and Ndola (Zambia). There was a strong association between HSV-2 seroprevalence and age, with infection rates generally rising rapidly between the ages of 15 and 29 years before becoming stable (Figure 1).¹³ The prevalence of HSV-2 infection was especially high among young women aged 15–19 years in Kisumu (39%) and Ndola (23%). The high level of HSV-2 infection is due likely in part to the younger age at marriage, and high levels of concomitant HIV infection in male partners in these two cities.

HSV-2 seroprevalence was 42.2% among 393 women attending two urban primary healthcare clinics in Zimbabwe between July 1999 and January 2000.¹⁴ The prevalence of antibodies rose with an increase in the number of sexual partners, although more than one-third of women who reported one lifetime sexual partner had HSV-2 antibodies. In common with other studies, the prevalence of HSV-2 antibodies increased with age. The HSV-2 seroprevalence among 2397 male Zimbabwean factory workers was 40%.⁹ The likelihood of HSV-2 seropositivity was associated with increasing age, ever having been married, a history of sexually transmitted diseases (STDs) and higher income. The latter factor, which is not consistently reported,^{15,16} may be linked to a higher risk of infection as it allows increased access to sexual partners, particularly sex workers. There was also a high prevalence of HSV-2 infection among adult factory workers in Addis Ababa, Ethiopia in 1997 (50% in males and 61% in females).¹⁷ HSV-2 infection in a community-based sample was similar among men (after adjustment for age), but significantly lower in women. In both populations, the predictors of HSV-2 infection were older age, higher

RECOMMENDATIONS AND STATEMENTS

- Polymerase chain reaction (PCR) should be used to evaluate the aetiology of GUD in the developing world. Such studies should recognize that co-pathogens can exist within one lesion. HSV culture should replace PCR, if the latter is not available (category 2 recommendation)
- Antiviral treatment should be incorporated into GUD management guidelines in areas in which HSV is a potential cause of GUD (category 3 recommendation)
- HIV testing should be offered to any person with GUD, including HSV-specific GUD, because of the association of GUD and HIV (category 3 recommendation)
- To allow comparison of seroepidemiological studies in developing countries, validation of type-specific serological assays are required to check performance in a range of populations. Development of non-invasive tests (e.g. using saliva or urine) or minimally invasive tests (e.g. finger prick samples) is also needed (research need recommendation)
- Further cohort studies of HSV-2 seroincidence are required to:
 - Investigate reasons for the high HSV-2 incidence among young people in developing countries

- Understand interaction of HSV-2 and HIV seroincidence
- Gain further insight into the natural history of HSV-2 infection (research need recommendation)
- Further seroprevalence studies of HSV-2 infection in eastern Europe, Asia and north Africa are required (research need recommendation)
- Studies are required to define the association between HSV and HIV acquisition, and the role HSV plays in HIV transmission. These studies should also assess interventions of antiherpetic therapy on HIV transmission and acquisition (research need recommendation)

RECOMMENDATION AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

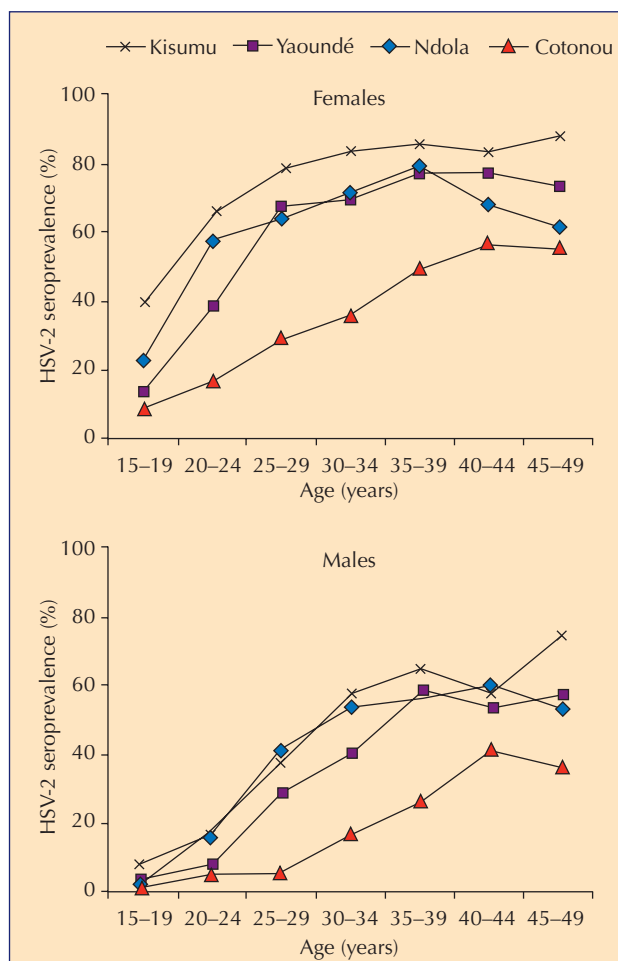


Figure 1: HSV-2 seroprevalence in four African cities by sex and age group.¹³ Reproduced with permission from Weiss HA, Buve A, Robinson NJ, Van Dyck E, Kahindo M, Anagonou S et al. *The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations*. *AIDS* 2001;15(Suppl 4):S97-S108. © Lippincott, Williams & Wilkins.

lifetime number of sexual partners, positive HIV serology and positive *Treponema pallidum* serology.

Similar risk factors have been seen in a recent study among urban women in Moshi, Tanzania, where prevalence increased from 23% among those aged 15–19 years to 49% among those aged 30–49. Increasing HSV-2 prevalence was also associated with earlier age at first sex and higher number of lifetime partners.^{18–20}

There is some evidence that HSV-2 prevalence is lower in west Africa. In Cotonou (Benin) 30% of women and 12% of men were infected,¹³ and similar figures were seen in The Gambia (32% in women and 5% in men aged 15–34).²¹ In both countries, HSV-2 prevalence increased with age. In Cotonou, HSV-2 seroprevalence was associated with marriage (the highest risk among those in polygamous relationships), and increasing number of lifetime partners. In The Gambia, risk was highest among women in polygamous relationships, or whose husbands had had previous marriages.¹⁹

In summary, the age-adjusted HSV-2 seroprevalence among low-risk adults in countries south of the Sahara ranges from 20% to 80%, with most studies recording an HSV-2 antibody prevalence towards the middle of this range (Table 1). HSV-2 seropositivity is uniformly higher in women than men, and increases with age, irrespective of geographical location. There are noticeably high prevalences of HSV-2 infection among young women (aged 15–19) in many cities, indicating a high incidence in this age group (Table 1).^{3–5,7}

HSV-2 SEROPREVALENCE IN HIGH-RISK GROUPS IN AFRICA

In recent studies of HSV-2 epidemiology in sub-Saharan Africa (Table 1), there were high rates of infection in high-risk populations. The HSV-2 seroprevalence rate among female sex workers (SWs) in Lagos, Nigeria, was 59%.²⁵ Higher HSV-2 seroprevalence was reported in a multicentre study of SWs in four sub-Saharan African cities.³⁰ The prevalence of HSV-2 antibodies was 90.9% (250/275) in Cotonou, 84.1% (269/320) in Yaoundé, 93.9% (278/296) in Kisumu and 87.1% (278/319) in Ndola. The study did not directly examine the factors related to HSV-2 seropositivity but it did find that neither the extent of sex work nor factors affecting

Table 1: HSV-2 prevalence estimates from non-high-risk and high-risk populations in Africa²⁹

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Central African Republic Bangui (1998–1999) ¹	Type-specific ELISA	Women attending a reproductive health centre	F	27 (15–48)	300	82
Eritrea Massawa (1995) ²²	Type-specific in-house ELISA	Pregnant women	F	28	113	23
		Rashaida tribe	F/M	35*	25/20	4.5*
		Children <1 y	F+M	<1	20	40
		Children 1–5 y	F+M	1–5	54	11
		Children >5 y	F/M	8.5*	27/57	1.4*
The Gambia Farafenni area (1999) ²	Type-specific peptide-55 ELISA	Random rural sample of women	F	15–54	1317	32
Tanzania Rural Mwanza (1992) ³	Type-specific MAb-blocking ELISA	Random cluster sample	F/M	15–54	259/231	42/19
				15–19	145/145	27/7
				20–24	62/38	48/26
				25–34	24/26	75/39
				35–54	28/22	79/63
Uganda Masaka (1990–1993) ⁴	Western blot	Random sample from population-based study of all residents from 15 neighbouring villages	F/M	15–≥45	541/367	71/36
				15–19	96/101	35/9.9
				20–24	88/52	74/27
				25–34	155/89	77/47
				35–44	121/66	88/49
		≥45	81/59	77/58		
Uganda Rural Masaka (1989–1990) ⁵	Western blot	All adults from two neighbouring villages	F+M	15–≥40	210	68
				15–19	38	34
				20–24	29	78
				25–29	28	82
				30–39	33	82
		≥40	82	71		
Uganda Rural Rakai District (1994–1995) ⁶	Type-specific immunoblot	Population-based sample of adolescents	F+M	22~ (15–29)	722	34.5
				15–19		21~
				20–24		43~
				25–29		54~
South Africa Gauteng Province (1999) ⁷	Type-specific ELISA (MRL)	Population-based ~70 000 mine workers	F/M	19/18 (14–24)	771/718	53/17
				14–16		19~/8~
				17–18		39~/10~
				20–21		67~/19~
				22–24		90~/43~
Zimbabwe Greater Harare (pre-1997) ⁸	Type-specific recombinant immunoblot assay (Chiron)	HIV-negative male factory workers	M	≤25–≥45	224	36
				≤25	68	7.4
				26–30	50	30
				31–35	30	33
				36–40	33	61
				41–45	20	65
				>45	23	74
Zimbabwe Harare (1993–1997) ⁹	Type-specific immunoblot (Chiron)	Male factory workers	M	18–≥46	2397	40
				18–20	154	6.5
				21–25	731	17
				26–30	433	41
				31–35	332	56
				36–40	306	60
				41–45	200	62
≥46	241	62				
Zimbabwe Mutasa and Nyanga Districts (1998) ¹⁰	Type-specific EIA (Gull)	Population-based survey	F/M	15–44/17–54	127/112	67/53

Table 1: HSV-2 prevalence estimates from non-high-risk and high-risk populations in Africa²⁹ (cont.)

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)	
High-risk populations							
Central African Republic Bangui (1998–1999) ¹	Competitive type-specific ELISA	HIV seropositive	F	27 (15–48)	58	91	
Democratic Republic of Congo (formerly Zaire) Kinshasa (1988) ²³	Western blot	Sex workers attending health center	F	26	265	82	
Kenya Mombasa (1993–1997) ²⁴	Western blot	Male truck drivers	M	29 (16–62)	752	47	
Nigeria Lagos (1990–1991) ^{25,26}	Western blot	Sex workers	F	25 (12–50)	470	59	
				10–19	37	46	
				20–29	310	59	
				30–50	123	63	
South Africa Cape Town, Durban, Johannesburg (1993–1994) ²⁷	Western blot	STD clinic attendees, with: GUD	M	26 (15–65)	554	49	
				15–19	45	31~	
				20–24	226	42~	
				25–29	161	50~	
				30–34	60	71~	
				35–39	26	58~	
				40–65	36	61~	
				GUD, HIV-negative	302~	40	
				GUD, HIV-positive	196~	63	
				Urethritis	27 (16–54)	589	42
					15–19	27	18~
					20–24	212	29~
	25–29	209	46~				
	30–34	74	61~				
	35–39	31	62~				
	40–54	36	62~				
	Urethritis, HIV-2 negative	435	37				
	Urethritis, HIV-positive	118	64				
Tanzania Dar es Salaam (1989–1993) ²⁸	Type-specific ELISA	STD clinic patients	F/M	11–20	27/23	55~/9.0~	
			F	21–50	52	65~	
			M	21–30	128	29~	
			M	31–50	50	59~	
Zimbabwe Greater Harare (pre-1997) ⁸	Type-specific recombinant immunoblot assay (Chiron)	HIV-positive male factory workers	M	≤25–>45	191	83	
				≤25	42	67	
				26–30	64	88	
				31–35	31	87	
				36–40	34	94	
	41–>45	20	75				

HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; EIA, enzyme immunoassay; STD, sexually transmitted disease; GUD, genital ulcer disease; MAb, monoclonal antibody; ~, estimated from graph or table or age range inferred from text; F, female; M, male; *, female and male combined. Adapted from Smith JS *et al.*²⁹

transmission (e.g. condom use) showed clear differences between cities with high (i.e. Kisumu and Ndola) and low HIV prevalence (i.e. Yaoundé and Cotonou). However, any factors determining HSV-2 infection may be difficult to identify in a population with a high seroprevalence.

In a prospective cohort of 1500 trucking company workers in Kenya, 47% were HSV-2 seropositive.²⁴ These truck drivers had a high HIV seroprevalence at

enrolment into the study (17.8%) and, among the men who were HIV-seronegative at entry, an annual HIV seroconversion of 3.1%. HIV acquisition was associated with factors (e.g. unprotected sex with a SW) that would be expected to increase the risk of infection with HSV-2. A similar HSV-2 seroprevalence was reported among 294 patients attending an STD clinic in Dar-es-Salaam, Tanzania.²⁸ The overall HSV-2 seroprevalence was 42.9%, with a higher prevalence of HSV-2 antibodies in women

(63%) than in men (35.5%). This difference was reflected in age-specific seroprevalence rates, 8.7% of the youngest men (<20 years of age) being HSV-2 seropositive compared with 55.6% of women aged 20 years or younger.

Similar findings were reported in a survey of 515 workers from bars and hotels in Moshi, Tanzania.³¹ The overall HSV-2 seroprevalence was 43.5%, with higher incidences recorded in women than in men. HSV-2 seroprevalence increased with age. HIV-seropositive women had a significantly increased risk of acquiring HSV-2 infection compared with HIV-seronegative women.³¹

HSV-2 Seroprevalence in Central and South America

HSV-2 SEROPREVALENCE IN NON-HIGH-RISK POPULATIONS IN CENTRAL AND SOUTH AMERICA
The HSV seroprevalence studies undertaken across Central and South America are featured in Table 2. The highest HSV-2 prevalence in Central and South America was from a seroepidemiological study among patients with cervical cancer. The prevalence of HSV-2 antibodies was 69% among 667 women attending a

Table 2: HSV-2 prevalence estimates from non-high-risk and high-risk populations in Central and South America²⁹

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Latin America (pre-1991) Colombia (Bogota), Costa Rica, Mexico (Mexico City), Panama ³⁵	Modified Western blot	Controls in cervical cancer study	F	18–69	1312	43
				18–29	86	30
				30–39	311	39
				40–49	363	40
				50–59	355	47
Brazil Campinas City (1993–1997) ³⁶	Type-specific ELISA	Women at delivery	F	14–42	102	23
				14–20	35	11
				21–29	40	35
				30–42	27	19
Brazil São Paulo (1990–1991) ³⁷	Screened with type-specific ELISA (Gull), confirmed all positive, borderline negative and equivocal sera with Western blot	Hospital-based controls from cervical cancer study	F	18–80	181	42
				18–40	26	42
				40–49	54	50
				50–59	46	33
Brazil São Paulo (pre-1993) ³⁸	Type-specific immunoblot	Of childbearing age (low/middle income)	F/F	28/27	173/127	42/31
Colombia Cali (1985–1988) ³³	Type-specific ELISA (gC2)	Random general population sample	F	39	270	50
				48	149	60
Costa Rica National (1984–1985) ^{39,40}	Type-specific glycoprotein antigen assay	Random sample	F	25–59	766	39
				25–29	122	33
				30–39	270	39
				40–49	194	45
				50–59	180	46
Haiti Cit� Soleil (pre-1992) ³⁴	Type-specific ELISA (HSV- 1/2 ratio)	Women attending prenatal clinics	F	25 (15–40)	89	54
Mexico Mexico City (1997) ⁴¹	Type-specific immunoblot assay	Population-based sample	F	15–82	730	30
				≤39	215	15
				40–49	210	24
				50–59	145	41
				≥60	160	45
Mexico Mexico City (1992) ⁴²	Type-specific immunoblot assay	Women seeking HIV testing	F	30 (11–67)	454	29

Table 2: HSV-2 prevalence estimates from non-high-risk and high-risk populations in Central and South America²⁹ (cont.)

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
High-risk populations						
Brazil Campinas City (1993–1997) ³⁶	Screened with in-house type-specific ELISA, confirmed with Western blot	STD clinic attendees	F/M		44/52	
			F+M	14–57	96	53
				14–25	44	41
				26–57	52	64
Haiti Cit� Soleil (pre-1992) ³⁴	Type-specific ELISA	HIV-positive women	F	26 (15–40)	95	88
Mexico Mexico City (1992) ⁴³	Type-specific immunoblot	Sex workers	F	16–>37	997	61
				16–22	302	45
				23–27	330	64
				28–32	187	66
				33–37	101	69
Mexico Mexico City (1992) ⁴⁴	Type-specific immunoblot	Sex workers	F	30 (17–76)	747	65
				17–23	214	50
				24–30	284	65
				31–37	169	73
				38–76	80	88
Mexico Mexico City (1993) ⁴⁵	Type-specific immunoblot	Bar workers	M	18–≥47	170	32
				18–25	57	5.3
				26–35	56	30
				36–46	34	59
				≥47	22	64

HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; STD, sexually transmitted disease; F, female; M, male. Adapted from Smith JS *et al.*²⁹

Honduran clinic for routine serological screening. The mean age of these women was 45 years (age range: 20–65) and the prevalence of HIV infection was 0.5%.³² The prevalence of HSV-2 antibodies was also high (60%) in Cali, Colombia, in a case-control study of women (mean age: 48 years) with cervical intra-epithelial neoplasia Grade III or invasive cervical cancer; among controls, the HSV-2 antibody prevalence was 31.4%.³³ A similar HSV-2 seroprevalence (54%) was observed in younger women attending an antenatal class in Haiti (mean age: 25 years).³⁴

Herpes simplex virus type 2 seroprevalence was lower in most other studies in Central and South America. In a population-based study in Mexico City of women who were predominantly middle-aged (range 15–82 years) and monogamous (82.5%), the overall HSV-2 prevalence was 29.8%. The prevalence increased with age ($P < 0.001$ for trend), reaching 45% among women over 60 years. HSV-2 seroprevalence among the controls in a case-control study of breast and cervical cancer in Costa Rica was 39%.³⁹ In adults from two municipal health centres in low socioeconomic areas of Peru, HSV-2 prevalence increased from 26% in women aged 18–20 years to 44% in those aged 31–36 years. In men, it remained consistently lower than in age-matched women.⁴⁶

In Campinas City, Brazil, HSV-2 seroprevalence was higher (23%) in 102 antenatal patients (aged 14–42 years) than in 101 female and male college students (aged 17–30 years; 6.9%).³⁶ The HSV-2 seroprevalence in 181 Brazilian middle-aged women (mean age: 52.4 years) participating as control subjects in two cervical cancer studies was 42%.⁴⁷ HSV-2 seropositivity did not appear to increase with age in older female participants

aged 40 years or over. It was 50% among women aged 40–49 years, 33% among women aged 50–59 years, and 42% among women over 60 years of age.⁴⁷ However, the lack of an apparent association of HSV-2 seropositivity with age may be because the majority of women in the study were older than 40 years; in other studies, the seroprevalence of HSV-2 reaches a plateau at older ages.^{3,48} Young age at first intercourse, number of sexual partners or a husband with other sexual partners were all significant risk factors for HSV-2 infection in Brazilian women.⁴⁷

Among 96 Yukpa Amerindians in Zulia State, Venezuela, the HSV-2 seroprevalence was 53.1%.⁴⁹ This was higher than the 21.1% seen among 76 urban individuals with a similar sex and age range distribution from Maracaibo, Zulia State, Venezuela. The Yukpa women aged 21–40 years had an HSV-2 prevalence of 66.7%, while among pregnant Yukpa women, the prevalence of antibodies against HSV-2 was 54.6%. Yukpa Amerindians start their sexual activity early in life and have frequent sexual relationships, which may explain the high prevalence of HSV-2 antibodies.

HSV-2 SEROPREVALENCE IN HIGH-RISK GROUPS IN CENTRAL AND SOUTH AMERICA

In Mexico City, 60.8% (606/997) of female SWs attending an STD clinic were HSV-2 seropositive.⁴³ The factors associated with HSV-2 seropositivity were age and time working as a SW, both of which are related to the period of exposure to the virus. There were also demographical and geographical differences in that women were more likely to be HSV-2 seropositive if they were born outside Mexico City, were of lower educational status and worked on street sites as a SW.

Female SWs working at the Mexican-Guatemalan Border had a HSV-2 prevalence of 85.7%.⁵⁰ Among STD clinic attendees aged 45–57 years in Campinas City, 53% had HSV-2 antibodies.⁴⁷

The prevalence of antibodies to HSV-2 in Brazilian populations at high risk for STDs (85 HIV-seropositive men, 20 female SWs) was evaluated by ELISA.⁵¹ HSV-2 infection was highest among those with HIV (73%; $P < 0.01$). HSV-2 prevalence was 72% for the two groups combined and infection was significantly and independently associated with years of sexual activity, a history of previous STDs, the number of sexual partners in the previous month, the number of pregnancies and previous induced abortions, as well as the percentage of sexual acts involving receptive anal intercourse.

HSV-2 SEROPREVALENCE IN NON-HIGH-RISK POPULATIONS IN ASIA AND THE INDIAN SUBCONTINENT

There is a paucity of data on the prevalence of HSV-2 antibodies in Asia. What information there is suggests that the prevalence of HSV-2 infection is lower than in Africa or in Central and South America (Table 3). The HSV-2 seroprevalence among Filipino women (mean age: 46.6 years) taking part in a study of cervical cancer was 9.2%, which was much lower than that of Brazilian women (42%) in the same study.⁴⁷ Compared with Filipino women, Brazilian participants were slightly older, had more lifetime sexual partners, less education and were more likely to be married to a husband who had other sexual partners. HSV-2 was independently associated with younger age at first intercourse in both

Table 3: HSV-2 prevalence estimates from non-high-risk and high-risk populations in Asia²⁹

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Non-high-risk populations						
Bangladesh Dhaka (1996–1998) ⁵⁴	Type-specific ELISA (Gull)	Antenatal clinic attendees	F	22	243	7.9
		Healthcare clinic attendees	F	23	144	9.8
		Family planning clients	F	27	555	11
		Women seeking pregnancy interruption	F	26	592	14
China Sichuan (1987–1988) ⁵⁵	Modified Western blot	Pre-pubertal children	F+M	1–12	79	2.5
		Attendees of gynaecological ward or clinic	F	52	146	29
China Hong Kong (1995) ⁵⁶	Western blot	General population	F/M	≥25	76/75	18/17
The Philippines Manila (1991–1993) ⁴⁷	Screened with ELISA (Gull), confirmed all positive, borderline negative and equivocal sera with Western blot	Hospital-based controls in cervical cancer study	F	18–80	371	9.2
				18–40	100	9.0
				40–49	104	8.7
				50–59	116	8.6
				60–80	51	12
Thailand Northern Thailand (1991) ⁵²	Type-specific immunodot	Male military conscripts	M	21–27	1115	15
				21	1061	14
				22–27	54	28
Thailand Northern Thailand (1991) ⁵³	Western blot	Random population sample without history of GUD	M	21	97	31
High-risk populations						
Bangladesh Dhaka (1998) ⁵⁷	Type-specific ELISA (Biokit)	Sex workers	F	>50% aged 18–30	203	63
Thailand Chiang Rai (1991–1994) ⁵⁸	Type-specific immunoblot	Sex workers	F	24 (≥16)	500	76
Thailand Northern Thailand (1991) ⁵³	Western blot	Male military conscripts with history of GUD	M	21	83	53

HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; GUD, genital ulcer disease; F, female; M, male. Adapted from Smith JS *et al.*²⁹

countries. More than one lifetime sexual partner, a husband with other sexual partners, urban/semi-urban residence, and no history of condom use were HSV-2 risk factors in Brazil, but not in the Philippines, where long-term hormonal contraceptive use was associated with increased risk.

The HSV-2 and HIV seroprevalence were 14.9% and 6.9% respectively, for a cohort of 1115 young male army conscripts who entered service in northern Thailand in 1991.⁵² Seroprevalence for both viruses was strongly related to early and frequent contact with female SWs, infrequent use of condoms with female SWs, and residence in the upper north region of Thailand. When differences in sexual behaviour between the upper north and lower north were controlled for, the seroprevalence of both viruses still differed significantly by region. In a case-control study of 180 military recruits in northern Thailand from 1991 to 1993, the seroprevalence of HSV-2 infection was 31% and HSV-2 seropositivity was a marker for high-risk sexual behaviour and a risk factor for HIV infection.⁵³

There was a high prevalence of HSV-2 infection among married women in Dhaka, Bangladesh.⁵⁴ In this cross-sectional study of 2335 women from 1996 to 1998, the overall seroprevalence of HSV-2 infection was 12%. HSV-2 infection was associated with a husband not living at home or suspected of being unfaithful or with a polygamous marriage. A subsequent study in rural Bangladesh recorded an HSV-2 seroprevalence of 5.6% (10/178) among single or married men and 6.0% (8/134) among married women.⁵⁹ For women, the risk factors associated with HSV-2 infection were working outside the home and current STI symptoms in their husband. Among men, no reported risk factors were associated with HSV-2 infection. The lack of any apparent risk factors may be because of the relatively small sample size and because of the difficulty of collecting information on sexual behaviour.

A study in Dhaka among 388 truck drivers and their assistants found a high HSV-2 seroprevalence (25.8%).⁶⁰ The likelihood of HSV-2 infection was 2.5-fold higher for the helpers than the drivers. Drivers have a much higher income than the assistants and, as with the Zimbabwean factory workers discussed earlier, this allows them to frequent brothel-based SWs rather than itinerant SWs. The former, more expensive SWs have lower rates of syphilis than the latter.⁶¹ Although specific HSV-2 data do not exist, it may be that men who have sex with itinerant SWs are at higher risk of acquiring STD infections.

A study of HIV-1 negative patients in Pune, India, found a prevalence of HSV-2 of 38% among male STI patients, 51% among female STI patients and 89% in female SWs. HSV-2 infection was significantly associated with increasing age, being married or separated, and increasing number of lifetime partners.²⁰

HSV-2 Seroprevalence in Non-High-Risk Populations in the Middle East

The relatively few studies conducted in the Middle East suggest a high HSV-2 prevalence in younger adults. Among Jordanian university students aged 18–24 years, it was high in both women (41%) and men (53%); the higher seroprevalence in men was attributed to a greater degree of sexual freedom (Table 4).⁶² An earlier study among pregnant women attending an antenatal clinic in Turkey recorded high levels of HSV-2 infection (42.2%) (Table 4). In the youngest group, aged 20–25 years, the HSV-2 seroprevalence was 38%.⁶³

Sociodemographic Factors Associated with HSV-2 Infection in the Developing World

- To allow comparison of seroepidemiological studies in developing countries, validation of type-specific serological assays are required to check performance in a range of populations. Development of non-invasive tests (e.g. using saliva or urine) or minimally invasive tests (e.g. finger prick samples) is also needed (research need recommendation)

A consistent finding from studies in the developing world is the association of HSV-2 infection with increasing age and female gender. A similar relationship is apparent from studies in industrialized countries. The difference in seroprevalence between men and women may be because women have a greater mucosal surface exposed, thereby increasing the risk of acquisition. Men may have a higher frequency of recurrences than women, which increases the risk of transmission to women⁶⁴ and, related to this, men may have a lower perception of discomfort with active lesions which may allow them to engage in sexual intercourse even when they are most likely to shed virus. The increasing prevalence of HSV-2 infection with age is because HSV-2 is a persistent infection with a relatively high rate of transmission. A common finding among the seroepidemiological surveys is that education, religion and socio-economic status have little effect.

The studies have generally found a variation in HSV-2 seroprevalence between regions and between populations with different demographical and sexual behaviour parameters. Some of this variation is likely to be due to variations in epidemiological factors, such as the dynamics of sexual mixing patterns, age at first sex, condom use, mobility and the presence of other STIs.

Another important influence on the dynamics of HSV-2 infection may be prior infection with HSV-1. This virus is common in Africa, with up to 90% of adults infected.⁶⁵ Although previous infection with HSV-1 gives little protection against acquisition of

Table 4: HSV-2 prevalence estimates from non-high-risk populations in the Middle East²⁹

	Test methodology	Population group	Sex	Mean or median age (range)	n	HSV-2 prevalence (%)
Jordan North (pre-2000) ⁶²	Type-specific ELISA (Ismunit)	University students	F/M	18–24	390/360	41/53
Turkey Erzurum (1991–1992) ⁶³	Type-specific ELISA (Clark Labs)	Pregnant women	F	20–40 20–25 26–30 31–40	295 148 107 40	42 38 48 37

HSV-2, herpes simplex virus type 2; ELISA, enzyme-linked immunosorbent assay; F, female; M, male. Adapted from Smith JS *et al.*²⁹

HSV-2, it may increase the proportion of asymptomatic seroconversions and moderate the clinical severity of HSV-2.⁶⁵ Consequently, HSV-1 infection may influence the spread of HSV-2. The epidemiology of HSV-1 in developing countries may be relevant for HSV-2 vaccine studies as an HSV-2 vaccine was ineffective in HSV-1 seropositive persons.⁶⁶

Another reason for the variation in HSV-2 prevalence worldwide is that some assays have varying specificity in different populations. For comparison of studies, validation of serological type-specific assays against a gold standard is required. In addition, development of a non-invasive test (e.g. using saliva or urine) or minimally invasive test (e.g. finger prick samples) would increase the feasibility of carrying out further seroepidemiological studies, especially in young people where incidence is highest.

Requirement for HSV-2 Seroepidemiology Studies in Eastern Europe, Asia and North Africa

- Further seroprevalence studies of HSV-2 infection in eastern Europe, Asia and North Africa are required (research need recommendation)

There have been few serological surveys of HSV-2 infection in eastern Europe, Asia and North Africa. Studies in these countries will help to improve our knowledge of the epidemiology of genital herpes. The pattern of infection in many countries suggests that young people and non-high-risk men should be surveyed.

Cohort Studies of HSV-2 Incidence

- Further cohort studies of HSV-2 seroincidence are required to:
 - Investigate reasons for the high HSV-2 incidence among young people in developing countries
 - Understand interaction of HSV-2 and HIV seroincidence
 - Gain further insight into the natural history of HSV-2 infection (research need recommendation)

The seroepidemiological studies reported above give an indication of the number of individuals infected with HSV-2 at any one time point. However, they cannot ascertain the temporal relationship between exposure and infection. Such incidence data are needed to:

- Inform intervention studies and vaccine trials;
- Understand reasons for high HSV-2 incidence among young women in developing countries;
- Understand the interaction between HSV-2 and HIV.

There have been relatively few epidemiological studies on the incidence of HSV-2 infection in the developing world, which is a handicap in terms of the design of appropriate control measures. The scarcity of surveys is largely due to the difficulties associated with conducting population-based longitudinal studies. In the Masaka region of Uganda, the HSV-2 prevalence was 36% in men and 71.5% in women.⁴ Over a 2-year follow-up period, there were 78 seroconversions (40 among women and 38 among men) among 373 people who were initially seronegative. The incidence rates were 73.2 and 122.9 per 1000 person-years for men and women, respectively. There were age-specific differences in seroincidence with the highest rates being in men and women aged 15–19 years (163.0 and 116.3 per 1000 person-years, respectively).

Seroincidence was similar in the Mwanza region of Tanzania, where the baseline HSV-2 seroprevalence was 43.5% (161/370) among women and 23.7% (70/295) among men.¹¹ During a 2-year follow-up period, HSV-2 seroconversion was documented in 17.5% of 206 women seronegative at baseline and in 11.3% of 221

men negative at baseline. The seroincidence of HSV-2 infection was 5% per year in men of all ages and women aged 20 years and over, but was much higher (10% per year) in women aged 15–19 years. Another important finding was that, compared with those remaining HSV-2 negative at follow up, HIV incidence was higher in men who were HSV-2-seropositive at baseline (adjusted odds ratio [OR]: 5.78) but even higher in those who seroconverted to HSV-2 during follow-up (adjusted OR: 13.2). The incidence rates in these studies are much higher than those in the developed world. For example, the estimated annual force of infection (defined as the per capita rate at which susceptibles become infected) in the USA in 1985 was 8.4 per 1000,⁶⁷ with the annual rates of HSV seroconversion in seroincidence studies in Europe and North America ranging from 5 to 24 seroconversions per 1000 people per year.^{67–71}

In contrast to these studies in Africa, a much lower HSV-2 seroincidence of 9 per 1000 person-years occurred among married women in Dhaka, Bangladesh.⁵⁴ However, a study in Pune, India, found an HSV-2 seroincidence of 10.8 per 100 person-years among male STI attendees, 15% among female STI attendees, and 34% among female SWs.²⁰ Incident HSV-2 infection was significantly associated with HIV-1 acquisition, with the highest HIV incidence (23 per 100 person-years) among those with a recent incident HSV-2 infection.

These findings suggest that prevention of HSV-2 infection may reduce the risk of HIV-1 acquisition. In countries with high HSV-2 seroprevalence, control measures for both HSV-2 and HIV prevention should focus on the young.

HSV-2 as a Cause of GUD

- PCR should be used to evaluate the aetiology of GUD in the developing world. Such studies should recognize that co-pathogens can exist within one lesion. HSV culture should replace PCR, if the latter is not available (category 2 recommendation)
- Antiviral treatment should be incorporated into GUD management guidelines in areas in which HSV is a potential cause of GUD (category 3 recommendation)
- HIV testing should be offered to any person with GUD, including HSV-specific GUD, because of the association of GUD and HIV (category 3 recommendation)
- Studies are required to define the association between HSV and HIV acquisition, and the role HSV plays in HIV transmission. These studies should also assess interventions of antiherpetic therapy on HIV transmission and acquisition (research need recommendation)

Genital ulcer disease has long been known as a risk factor for heterosexual HIV transmission in Africa.^{72–74} Genital ulcers increase the risk of transmission of HIV because the mucosal disruption provides a direct site of entry for the virus. Moreover, the thinning of the epithelium and phimosis that follow healing of genital ulcers may make individuals at increased risk of HIV infection via minor abrasions during sexual intercourse or through secondary infection as a consequence of poor hygiene.⁷⁵ Although chancroid, syphilis and genital herpes are all causes of GUD in developing countries, the importance of genital herpes has increased considerably in recent years. In African countries worst affected by HIV infection, genital herpes was identified as the cause of up to 40% of ulcers in studies conducted up until the mid-1990s.⁷⁵

More recent studies using sensitive PCR record higher prevalences and confirm that HSV-2 is an important aetiological agent for GUD. In a study among HIV-infected and HIV-uninfected men attending STD clinics

in Durban, Johannesburg and Cape Town, South Africa, HSV-2 was the most common pathogen identified in GUD specimens. The cross-sectional study enrolled 558 men with genital ulcers and 602 men with urethritis. HSV-2 was detected in 35.9% of ulcer specimens, and was found in more specimens from HIV-infected patients than in those from HIV-uninfected patients (47.4% versus 28.2%, $P \leq 0.001$). Patients with GUD were more likely to be infected with HIV than patients with urethritis (39.4% versus 21.4%, $P \leq 0.001$). Patients infected with HIV were significantly more likely to be HSV-2 seropositive than patients not infected with HIV (63.1% versus 38.5%, $P \leq 0.001$). This suggests a strong association between HSV-2 infection and HIV among patients who present with GUD.²⁷ A very high percentage (64.3%; 45/70) of GUD samples from persons attending an STD clinic in Dar es Salaam, Tanzania, contained HSV-2 DNA.⁷⁶ The prevalence of HSV-2 antibody in these people was 79.7%, and antibodies to HIV were detected in 42% of sera. Although there was a significant positive association between HIV and HSV-2 seropositivity, HSV-2 DNA in genital ulcers was not more prevalent among HIV-seropositive than among HIV-seronegative individuals. HSV-1 was not found in any genital ulcer among the population.

Herpes simplex virus type 2 was also the most common cause of GUD in countries outside Africa. Among 302 patients attending an STD clinic in Pune, India from 1994 to 1996, HSV DNA was detected by multiplex PCR in 26% of samples, *Haemophilus ducreyi* was detected in 23% and *Treponema pallidum* in 10%.⁷⁷ The seroprevalence of HIV was 22.2% and HIV seroprevalence was higher among those patients positive for HSV compared with other aetiologies (OR=2.1; CI, 1.2–3.7; $P=0.01$). Multiplex PCR assay of GUD samples from 38 patients at a Thai STD clinic found that HSV was the most common pathogen. Of the specimens, 81.6% were positive for HSV, 2.3% for both HSV and *T. pallidum*, and none for *H. ducreyi* or *T. pallidum* alone, while 15.8% of specimens were negative for all three pathogens.⁷⁸ In the developed world, HSV is also commonly detected by PCR in genital ulcers; in a study in ten cities in the USA, HSV-2 was the most common pathogen.⁷⁹ It was detected in 62.5% (320/512) of ulcers compared with 3% for *H. ducreyi* and 10% for *T. pallidum*.⁷⁹ Similarly, in a study in Amsterdam, The Netherlands, HSV-2 was the most common aetiological agent of GUD in a study of specimens from the ulcers of 372 patients (48% contained HSV-2 DNA, 3.3% *T. pallidum* DNA and 0.8% [3/368] *H. ducreyi* DNA).⁸⁰

Herpes simplex virus type 2 was not the most frequently detected micro-organism associated with GUD in all studies in the developing world.^{81,82} In

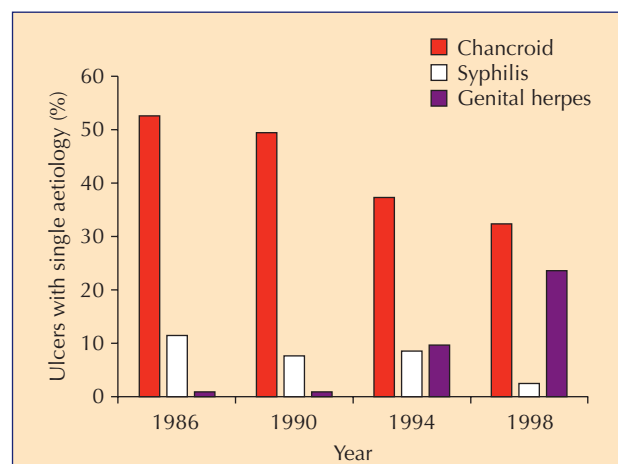


Figure 2: Aetiology of genital ulcer disease from a sexually transmitted infection clinic in a gold mine, South Africa 1986–1998.⁸³

186 South African mine workers, most (54%) of the ulcers were chancroidal, although HSV-2 DNA was the second most common pathogen being found in 18% of ulcers. Notably, more than one micro-organism was detected in 9.1% of the ulcers.⁸² Among STD clinic attendees in Dakar, Senegal, a similarly low proportion of ulcers were HSV-DNA positive (12.8%; 5/39 specimens compared with 56% for *H. ducreyi* and 15% for *T. pallidum*).⁸¹

Genital herpes is of growing importance as a cause of STDs and GUD, and this is illustrated by data from an STI clinic in a South African gold mine from 1986 to 1998.⁸³ The proportions of GUD due to chancroid and syphilis decreased during the 12 years of the study (Figure 2). In parallel, there was a rapid increase among both HIV-positive and negative subjects in the proportion of herpetic ulcers; in 1986, 3% of ulcers were due to HSV-2 compared with 34% in 1998.

Compared with the low number of seroprevalence studies, there have been even fewer studies on the contribution of HSV-2 to GUD in the developing world. Given the importance of GUD in facilitating HIV transmission and acquisition, more studies are required. Such studies would benefit from a rapid (and inexpensive) diagnostic test with high sensitivity and specificity. Moreover, these studies should look at GUD trends over time, be stratified according to gender and HIV status, and should investigate the proportion of genital ulcers due to HSV-1.

Conclusions

There is a high prevalence of HSV-2 infection among non-high-risk populations in Africa and many other countries in the developing world. In sub-Saharan Africa, where most studies have been among men and women aged 15–54 years, seroprevalence higher than 70% in women and 50% in men aged over 30 years is common. As in the developed world, HSV-2 seroprevalence in African countries increases with age and is higher in women than men. In Central and South America, data on HSV-2 seroprevalence are predominantly from women, in whom HSV-2 prevalence ranges from 30% to 54% in those aged between 25 and 39 years. In studies from Peru and Brazil that include both sexes, HSV-2 infection is less common in men than in women. Similar high levels of HSV-2 infection are also reported in the Middle East, for example, from 32% among kidney transplant patients (mean age: 27 years) in Syria to 53% among Jordanian men (age range: 18–24 years). There are currently few data on HSV-2 seroprevalence among non-high-risk individuals in developing countries in Asia but those available suggest a lower prevalence of HSV infection (e.g. 9% in the Philippines) than the rest of the developing world. In general, as expected, core groups such as STI clinic attendees and sex workers had higher prevalences of HSV-2 antibodies than non-high-risk groups.

There are variations in the seroprevalence of HSV-2 between countries, which are likely to reflect both methodological variation, and socio-demographic and behavioural differences between the populations studied. An important finding is that both the seroprevalence and seroincidence of HSV-2 infection is high among young adults, particularly women. This suggests that any disease control measures should consider this age stratum.

Address for correspondence:
Dr Helen Weiss, London School of Hygiene and Tropical Medicine,
Keppel Street, London WC1E 7HT, UK.

E-mail: helen.weiss@lshtm.ac.uk

Received for publication: 6 August 2003

Accepted for publication: 19 September 2003

- Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M *et al*. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000;**182**:1090–1096.
- Walraven G, Scherf C, West B, Ekpo G, Paine K, Coleman R *et al*. The burden of reproductive-organ disease in rural women in The Gambia, West Africa. *Lancet* 2001;**357**: 1161–1167.
- Obasi A, Mosha F, Quigley M, Sekirassa Z, Gibbs T, Munguti K *et al*. Antibody to herpes simplex virus type 2 as a marker of sexual risk behavior in rural Tanzania. *J Infect Dis* 1999;**179**:16–24.
- Kamali A, Nunn AJ, Mulder DW, Van Dyck E, Dobbins JG, Whitworth JA. Seroprevalence and incidence of genital ulcer infections in a rural Ugandan population. *Sex Transm Infect* 1999;**75**: 98–102.
- Wagner HU, Van Dyck E, Roggen E, Nunn AJ, Kamali A, Schmid DS *et al*. Seroprevalence and incidence of sexually transmitted diseases in a rural Ugandan population. *Int J STD AIDS* 1994;**5**:332–337.
- Wawer MJ, Eng SM, Serwadda D, Sewankambo NK, Kiwanuka N, Li C *et al*. Prevalence of Kaposi sarcoma-associated herpesvirus compared with selected sexually transmitted diseases in adolescents and young adults in rural Rakai District, Uganda. *Sex Transm Dis* 2001;**28**:77–81.
- Auvert B, Ballard R, Campbell C, Carael M, Carton M, Fehler G *et al*. HIV infection among youth in a South African mining town is associated with herpes simplex virus-2 seropositivity and sexual behaviour. *AIDS* 2001;**15**: 885–898.
- Gwanzura L, McFarland W, Alexander D, Burke RL, Katzenstein D. Association between human immunodeficiency virus and herpes simplex virus type 2 seropositivity among male factory workers in Zimbabwe. *J Infect Dis* 1998;**177**: 481–484.
- McFarland W, Gwanzura L, Bassett MT, Machezano R, Latif AS, Ley C *et al*. Prevalence and incidence of herpes simplex virus type 2 infection among male Zimbabwean factory workers. *J Infect Dis* 1999;**180**: 1459–1465.
- Gregson S, Mason PR, Garnett GP, Zhuwau T, Nyamukapa CA, Anderson RM *et al*. A rural HIV epidemic in Zimbabwe? Findings from a population-based survey. *Int J STD AIDS* 2001;**12**:189–196.
- del Mar Pujades Rodriguez M, Obasi A, Mosha F, Todd J, Brown D, Changalucha J *et al*. Herpes simplex virus type 2 infection increases HIV incidence: a prospective study in rural Tanzania. *AIDS* 2002;**16**:451–462.
- Kamali A, Quigley M, Nakiyingi J, Kinsman J, Kengeya-Kayondo J, Gopal R *et al*. Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *Lancet* 2003;**361**:645–652.
- Weiss HA, Buve A, Robinson NJ, Van Dyck E, Kahindo M, Anagonou S *et al*. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. *AIDS* 2001;**15** (Suppl 4): S97–S108.
- Mbizvo EM, Msuya Sia E, Stray-Pedersen B, Chirenje MZ, Munjoma M, Hussain A. Association of herpes simplex virus type 2 with the human immunodeficiency virus among urban women in Zimbabwe. *Int J STD AIDS* 2002;**13**:343–348.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK *et al*. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;**337**: 1105–1111.
- Breinig MK, Kingsley LA, Armstrong JA, Freeman DJ, Ho M. Epidemiology of genital herpes in Pittsburgh: serologic, sexual, and racial correlates of apparent and inapparent herpes simplex infections. *J Infect Dis* 1990;**162**:299–305.
- Mihret W, Rinke de Wit TF, Petros B, Mekonnen Y, Tsegaye A, Wolday D *et al*. Herpes simplex virus type 2 seropositivity among urban adults in Africa: results from two cross-sectional surveys in Addis Ababa, Ethiopia. *Sex Transm Dis* 2002;**29**: 175–181.
- Msuya SE, Mbizvo E, Hussain A, Sam NE, Jeansson S, Stray-Pedersen B. Seroprevalence and correlates of herpes simplex virus type 2 among urban Tanzanian women. *Sex Transm Dis* 2003;**30**:588–592.
- Halton K, Ratcliffe AA, Morison L, West B, Shaw M, Bailey R *et al*. Herpes simplex 2 risk among women in a polygynous setting in rural West Africa. *AIDS* 2003;**17**: 97–103.
- Reynolds SJ, Risbud AR, Shepherd ME, Zenilman JM, Brookmeyer RS, Paranjape RS *et al*. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. *J Infect Dis* 2003;**187**:1513–1521.
- Shaw M, van der Sande M, West B, Paine K, Ceasay S, Bailey R *et al*. Prevalence of herpes simplex type 2 and syphilis serology among young adults in a rural Gambian community. *Sex Transm Infect* 2001;**77**: 358–365.
- Ghebrekidan H, Ruden U, Cox S, Wahren B, Grandien M. Prevalence of herpes simplex virus types 1 and 2, cytomegalovirus, and varicella-zoster virus infections in Eritrea. *J Clin Virol* 1999;**12**:53–64.
- Nzila N, Laga M, Thiam MA, Mayimona K, Edidi B, Van Dyck E *et al*. HIV and other sexually transmitted diseases among female prostitutes in Kinshasa. *AIDS* 1991;**5**: 715–721.
- Rakwar J, Lavreys L, Thompson ML, Jackson D, Bwayo J, Hassanali S *et al*. Cofactors for the acquisition of HIV-1 among heterosexual men: prospective cohort study of trucking company workers in Kenya. *AIDS* 1999;**13**: 607–614.
- Dada AJ, Ajayi AO, Diamondstone L, Quinn TC, Blattner WA, Biggar RJ. A serosurvey of *Haemophilus ducreyi*, syphilis, and herpes simplex virus type 2 and their association with human immunodeficiency virus among female sex workers in Lagos, Nigeria. *Sex Transm Dis* 1998;**25**:237–242.
- Dada AJ, Oyewole F, Onofowokan R, Nasidi A, Harris B, Levin A *et al*. Demographic characteristics of retroviral infections (HIV-1, HIV-2, and HTLV-I) among female professional sex workers in Lagos, Nigeria. *J Acquir Immune Defic Syndr* 1993;**6**:1358–1363.
- Chen CY, Ballard RC, Beck-Sague CM, Dangor Y, Radebe F, Schmid S *et al*. Human immunodeficiency virus infection and genital ulcer disease in South Africa: the herpetic connection. *Sex Transm Dis* 2000;**27**:21–29.
- Langeland N, Haarr L, Mhalu F. Prevalence of HSV-2 antibodies among STD clinic patients in Tanzania. *Int J STD AIDS* 1998;**9**:104–107.
- 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–S28.
- Lagarde E, Auvert B, Chege J, Sukwa T, Glynn JR, Weiss HA *et al*. Condom use and its association with HIV/sexually transmitted diseases in four urban communities of sub-Saharan Africa. *AIDS* 2001;**15** (Suppl 4):S71–S78.
- Kapiga SH, Sam NE, Shao JF, Masenga EJ, Renjifo B, Kiwelu IE *et al*. Herpes simplex virus type 2 infection among bar and hotel workers in northern Tanzania: prevalence and risk factors. *Sex Transm Dis* 2003;**30**:187–192.
- Ferrera A, Baay MF, Herbrink P, Figueroa M, Velema JP, Melchers WJ. A sero-epidemiological study of the relationship between sexually transmitted agents and cervical cancer in Honduras. *Int J Cancer* 1997;**73**:781–785.
- de Sanjose S, Munoz N, Bosch FX, Reimann K, Pedersen NS, Orfila J *et al*. Sexually transmitted agents and cervical neoplasia in Colombia and Spain. *Int J Cancer* 1994;**56**:358–363.
- Boulos R, Ruff AJ, Nahmias A, Holt E, Harrison L, Magder L *et al*. Herpes simplex virus type 2 infection, syphilis, and hepatitis B virus infection in Haitian women with human immunodeficiency virus type 1 and human T lymphotropic virus type I infections. The Johns Hopkins University (JHU)/Centre pour le Developpement et la Sante (CDS) HIV Study Group. *J Infect Dis* 1992;**166**: 418–420.
- Hildesheim A, Mann V, Brinton LA, Szklo M, Reeves WC, Rawls WE. Herpes simplex virus type 2: a possible interaction with human papillomavirus types 16/18 in the development of invasive cervical cancer. *Int J Cancer* 1991;**49**:335–340.
- Carvalho M, de Carvalho S, Pannuti CS, Sumita LM, de Souza VA. Prevalence of herpes simplex type 2 antibodies and a clinical history of herpes in three different populations in Campinas City, Brazil. *Int J Infect Dis* 1998;**3**:94–98.
- Copas A, Mindel A, Cowan F. Risk scores to improve serological screening for herpes. *Int J STD AIDS* 2001;**12** (Suppl 2):170.
- Weinberg A, Canto CL, Pannuti CS, Kwang WN, Garcia SA, Zugaib M. Herpes simplex virus type 2 infection in pregnancy: asymptomatic viral excretion at delivery and seroepidemiologic survey of two socioeconomically distinct populations in Sao Paulo, Brazil. *Rev Inst Med Trop Sao Paulo* 1993;**35**: 285–290.
- Stone KM, Zaidi A, Rosero-Bixby L, Oberle MW, Reynolds G, Larsen S *et al*. Sexual behavior, sexually transmitted diseases, and risk of cervical cancer. *Epidemiology* 1995;**6**:409–414.
- Oberle MW, Rosero-Bixby L, Lee FK, Sanchez-Braverman M, Nahmias AJ, Guinan ME. Herpes simplex virus type 2 antibodies: high prevalence in monogamous women in Costa Rica. *Am J Trop Med Hyg* 1989;**41**:224–229.
- Lazcano-Ponce E, Smith JS, Munoz N, Conde-Glez CJ, Juarez-Figueroa L, Cruz A *et al*. High prevalence of antibodies to herpes simplex virus type 2 among middle-aged women in Mexico City, Mexico: a population-based study. *Sex Transm Dis* 2001;**28**:270–276.
- Hernandez-Giron C, Uribe-Salas F, Conde-Gonzalez C, Cruz-Valdez A, Juarez-Figueroa L, Uribe-Zuniga P *et al*. [Seroprevalence of various viruses and socio-demographic characteristics of women seeking HIV screening]. *Rev Invest Clin* 1997;**49**:5–13.
- Conde-Glez CJ, Juarez-Figueroa L, Uribe-Salas F, Hernandez-Nevarez P, Schmid DS, Calderon E *et al*. Analysis of herpes simplex virus 1 and 2 infection in women with high risk sexual behaviour in Mexico. *Int J Epidemiol* 1999;**28**:571–576.
- Uribe-Salas F, Hernandez-Avila M, Juarez-Figueroa L, Conde-Glez CJ, Uribe-Zuniga P. Risk factors for herpes simplex virus type 2 infection among female commercial sex workers in Mexico City. *Int J STD AIDS* 1999;**10**: 105–111.
- Uribe-Salas F, Hernandez-Giron C, Conde-Gonzalez C, Cruz-Valdez A, Juarez-Figueroa L, Hernandez-Avila M. [Characteristics related to STD/HIV in men working in Mexico City bars where

- female prostitution takes place]. *Salud Publica Mex* 1995;**37**:385–393.
46. Sanchez J, Gotuzzo E, Escamilla J, Carrillo C, Phillips IA, Barrios C *et al*. Gender differences in sexual practices and sexually transmitted infections among adults in Lima, Peru. *Am J Public Health* 1996;**86**: 1098–1107.
 47. Smith JS, Herrero R, Munoz N, Eluf-Neto J, Ngelangel C, Bosch FX *et al*. Prevalence and risk factors for herpes simplex virus type 2 infection among middle-age women in Brazil and the Philippines. *Sex Transm Dis* 2001;**28**: 187–194.
 48. 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**: 1325–1329.
 49. Monsalve F, Estevez J, Costa L, Salas M, Hernandez M, Olaya J *et al*. [Seroepidemiology of Herpes simplex virus type 2 in the Amerindian Yukpa population of Zulua state, Venezuela]. *Rev Med Chil* 2001;**129**:247–252.
 50. Uribe-Salas F, Conde-Glez CJ, Juarez-Figueroa L, Hernandez-Castellanos A. Sociodemographic dynamics and sexually transmitted infections in female sex workers at the Mexican-Guatemalan border. *Sex Transm Dis* 2003;**30**:266–271.
 51. Da Rosa-Santos OL, Goncalves Da Silva A, Pereira AC, Jr. Herpes simplex virus type 2 in Brazil: seroepidemiologic survey. *Int J Dermatol* 1996;**35**:794–796.
 52. Dobbins JG, Mastro TD, Nopkesorn T, Sangkharomya S, Limpakarnjanarat K, Weniger BG *et al*. Herpes in the time of AIDS: a comparison of the epidemiology of HIV-1 and HSV-2 in young men in northern Thailand. *Sex Transm Dis* 1999;**26**:67–74.
 53. Nelson KE, Eiumtrakul S, Celentano D, Maclean I, Ronald A, Suprasert S *et al*. The association of herpes simplex virus type 2 (HSV-2), *Haemophilus ducreyi*, and syphilis with HIV infection in young men in northern Thailand. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;**16**:293–300.
 54. Bogaerts J, Ahmed J, Akhter N, Begum N, Rahman M, Nahar S *et al*. Sexually transmitted infections among married women in Dhaka, Bangladesh: unexpected high prevalence of herpes simplex type 2 infection. *Sex Transm Infect* 2001;**77**:114–119.
 55. Peng HQ, Liu SL, Mann V, Rohan T, Rawls W. Human papillomavirus types 16 and 33, herpes simplex virus type 2 and other risk factors for cervical cancer in Sichuan Province, China. *Int J Cancer* 1991;**47**:711–716.
 56. Lo JY, Lim WW, Ho DW, Field PR, Cunningham AL. Difference in seroprevalence of herpes simplex virus type 2 infection among antenatal women in Hong Kong and southern China. *Sex Transm Infect* 1999;**75**:123.
 57. Rahman M, Alam A, Nessa K, Hossain A, Nahar S, Datta D *et al*. Etiology of sexually transmitted infections among street-based female sex workers in Dhaka, Bangladesh. *J Clin Microbiol* 2000;**38**:1244–1246.
 58. Limpakarnjanarat K, Mastro TD, Saisorn S, Uthavoravit W, Kaewkungwal J, Korattana S *et al*. HIV-1 and other sexually transmitted infections in a cohort of female sex workers in Chiang Rai, Thailand. *Sex Transm Infect* 1999;**75**:30–35.
 59. Hawkes S, Morison L, Chakraborty J, Gausia K, Ahmed F, Islam SS *et al*. Reproductive tract infections: prevalence and risk factors in rural Bangladesh. *Bull World Health Organ* 2002;**80**: 180–188.
 60. Gibney L, Saquib N, Macaluso M, Hasan KN, Aziz MM, Khan AY *et al*. STD in Bangladesh's trucking industry: prevalence and risk factors. *Sex Transm Infect* 2002;**78**:31–36.
 61. Azim T, Islam MN, Bogaerts J, Mian MA, Sarker MS, Fattah KR *et al*. Prevalence of HIV and syphilis among high-risk groups in Bangladesh. *AIDS* 2000;**14**:210–211.
 62. Abuharfeil N, Meqdam MM. Seroepidemiologic study of herpes simplex virus type 2 and cytomegalovirus among young adults in northern Jordan. *New Microbiol* 2000;**23**:235–239.
 63. Arseven G, Tuncel E, Tuncel S, Sonmez E, Gulen AK. [Distribution of HSV-1 and HSV-2 antibodies in pregnant women]. *Mikrobiyol Bul* 1992;**26**:359–366.
 64. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. *Clin Infect Dis* 1998;**26**:541–553.
 65. Whitley RJ, Roizman B. Herpes simplex virus infections. *Lancet* 2001;**357**: 1513–1518.
 66. Corey L, Langenberg AG, Ashley R, Sekulovich RE, Izu AE, Douglas JM, Jr *et al*. Recombinant glycoprotein vaccine for the prevention of genital HSV-2 infection: two randomized controlled trials. Chiron HSV Vaccine Study Group. *JAMA* 1999;**282**: 331–340.
 67. Armstrong GL, Schillinger J, Markowitz L, Nahmias AJ, Johnson RE, McQuillan GM *et al*. Incidence of herpes simplex virus type 2 infection in the United States. *Am J Epidemiol* 2001;**153**:912–920.
 68. Christenson B, Bottiger M, Svensson A, Jeansson S. A 15-year surveillance study of antibodies to herpes simplex virus types 1 and 2 in a cohort of young girls. *J Infect* 1992;**25**:147–154.
 69. Brown ZA, Selke S, Zeh J, Kopelman J, Maslow A, Ashley RL *et al*. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997;**337**: 509–515.
 70. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;**69**:19–36.
 71. Langenberg AG, Corey L, Ashley RL, Leong WP, Straus SE. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. *N Engl J Med* 1999;**341**:1432–1438.
 72. Rubin DI, Daube JR. Subacute sensory neuropathy associated with Epstein-Barr virus. *Muscle Nerve* 1999;**22**: 1607–1610.
 73. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect* 1999;**75**: 3–17.
 74. Orroth KK, Gavyole A, Todd J, Moshafiq F, Ross D, Mwijarubi E *et al*. Syndromic treatment of sexually transmitted diseases reduces the proportion of incident HIV infections attributable to these diseases in rural Tanzania. *AIDS* 2000;**14**:1429–1437.
 75. O'Farrell N. Targeted interventions required against genital ulcers in African countries worst affected by HIV infection. *Bull World Health Organ* 2001;**79**: 569–577.
 76. Mwansasu A, Mwakagile D, Haarr L, Langeland N. Detection of HSV-2 in genital ulcers from STD patients in Dar es Salaam, Tanzania. *J Clin Virol* 2002;**24**:183–192.
 77. Risbud A, Chan-Tack K, Gadkari D, Gangakhedkar RR, Shepherd ME, Bollinger R *et al*. The etiology of genital ulcer disease by multiplex polymerase chain reaction and relationship to HIV infection among patients attending sexually transmitted disease clinics in Pune, India. *Sex Transm Dis* 1999;**26**:55–62.
 78. Beyrer C, Jitwatcharanan K, Natpratan C, Kaewvichit R, Nelson KE, Chen CY *et al*. Molecular methods for the diagnosis of genital ulcer disease in a sexually transmitted disease clinic population in northern Thailand: predominance of herpes simplex virus infection. *J Infect Dis* 1998;**178**:243–246.
 79. Mertz KJ, Trees D, Levine WC, Lewis JS, Litchfield B, Pettus KS *et al*. Etiology of genital ulcers and prevalence of human immunodeficiency virus coinfection in 10 US cities. The Genital Ulcer Disease Surveillance Group. *J Infect Dis* 1998;**178**:1795–1798.
 80. Bruisten SM, Cairo I, Fennema H, Pijl A, Buimer M, Peerbooms PG *et al*. Diagnosing genital ulcer disease in a clinic for sexually transmitted diseases in Amsterdam, The Netherlands. *J Clin Microbiol* 2001;**39**: 601–605.
 81. Totten PA, Kuypers JM, Chen CY, Alfa MJ, Parsons LM, Dutro SM *et al*. Etiology of genital ulcer disease in Dakar, Senegal, and comparison of PCR and serologic assays for detection of *Haemophilus ducreyi*. *J Clin Microbiol* 2000;**38**:268–273.
 82. Ballard RC, Fehler HG, Htun Y, Radebe F, Jensen JS, Taylor-Robinson D. Coexistence of urethritis with genital ulcer disease in South Africa: influence on provision of syndromic management. *Sex Transm Infect* 2002;**78**: 274–277.
 83. Htun Y, Fehler G, Tshabalala V, Radebe F, Ballard R. Genital ulcer diseases in Africa: epidemiological trends. *WHO/UNAIDS/LSHTM Workshop on HSV2: Programmatic and Research Priorities in Developing Countries*, London, UK, 2001.

The Interaction between Herpes Simplex Virus and Human Immunodeficiency Virus

Connie L. Celum, University of Washington, Seattle, WA, USA.

KEY WORDS

■ HSV ■ HIV ■ RISK ■ ACQUISITION ■ LESION ■ SHEDDING ■ THERAPY
■ TESTS ■ ANTIVIRAL ■ SUPPRESSION ■ PREVENTION ■ TRANSMISSION
■ INTERACTION ■ STI ■ EPIDEMIOLOGY ■ ASYMPTOMATIC
■ MANAGEMENT

SUMMARY

Many studies indicate that herpes simplex virus (HSV) seropositivity increases the risk of acquiring HIV, with fewer studies also indicating that HSV-2 infection increases the risk of transmitting HIV. In a recent meta-analysis, HSV-2 infection increased the risk of HIV-acquisition two-fold. This increased risk may occur by HSV-2 reactivation disrupting the epithelial barrier and recruiting activated CD4 cells, which are target cells for HIV infection, into the lesion. *In vivo* and *in vitro* studies assessing the effect of HSV-2 on HIV transmission demonstrate that HIV-infected CD4 cells are recruited to HSV-infected lesions and that HSV regulatory proteins (ICP0, ICP4, VP16) may upregulate HIV replication, thus increasing the frequency and titre of mucosal HIV shedding. This may occur during both clinical and asymptomatic HSV reactivation. Plausibly, antiherpetic therapy could reduce HIV transmission by decreasing HIV plasma load and/or mucosal HIV shedding, but a proof-of-concept trial is needed to demonstrate this. It also appears that individuals co-infected with HIV and HSV-2 have more frequent HSV recurrences than individuals infected with HSV-2 alone. There is a strong correlation between decreasing CD4 count and increasing rates of HSV reactivation, suggesting that reactivation is linked to immunosuppression. The IHMF recommends that individuals with HIV should be serologically tested for HSV-2. HSV-2 infection should be targeted as a modifiable risk factor for HIV acquisition by testing, counselling and preventing acquisition through behavioural interventions, treatment and antiviral suppression.

Introduction

THE SPREAD OF HIV, particularly in Africa, is facilitated by the high prevalence of genital ulceration caused by untreated sexually transmitted infections (STIs).¹ This is a risk factor for HIV infection as it provides a direct portal for HIV entry through mucosal disruption. In this context, the relationship between HIV infection and herpes simplex virus type 2 (HSV-2) infection is of particular importance as HSV-2 is the most common cause of genital ulcers in the developed world^{2,3} and the developing world.⁴⁻⁷ Persistent anogenital lesions due to HSV were among the first opportunistic infections described in those with AIDS.⁸ There has since been a large number of seroepidemiological studies of HSV and HIV infection, together with a smaller number of *in vitro* studies that demonstrate an association between HSV infection and HIV reactivation, linking HSV-2 infection to both susceptibility to and infectiousness of HIV. However, it is less clear whether or not the effect of HSV-2 on increasing the risk of HIV acquisition is primarily during symptomatic genital herpes (e.g. genital ulceration) or if HIV acquisition/transmission is also

enhanced during asymptomatic infection. Recent data suggest that asymptomatic HSV-2 infection is also an important contributor to the acquisition and transmission of HIV infection. This paper considers the evidence for a synergistic interaction between HSV-2 and HIV infection, and potential strategies for incorporating antiherpetic therapy into HIV management protocols.

Contribution of HSV Infection to HIV Acquisition

MECHANISMS BY WHICH HSV-2 MAY INCREASE THE RISK OF HIV ACQUISITION

The increased risk of HIV acquisition in HSV-2 seropositive individuals is consistent with the biology of HSV-2 reactivation. Recurrent genital HSV infection involves disruption of the epithelial surface and recruitment of activated CD4+ cells to the area.⁹ These activated immune cells may then be targets for HIV, facilitating HIV acquisition when in contact with HIV-infected genital fluids.

META-ANALYSIS OF STUDIES ON THE EFFECT OF HSV-2 INFECTION ON HIV ACQUISITION

The risk of HIV acquisition is increased approximately two-fold in HSV-2-seropositive persons according to a meta-analysis of the large body of literature on co-infection with the viruses.¹⁰ Thirteen studies assessed the temporal relationship between HSV-2 and HIV infection; these studies included four longitudinal studies, all of which were conducted in the developed world, together with five nested case-control studies and four case-control studies. Of the latter studies, two were performed in developing countries and seven in the developed world. The remaining 18 studies were cross-sectional and comprised 14 studies from developing countries and four from the USA.

Estimates of the risk of HIV infection in HSV-2 seropositive persons:

The estimates of risk of HSV-2 seropositivity from the meta-analysis differed according to the type of study (Figure 1).¹⁰ In the nine cohort and nested case-control studies that assessed the temporal relationship between HSV-2 and HIV infection, the relative risk (RR) of HSV-2 infection preceding HIV infection was 2.1 (95% confidence interval [CI], 1.4–3.2). In comparison, the summary estimate odds ratio (OR) for the 22 case-control and cross-sectional studies was 3.9 (95% CI, 3.1–5.1). There was statistically significant heterogeneity in the overall risk of HIV infection in HSV-2 seropositive persons among all the studies ($P < 0.001$).

Cohort and nested case-control studies: The cohort and nested case-control studies, which assessed the temporal relationship between HIV and HSV infection, showed that the risk of acquiring HIV infection was increased in HSV-2-seropositive heterosexual men (RR, 2.2; 95% CI, 1.3–3.8) and in HSV-2-seropositive men

RECOMMENDATIONS AND STATEMENTS

- HSV-2 reactivation increases the frequency and titre of mucosal HIV shedding (category 1 recommendation)
- HIV-positive persons should be serologically tested for HSV-2 infection and counselled about clinical and public health implications (category 3 recommendation)
- Through serological testing and counselling, and by prevention of acquisition (e.g. through behavioural interventions), herpes treatment and antiviral suppression, HSV-2 should be targeted as a modifiable risk factor for HIV acquisition (category 3 recommendation)
- Substantial epidemiological evidence indicates that HSV-2 infection increases the risk of acquiring HIV by approximately two-fold. However, data are unavailable to determine if treating HSV-2 infection can substantially reduce the risk of HIV acquisition. A proof-of-concept intervention trial is required to establish whether or not HSV-2 suppressive therapy in populations with high prevalence of HSV-2 and

HIV can lower the risk of HIV acquisition or transmission (research need recommendation)

- Additional biological and epidemiological studies are needed to characterize HSV-2 as a risk factor for HIV transmission (research need recommendation)

RECOMMENDATION AND STATEMENT CATEGORIES

Category 1

Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

Category 2

Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

Category 3

Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Research Need

Area in which research is warranted.

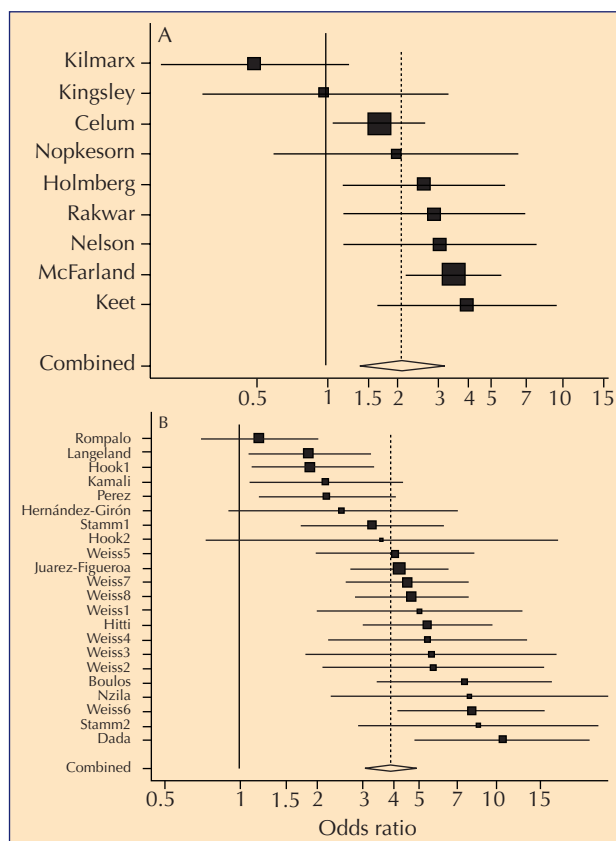


Figure 1: Summary of the estimates of risk of HIV infection in HSV-2 infected persons. A) Results from nine cohort and nested case-control studies. B) Results from 22 case-control and cross-sectional studies.¹⁰ Reproduced with permission from Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002;185:45–52. University of Chicago. © 2002 by the Infectious Diseases Society of America. All rights reserved.

who have sex with men (MSM) (RR, 2.1; 95% CI, 1.3–3.4).¹⁰ There was only one longitudinal study of HIV acquisition in HSV-2-seropositive women in whom the risk was not increased (RR, 0.5; 95% CI, 0.2–1.1). The risk of HIV infection was similar in developing (RR, 2.1; 95% CI, 1.0–4.2) and developed (RR, 2.1; 95% CI, 1.3–3.4) countries.

Case-control and cross-sectional studies: The case-control and cross-sectional studies indicated a higher risk estimate in the developing world (OR, 4.6; 95% CI, 3.5–5.9) than the developed world (OR, 2.9; 95% CI, 1.7–4.7), but the difference was not statistically significant.¹⁰ The risk of HIV infection in HSV-2-seropositive individuals was increased in all populations studied: women (OR 3.9; 95% CI, 2.7–5.5), heterosexual men (OR, 4.1; 95% CI, 2.9–5.8) and MSM (OR, 4.3; 95% CI, 2.4–7.6).

A cross-sectional study published after the meta-analysis also demonstrated an association between HSV-2 and HIV among 393 urban women attending primary healthcare clinics in Zimbabwe.¹¹ HSV-2-seropositive women had twice the risk of being HIV infected compared with those who were HSV-2-seronegative (OR, 2.1; 95% CI, 1.3–3.2). A study of heterosexual men also found that people infected with HIV were also more likely to be HSV-2-seropositive than HIV-negative individuals (63.1% versus 38.5%, $P \leq 0.001$).⁴

STUDY OF MSM IN THE USA

The studies included in the meta-analysis showing the association between HSV-2 and HIV acquisition mainly considered heterosexuals. Studies of the epidemiology of HSV and HIV infections in MSM further support the importance of HSV-2 infection in increasing the risk of HIV infection.

The seroprevalence of HSV-2 is high among MSM: 30–50% among those who are HIV-negative and up to 80% among individuals who are HIV-infected.^{12,13} In some,^{14,15} but not all studies of MSM,¹⁶ HSV-2 infection was associated with an increased risk of HIV seroconversion. The differences between these studies could be due to the small number of subjects in each study, as well as the challenges of controlling for sexual behaviour and exposure to HIV in the analysis.

The largest study to date, which was included in the meta-analysis, confirmed HSV-2 infection as a risk factor for increased risk of HIV acquisition in high-risk MSM,¹⁷ which included 116 HIV seroconverters and 342 controls (men who remained HIV-seronegative). Another important finding of the study was the contribution of asymptomatic HSV-2 infections to HIV acquisition.

In multivariate analysis, independent risk factors for HIV acquisition were prior HSV-2 infection (either HSV-2 seropositive at study entry or HSV-2 seroconversion between study enrolment and prior to HIV acquisition; OR, 1.8; 95% CI, 1.1–2.9), a lack of reported genital herpes recurrences in the previous 12 months and number of sex partners (Table 1). The risk of HIV acquisition was somewhat higher (OR, 2.8; 95% CI,

Table 1: Risk factors for HIV acquisition among HSV-2-positive MSM in USA¹⁷

		OR	95% CI	P-value
HSV-2 seropositive		1.8*	1.1–2.9	0.03
Reported HSV outbreaks		0.3	0.1–0.8	0.02
Sex partners in the past 12 months (n)	<3	–	–	–
	3–5	1.4	0.7–3.0	0.3
	6–12	1.5	0.7–3.1	0.3
	>12	2.9	1.4–6.3	0.006
Bacterial STIs		1.4	0.7–2.8	0.7

* Adjusted for age, race, health insurance, city, year of HIV seroconversion, condom breakage, any HIV-positive partner or partner of unknown status in prior 12 months, frequency of unprotected receptive anal sex. HSV, herpes simplex virus; MSM, men who have sex with men; STI, sexually transmitted infection; OR, odds ratio; CI, confidence interval. Reproduced from Renzi *et al.*¹⁷

0.8–10.1) among MSM who seroconverted to HSV-2 after study entry compared with those who did not seroconvert to HSV-2, after adjusting for sexual behaviour and possible HIV exposure, although the study had limited power to compare the HIV acquisition risk among those with prevalent HSV-2 infection with the risk among those with incident HSV-2 infection. Importantly, as only 15% of the MSM reported a genital herpes outbreak in the last year, HSV-2 increases the risk of HIV acquisition independent of recognized lesions. The risk may be increased, as microscopic lesions, which could provide a portal for HIV entry, may accompany apparently asymptomatic episodes.

TEMPORAL RELATIONSHIP BETWEEN HIV AND HSV-2 ACQUISITION

The risk of HSV-2 acquisition is also increased in HIV-infected individuals compared with HIV-uninfected persons, which means that the estimates of risk in cross-sectional and case-control studies could be overestimated. The importance of knowing the temporal relationship between HSV-2 infection and HIV acquisition is illustrated by two studies on the effect of prior HIV infection on HSV-2 acquisition.^{18,19} In a prospective study of 111 male factory workers in Zimbabwe, the RR was 4.7-times (95% CI, 3.3–6.7) higher in HIV-seropositive individuals than for those who were HIV-seronegative.¹⁸ In a study in rural Uganda, the RR of incident HSV-2 infection was 3.7-fold (95% CI, 2.1–6.6) higher in HIV-seropositive individuals than HIV-seronegative persons.¹⁹ As these two studies demonstrate, HIV-positive individuals are at approximately four-fold increased risk of HSV-2 acquisition compared to HIV-negative persons. Thus, cross-sectional and case-control studies, which cannot discern the timing of HSV-2 infection versus HIV acquisition, probably overestimate the association between HSV-2 and HIV acquisition.

DETERMINING THE PROPORTION OF HIV INFECTIONS ATTRIBUTABLE TO HSV-2 INFECTION

To determine a causal relationship between any two infections, prospective studies documenting the temporal sequence of the two events are needed, and thus longitudinal studies provide more reliable estimates of the relative contribution of HSV-2 to the risk of HIV infection. Therefore, the authors of the meta-analysis discussed earlier¹⁰ used the estimate of a 2.1-fold increase in the risk of HIV infections in HSV-2-seropositive individuals, obtained from the cohort and nested case-control studies, to calculate the HIV-acquisition risk attributable to HSV-2 infection. Using the RR of 2.1, then among HSV-2 seropositive individuals, the attributable fraction of HIV due to HSV-2 infection is 52%.¹⁰ Within a population, the population-attributable risk percentage (which is the

estimated percentage reduction in risk for HIV infection if HSV-2 infection were eliminated) will vary with HSV-2 seroprevalence (Figure 2).¹⁰ For example, if HSV-2 seroprevalence in the general population in the USA is 22%, as determined in the National Health and Nutrition Examination Surveys III study in the USA,² then 19% of HIV infections can be attributed to HSV-2. Similarly, among women in sub-Saharan Africa whose rates of HSV-2 infection approach 80%, approximately 47% of HIV infections can be attributed to HSV-2 infection. Consequently, a large fraction of HIV infection can be attributed to HSV-2 infections, even using a conservative estimate of a 2.1-fold increase in the risk of HIV infection in HSV-2 seropositive individuals.

INCIDENT HSV-2 AND THE RISK OF HIV ACQUISITION

The risk of HIV acquisition is greater with recent (incident) HSV-2 infection than with prevalent (chronic) HSV-2 infection in two studies published after the meta-analysis. The studies took place among HIV seroconverters in Tanzania, and in patients recruited from STI clinics in Pune, India.^{20,21}

Tanzanian study: In the study in Tanzania, incident HSV-2 infection increased the risk of HIV acquisition more than prevalent HSV-2 infection.²⁰ In the study, 127 HIV-

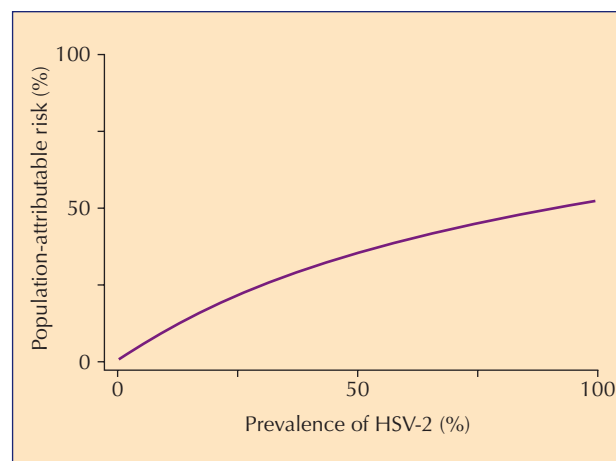


Figure 2: Population-attributable risk percentage of HIV infection due to HSV-2 infection, by HSV-2 seroprevalence.¹⁰ Reproduced with permission from Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002;**185**:45–52. University of Chicago. © 2002 by the Infectious Diseases Society of America. All rights reserved.

seroconverters from the Mwanza region were matched with 636 controls who remained HIV-seronegative. HSV-2 serology was performed at baseline and at 2-year follow up. The OR for HSV-2 on HIV acquisition was higher for incident (recent) HSV-2 infection than prevalent (chronic) HSV-2 infection in both men and women, although the association was stronger in men (Table 2). The population-attributable fractions of incident HIV infection due to HSV-2 were estimated as 74% in men and 22% in women.

Study in Pune, India: Recent HSV-2 infection was also found to increase the risk of HIV acquisition by approximately three-fold in a study among patients recruited from STI clinics in Pune, India.²¹ In a retrospective cohort study, HSV-2 seroprevalence and seroincidence were established from 2732 HIV-1-seronegative persons who attended STI or gynaecology clinics. In the study, incident HSV-2 infection was categorized as recent or remote (within the past 6 months or more than 6 months, respectively), based on repeat HSV-2 serological testing.

The baseline HSV-2 seroprevalence was 43.0% (1175/2732). Among those initially HSV-2 seronegative, the HSV-2 incidence was 11.4/100 patient-years (95% CI, 9.9–13.0). Based on a median follow-up time of 11 months, the incidence of HIV was 5.8/100 patient-years (95% CI, 5.0–6.6). After adjusting for known HIV risk factors, the RR of HIV acquisition associated with prevalent (chronic) HSV-2 infection was 1.6 (95%CI, 1.2–2.3; $P=0.001$) and 1.8 (95% CI 1.0–3.0; $P=0.02$) with remote primary HSV-2 infection. In contrast, recent HSV-2 infection (i.e. within the previous 6 months) was independently associated with a 3.6-fold increased risk of primary HIV infection (95% CI, 1.7–7.7; $P<0.001$).²²

The findings of these recent studies suggest that there is an increased risk associated with incident HSV-2 infection compared with prevalent HSV-2 infection. This risk may, in part, be explained by the greater severity of incident HSV-2 infection and more frequent recurrences in the first year after HSV-2 acquisition.

IMPLICATION OF STUDIES ON HSV-2 INFECTION AND THE RISK OF HIV ACQUISITION

The meta-analysis discussed above¹⁰ and subsequent studies support the hypothesis that mucosal ulceration from HSV-2 infection facilitates HIV acquisition. A corollary is that prevention of primary HSV-2 infection or suppression of HSV-2 reactivation may significantly reduce the risk of HIV infection in these settings.

HSV-2 and HIV Transmission

While the risk of HIV acquisition is increased by prior HSV-2 infection, less is known about the effects of HSV infection on HIV transmission.

- HSV-2 reactivation increases the frequency and titre of mucosal HIV shedding (category 1 recommendation)

MECHANISMS BY WHICH HSV-2 MAY INCREASE THE RISK OF HIV TRANSMISSION

A biological explanation can be proposed for the increased risk of HIV transmission with HSV-2 infection. HSV and HIV can co-infect lymphocytes *in vitro* and *in vivo*,^{23,24} and several HSV regulatory proteins (e.g. infected cell proteins [ICP-0 and ICP-4]) upregulate HIV replication through their interaction with the HIV long terminal repeat region.^{25–27} Similarly, viral protein 16, which is the transactivating protein of HSV, acts synergistically with the HIV Tat protein to increase HIV transcription.²⁷ HSV-2 may also increase HIV load as HSV-infected lesions are characterized by an influx of activated CD4+ cells.²⁸ The activation of CD4+ cells has been shown markedly to upregulate HIV replication.²⁹ Thus, the recruitment of HIV-infected CD4+ cells into mucosal ulcerations due to HSV reactivation, along with the potential *in vivo* interaction between the two viruses, may account for the high titre of HIV in genital HSV lesions. In support of this hypothesis, acute genital HSV episodes result in transient increases in plasma levels of HIV RNA in humans.^{30,31}

Effect of aciclovir on HIV load: In a recent study, HSV suppression was associated with a significant decrease in plasma HIV load.³¹ Twenty-seven people co-infected with HSV and HIV were enrolled into a prospective, longitudinal study in which daily home cultures were taken and diaries of HSV symptoms kept. At the first sign of symptoms, subjects came to a clinic for cultures and HIV-load measurements. A subset of 12 patients entered a 24-week substudy (three cycles of 8 weeks) during which plasma HIV RNA was measured each week and daily home cultures performed for the entire 24 weeks. During the first cycle, patients received no anti-HSV therapy, patients received suppressive aciclovir (800 mg three times daily) in the second cycle, and no anti-HSV therapy was administered during the third cycle. Patients were followed-up for a median of 87 days during which lesions were present for a median of 21.8% of days. These revealed 453 episodes of HSV shedding among 27 patients, and asymptomatic HSV shedding occurred on 40% of days on which the cultures were positive. Thus, in keeping with other studies, many episodes of HSV reactivation in HIV-positive individuals are asymptomatic.

In the study, there was a lack of association between recognized HSV recurrences and HIV load, the median plasma HIV RNA level when lesions were present was 24 800 copies/ml compared with 24 400 copies/ml when lesions were absent ($P=0.083$). The absence of a correlation may reflect the fact that plasma HIV load was measured rather than genital HIV shedding. However, the total HSV shedding rate was positively correlated with plasma HIV RNA load ($r=0.54$; $P=0.004$). In an analysis adjusted for CD4+ cell count, there was a significant direct relationship between clinical HSV reactivation and plasma HIV load.

Daily aciclovir was associated with a reduction in plasma HIV load; the median plasma HIV level decreased by 5100 copies/ml (Figure 3).³¹ Moreover, as

Table 2: Incident HSV-2 increases the risk of HIV acquisition in Tanzania²⁰

	Adjusted OR (95% CI)	
	Men	Women
Prevalent HSV-2	6.1 (2.5–14.9)	1.3 (0.6–2.8)
Incident HSV-2	16.8 (6–46)	2.4 (0.8–6.5)

HSV-2, herpes simplex virus type 2; OR, odds ratio; CI, confidence interval. Reproduced from del Mar Pujades Rodriguez *et al.*²⁰

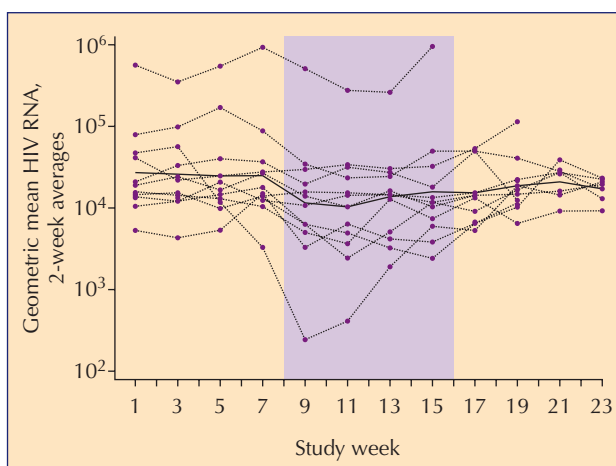


Figure 3: Plasma HIV load with HSV suppression (purple area, 8–16 weeks) and without HSV suppression (yellow areas, 1–8, 16–23 weeks).³¹ Reproduced with permission from Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis* 2002;**186**:1718–1725. University of Chicago. © 2002 by the Infectious Diseases Society of America. All rights reserved.

one-third of episodes were asymptomatic, HIV replication may be influenced by asymptomatic HSV reactivation. Furthermore, as the median CD4+ cell count at study entry was 333 cells/mm³, HSV is shed at high rates even in HIV-positive persons with high CD4+ cell counts. The contribution of HSV reactivation and HIV replication to 'blips' in HIV RNA levels requires further study, as does the addition of anti-HSV therapy to 'salvage' therapy as HSV shedding rates are high in persons with lower CD4+ cell counts.

An Italian study investigated the possibility that aciclovir treatment may decrease the rate of HIV disease progression in individuals co-infected with HIV and HSV-2.³² A cohort of 126 HIV-positive individuals with a known seroconversion date who were HSV-2 seropositive were followed. Treatment with aciclovir provided a 37% protective effect in multivariate analysis when antiretroviral therapy was not included in the model. The aciclovir protective effect dropped to 9% when antiretroviral therapy was included. The protective effect of antiretroviral therapy was 43% for monotherapy and 36% for dual therapy. These findings suggest that most of the protective effect of aciclovir in

the first model was due to antiretroviral therapy. Thus, treatment with aciclovir does not significantly delay progression to AIDS among HIV-positive individuals who are co-infected with HSV-2.

THE IMPORTANCE OF GENITAL ULCERATION IN HIV TRANSMISSION

A study conducted in Rakai, Uganda, indicates that genital ulcer disease (GUD), not HSV-2 seropositivity *per se*, increases the risk of HIV transmission.³³ In a study of 174 monogamous couples, the risk of HIV transmission per sex act was similar among HIV-positive partners who were HSV-2-seronegative and those who were HSV-2-seropositive (Table 3). However, 80% of the HIV-positive partners were HSV-2-seropositive, making it difficult to detect an effect of HSV-2-seropositivity on HIV transmission, given the small number of HIV-infected persons who were HSV-2-seronegative. In contrast, a history of GUD was associated with a five-fold increased risk of HIV transmission per sex act (Table 3). The importance of GUD was also apparent when the probability of HIV transmission by viral load was compared for those with and without recent genital ulceration; the probability was substantially higher in the presence of an ulcer for all viral loads greater than 1700 copies/ml (Table 3). Thus, even though an association between HIV transmission and HSV-2 infection could not be demonstrated, possibly due to the small numbers of HSV-2 negative persons limiting the power, the importance of GUD in HIV transmission and the finding of HIV in ulcers due to HSV-2 infection suggest that genital HSV disease contributes to an increased likelihood of HIV transmission.

HIV in ulcers due to HSV-2 infection: HIV was detected in samples from genital ulcers in a number of studies.^{4,34,35} Of the genital ulcer exudates from all causes (including HSV, chancroid and syphilis) collected from 1160 men from South Africa, HSV-2 was the most common pathogen identified in ulcer specimens (35.9%).⁴ HSV-2 was also found in a significantly higher percentage of ulcer specimens from HIV-infected individuals than HIV-negative individuals (47.4% versus 28.2%, $P < 0.001$).

The titres of HIV are also high in genital ulcers due to HSV. In a study of HIV and HSV-2 co-infected MSM, 12 HIV-infected men were followed for 26 HSV-2 reactivation episodes to ascertain the amount of HIV RNA in herpes lesions.³⁵ HIV RNA was detected in most (25/26) of the episodes, in 63.9% (108/169) of the swabs and on 67% of the days sampled. The HIV RNA titre exceeded 10 000 copies/ml of swab sample in 75% of

Table 3: Probabilities of HIV transmission per coital act in Rakai study³³

	Age (years)	Age*	Viral load (copies/ml)			
			<1700	1700–12 499	12 500–38 500	>38 500
			Age and viral load [†]			
	15–24	0.0013	0.0001	0.0020	0.0019	0.0032
	25–29	0.0017	0.0001	0.0018	0.0026	0.0048
	30–34	0.0006	0.00003	0.0005	0.0005	0.0014
	35–59	0.0009	0.00004	0.0007	0.0008	0.0020
	Viral load**		0.0001	0.0013	0.0014	0.0023
	GUD^{††}					
	No	0.0011	0.0001	0.0012	0.0014	0.0018
	Yes	0.0041	0.0002	0.0033	0.0039	0.0049

*, model for age alone; **, model for viral load alone; †, model for age and viral load; ††, model for genital ulcer disease and viral load; GUD, genital ulcer disease. Reproduced from Gray *et al.*³³

samples. HIV RNA was detected in genital lesions, regardless of whether or not an individual had a low or high plasma titre of HIV RNA; there was no relationship between genital lesion HIV load and plasma HIV load. Moreover, increased HIV RNA titres were found irrespective of the anatomical site sampled. Although the study did not determine HSV-2 DNA levels, the consistent detection of HIV RNA, often at high titres, in genital ulcers attributed to HSV-2 suggests that genital herpes increases the efficiency of sexual transmission of HIV.

HIV in cervicovaginal secretions during HSV-2 reactivation: An association between genital HIV RNA levels and HSV-2 DNA levels reported in a study of 300 women (median age of 27 years) from Bangui, Central African Republic, further supports the importance of HSV in increasing HIV infectiousness.³⁶ HSV-2 DNA and HIV RNA were quantified in the cervicovaginal lavages of 300 women who attended an STI clinic. Sera taken from the women were tested for antibodies to syphilis, HIV and HSV.

In total, 26.3% (79/300) of the women were infected with HIV, and 82.3% (247/300) were HSV-2 seropositive in the Bangui study. The HIV-positive women were significantly more likely to be HSV-2-seropositive than were HIV-negative women (91% versus 78%, $P=0.02$). There were no significant differences between HIV-seropositive and HIV-seronegative women with respect to other STIs, bacterial vaginosis, contraceptive use or pregnancy status. HSV-2 DNA was detected in the cervicovaginal lavages of 46.0% (23/50) HIV-seropositive women and 22.0% (31/141) of HIV-seronegative women ($P=0.003$). An important determinant of genital HIV shedding may be HIV plasma load. There was an association of borderline significance between HIV RNA levels in the plasma (geometric mean HIV RNA load 3.24 log copies/ml) and genital tract (2.39 log copies/ml [$r=0.24$; $P=0.07$]). The data may support the principle of compartmentalization of HIV replication, in which distinct HIV variants and immunological responses are demonstrable in the peripheral blood and female genital tract.³⁷ There was a significant correlation between genital HIV RNA and genital HSV-2 DNA among the subset of 23 HIV-seropositive women who shed HSV-2 ($r=0.47$; $P=0.02$, Figure 4).

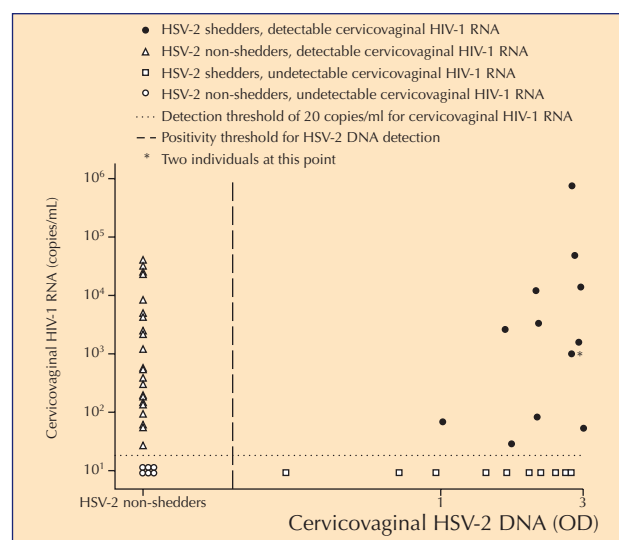


Figure 4: Distribution of HIV RNA and herpes simplex virus (HSV) DNA in cervicovaginal lavages of 53 women with HSV and HIV infection.³⁶ Reproduced with permission from Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M et al. *Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention.* *J Infect Dis* 2000;**182**:1090–1096. University of Chicago. © 2000 by the Infectious Diseases Society of America. All rights reserved.

HIV and the Natural History of HSV-2 Infection

There is a bi-directional interaction between HSV-2 and HIV. Not only does HSV-2 probably affect the risk of HIV acquisition and transmission, but the natural history of HSV-2 is altered in individuals with HIV infection. When comparing prospective studies with HIV-negative MSM, there are significantly more HSV-2 reactivation episodes in persons co-infected with HSV-2 and HIV.^{12,38} The majority of these reactivations (79.1% [355/449] of positive cultures) occurred in the perirectal region; and most episodes (67.5%, 112/166) took place when the patient was not aware of the presence of the lesions (i.e. asymptomatic reactivations).¹² The high rate of apparently asymptomatic reactivations may be due to the difficulty of self-examination of the perirectal region and the many non-specific symptoms that are common to that area. If patients are educated about the typical signs and symptoms of HSV-2 recurrences, then recognition of an outbreak increases substantially.³⁸ However, many reactivations are truly asymptomatic and a cohort study suggests that the natural history of HSV-2 may be similar in MSM regardless of their HIV status. In 30 MSM without HIV infection, the majority of HSV reactivations were perirectal (83.3%, 65/78 isolates) and asymptomatic (68% of days when HSV-2 isolated).¹³

An important factor that influences HSV reactivation is the degree of immunosuppression, which is influenced by HIV infection. There is a direct relationship between CD4+ cell count and the rate of HSV-2 reactivation. In a group of 68 HIV-positive men, the OR of anogenital HSV-2 shedding for those with a CD4+ cell count <200 cells/mm³ was 2.5 (95% CI, 1.1–5.4) when compared with a CD4+ cell count >500 cells/mm³.¹²

There is also a relationship between CD4+ cell count and the rate of HSV-2 reactivation among women. The rate of HSV-2 shedding increased as CD4+ cell count decreased in 106 HIV-positive women from New York, USA.³⁹ Among HIV-infected women in Kenya, the probability of detecting HSV DNA from the cervix increased with decreasing CD4+ cell count ($P=0.01$), although only women with cell counts <200 cells/mm³ had a significant increase in the odds of shedding HSV (OR, 4.8; 95% CI, 1.1–29.4). However, no association was observed when adjusted for vitamin A status (vitamin A deficiency compromises epithelial integrity).⁴⁰ The deficiencies in vitamin A were associated with increased odds of cervical HSV shedding.⁴⁰ Therefore, vitamin A levels may play a part in the link between genital ulceration and HSV shedding. Among the same population of HIV/HSV-2 co-infected women in Kenya, McClelland and colleagues⁴¹ found that the quantity of HSV DNA in cervical secretions was associated with cervical HIV RNA and proviral DNA levels.

The relationship between CD4+ cell count and HSV-2 shedding may reflect the quantity or function of HSV-specific cytotoxic T cells (CTLs). The severity of genital HSV lesions is directly related to the frequency of HSV-specific CD8+ CTLs, which is associated with the absolute CD4+ cell count.⁴² Regardless of whether it is the CD4+ count or CD8+ CTL frequency that is a predictor, the clinical course of, and amount of shedding during, genital HSV infection appears to be exacerbated by HIV infection.

On a population level, the interaction between HIV and HSV-2 may give rise to positive feedback in which HSV-2 infection enhances HIV acquisition and transmission; HIV infection in turn increases the risk of HSV-2 transmission. Importantly, the data from these studies were collected prior to, or in countries where there is not, the widespread use of highly active antiretroviral therapy (HAART). This is significant as HAART has resulted in a reduction in the number of opportunistic infections among HIV-infected individuals.⁴³ However, the effect of HAART on HSV and HIV shedding requires further study.

The Interaction between HSV-2 and HIV: Priorities for Research and Clinical Care

- HIV-positive persons should be serologically tested for HSV-2 infection and counselled about clinical and public health implications (category 3 recommendation)
- Through serological testing and counselling, and by prevention of acquisition (e.g. through behavioural interventions), herpes treatment and antiviral suppression, HSV-2 should be targeted as a modifiable risk factor for HIV acquisition (category 3 recommendation)
- Additional biological and epidemiological studies are needed to characterize HSV-2 as a risk factor for HIV transmission (research need recommendation)
- Substantial epidemiological evidence indicates that HSV-2 infection increases the risk of acquiring HIV by approximately two-fold. However, data are unavailable to determine if treating HSV-2 infection can substantially reduce the risk of HIV acquisition. A proof-of-concept intervention trial is required to establish whether or not HSV-2 suppressive therapy in populations with high prevalence of HSV-2 and HIV can lower the risk of HIV acquisition or transmission (research need recommendation)

CAUSALITY AND THE EFFECT OF HSV ON HIV ACQUISITION/TRANSMISSION

There are several criteria that can be used to determine causality in observational epidemiological studies (Table 4). That HSV facilitates HIV acquisition is supported as all the criteria are fulfilled but it is not possible to state categorically that HSV influences HIV transmission because the epidemiological data are limited to the few transmission studies conducted. Nevertheless, it is biologically plausible that the likelihood of HIV transmission is increased by HSV-2 infection, and the Rakai data^{33,48} support this hypothesis.

Based on the available data regarding HSV-2 infection and HIV acquisition/transmission, there is a need to consider the role of anti-HSV therapy in preventing HIV acquisition or transmission. In doing so, it is first necessary to determine whether or not the use of anti-HSV therapy would be a valuable and feasible strategy to impact on the HIV epidemic. Even in the context of widespread use of HAART, treatment for HSV may still be useful as:

- GUD increases the per contact probability of HIV acquisition even at low HIV load in the HIV-positive partner;
- HSV-2 infection is a major cause of GUD;
- Aciclovir is less expensive than HAART and requires no safety monitoring;

- Treatment with antiviral therapy is applicable to a larger proportion of HIV-positive individuals than HAART, if HAART is offered only to those with CD4+ cell counts <200 cells/mm³ or symptoms.

It must, therefore, be established whether HSV-2 suppressive therapy can lower the risk of HIV acquisition or transmission. To this end, a placebo-controlled intervention trial is underway to determine if aciclovir (400 mg twice daily) can prevent HIV acquisition. The trial populations are 1800 HIV-negative, HSV-2 positive heterosexual women (in Zimbabwe and Zambia) and 1800 high-risk HIV-negative, HSV-2 positive MSM (in Peru, Seattle and New York). The primary end-point will be the incidence of HIV infection, which is estimated to be 3.5%/year in the placebo arm. A similar study is also planned in Tanzania. A study of the effects of HSV-2 on HIV transmission will be conducted in a randomized, controlled, double-blind trial of aciclovir suppressive therapy among HIV-discordant couples where the HIV-infected partner has HSV-2 infection, recruited in African and Indian sites. If anti-HSV therapy proves to be effective, it should lead to several recommendations, as suggested below.

ADDITION OF ACICLOVIR TO WHO GUIDELINES FOR SYNDROMIC MANAGEMENT OF GUD

The two- to four-fold increase in the risk of HIV acquisition associated with genital ulceration,^{44,45} alongside evidence of a decrease in the amount of HIV in genital secretions following treatment with antibiotics,⁴⁶ resulted in two community-based studies of the impact of syndromic treatment on the incidence of HIV.^{47,48} The Mwanza study in Tanzania recorded a 40% reduction in the incidence of HIV, demonstrating that improved STI management was an important additional HIV prevention strategy.⁴⁷ No reduction in HIV incidence was documented in the Rakai study in Uganda,⁴⁸ and among the reasons postulated was a higher prevalence of bacterial STIs in Mwanza, and the high prevalence of genital herpes which was not addressed in the intervention.⁴⁹ Thus, the failure of mass antibacterial treatment to control HIV might be partly explained by HSV infection.

An approach to impacting the HIV/AIDS epidemic may be to add anti-HSV therapy to the syndromic management approaches for GUD. Currently treatable STIs such as syphilis, gonorrhoea, chlamydia, chancroid, trichomoniasis and candidiasis are targeted in syndromic management.⁵⁰ Adding herpes to this list would impact positively on the dynamics of HIV infection and the treatment of genital HSV infection would, in itself, improve the clinical care of HIV-positive patients. However, there is a question as to whether episodic therapy or suppressive regimens

Table 4: Criteria to assess causality of an association between HSV infection and HIV acquisition and transmission

	HIV acquisition	HIV transmission
Strength of the association	+	+
Consistency of the association	+	±
		Limited data
Temporal relationship of the association	+	+
Specificity of the association	+	±
		Shown for GUD in setting of 80% HSV-2 seroprevalence
Biological plausibility of the association	+	+

GUD, genital ulcer disease; HSV-2, herpes simplex virus type 2.

should be employed. Patients without a diagnosis of genital HSV infection are likely to experience recurrences, and shed HSV, for some time before treatment. Even for those with a diagnosis, recognition of outbreaks may be poor, although it can be improved by education. Thus, episodic treatment is likely to have little impact on HIV infection dynamics unless it is accompanied by successful campaigns targeting early symptom recognition and prompt treatment. Given the poor recognition of genital herpes and the likely contribution of asymptomatic periods and unrecognized lesions to HIV acquisition, suppressive therapy is likely to be more effective in preventing HIV infection. Continuous suppressive therapy represents a more intensive strategy but issues of compliance, cost and logistics of implementation may hinder its widespread provision. A more achievable approach may be to target groups with high-risk behaviour or offer therapy only to those who experience frequent and severe recurrences.

HSV-2 SEROLOGICAL TESTING IN HIV-POSITIVE PERSONS

- HIV-positive persons should be serologically tested for HSV-2 infection and counselled about clinical and public health implications (category 3 recommendation)

Given the low proportion of HSV-2 seropositive persons who recognize genital herpes outbreaks, even among HIV-positive persons, addition of anti-HSV therapy to syndromic management of GUD will only cover a minority of HSV-2 reactivations, during which HIV, HSV-2 co-infected persons could be more infectious. Thus, a syndromic approach incorporating anti-HSV therapy is reasonable for settings with a high seroprevalence of HSV, particularly for those who participate in high-risk sexual behaviour. An alternative strategy, given the low proportion of people with genital HSV infection who recognize lesions, is to use serological testing to identify HIV-positive individuals who are HSV-2 seropositive, which is the majority in most settings. Anti-HSV suppressive therapy could then be employed to reduce HSV-2 reactivation and, thus, HIV shedding and infectiousness. The benefit of such an approach is likely to be greatest in those with a low CD4+ count (e.g. <200 cells/mm³) and a higher plasma virus load but resources may be a limitation. As above, antiherpetic therapy itself would be of clinical benefit to an HIV-positive individual co-infected with HSV-2.

HSV-2 SEROLOGICAL TESTING AMONG PERSONS AT HIGH RISK OF HIV ACQUISITION

- Through serological testing and counselling, and by prevention of acquisition (e.g. through behavioural interventions), herpes treatment and antiviral suppression, HSV-2 should be targeted as a modifiable risk factor for HIV acquisition (category 3 recommendation)

Herpes simplex virus type 2 serological testing of individuals in high-risk populations could potentially reduce the risk of HIV acquisition. If individuals are found to be HSV-2-seropositive, then they may be counselled about the natural history and clinical manifestations of genital herpes, and about the importance of asymptomatic shedding. However, the success of such an approach depends on the availability of effective intervention; many of those currently available are of limited value on a population basis (e.g. education, condoms). As recently acquired HSV-2 infection appears to increase the risk of HIV acquisition, those with incident HSV-2 infection could be counselled, and sexually active persons targeted to receive suppressive anti-HSV therapy.

Identifying HIV-positive individuals who are infected with HSV-2 and counselling them on ways to reduce the risk of HIV transmission may impact on the spread of HIV. There are several caveats regarding this strategy.

The positive predictive value of testing depends on the background HSV-2 seroprevalence and on the performance of the test being used. Commercially available tests need to be validated in African populations, given previous reports of lower specificity in samples from eastern Africans. Another concern is the efficacy of the interventions. For example, behavioural approaches are largely unproven in this context and adherence to them may be limited. The reduction in HIV shedding would only occur if individuals decrease their sexual activity when they recognized genital HSV lesions. However, recognition of genital HSV is poor, although it can be improved by education. Moreover, asymptomatic HSV shedding may also contribute to HIV transmission, which could only be addressed by using suppressive antiviral therapy. Although the combination of anti-HSV therapy and behavioural interventions in HIV and HSV-2 co-infected individuals could potentially minimize HIV transmission, a therapeutic trial must be conducted before HSV-2 suppressive therapy is recommended for this public health indication.

Conclusions

The large number of seroepidemiological studies of HSV and HIV infection, together with biological interactions of the two viruses, provide evidence for a link between HSV infection and HIV acquisition and transmission. The association is strongest for an effect of HSV-2 infection on the risk of HIV acquisition, with indications that the risk is greater with incident HSV-2 infection. In a recent meta-analysis, HSV-2 infection was associated with a 2.1-fold increased risk of HIV acquisition in nine studies in which HSV-2 infection was documented before HIV acquisition. The case for an increased risk of HIV transmission with concomitant HSV-2 infection is weaker, but remains biologically plausible. What is not yet fully defined is whether or not the increased risk of HIV transmission due to HSV-2 is only apparent during clinical reactivation or is also enhanced during asymptomatic shedding. Recent data support the importance of asymptomatic HSV-2 infection for both the acquisition and transmission of HIV infection.

The importance of HSV infection in the dynamics of HIV acquisition and infection supports anti-HSV therapy being considered as part of a management strategy for the prevention of HIV infection. To date, control programmes have not incorporated measures to manage HSV-2 infection. Such a decision may depend on further evidence of the link between HIV and HSV-2 infection, proof from an ongoing prospective, placebo-controlled trial that antiherpetic therapy is effective, or the outcome of empirical trials incorporating antiherpetic therapy into current syndromic management protocols. Even if there is conclusive evidence that antiherpetic therapy decreases the risk of HIV infection, issues of compliance, cost and feasibility must be addressed to aid implementation strategies.

Address for correspondence:

Dr Connie L Celum, University of Washington, Cabrini Medical Tower, 901 Boren Avenue, Suite 1300, Seattle, WA 98104, USA.

E-mail: ccelum@u.washington.edu

Received for publication: 6 August 2003

Accepted for publication: 19 September 2003

- O'Farrell N. Targeted interventions required against genital ulcers in African countries worst affected by HIV infection. *Bull World Health Organ* 2001;**79**: 569–577.
- Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK *et al*. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;**337**: 1105–1111.
- Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;**98**:958–972.
- Chen CY, Ballard RC, Beck-Sague CM, Dangor Y, Radebe F, Schmid S *et al*. Human immunodeficiency virus infection and genital ulcer disease in South Africa: the herpetic connection. *Sex Transm Dis* 2000;**27**:21–29.
- Behets FM, Andriamiadana J, Randrianasolo D, Randriamanga R, Rasamilalao D, Chen CY *et al*. Chancroid, primary syphilis, genital herpes, and lymphogranuloma venereum in Antananarivo, Madagascar. *J Infect Dis* 1999;**180**: 1382–1385.
- Morse SA, Trees DL, Htun Y, Radebe F, Orle KA, Dangor Y *et al*. Comparison of clinical diagnosis and standard laboratory and molecular methods for the diagnosis of genital ulcer disease in Lesotho: association with human immunodeficiency virus infection. *J Infect Dis* 1997;**175**:583–589.
- Limpakarnjanarat K, Mastro TD, Saisorn S, Uthairavit W, Kaewkungwal J, Korattana S *et al*. HIV-1 and other sexually transmitted infections in a cohort of female sex workers in Chiang Rai, Thailand. *Sex Transm Infect* 1999;**75**:30–35.
- Siegal FP, Lopez C, Hammer GS, Brown AE, Kornfeldt SJ, Gold J *et al*. Severe acquired immunodeficiency in male homosexuals, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981;**305**: 1439–1444.
- Koelle DM, Abbo H, Peck A, Ziegweid K, Corey L. Direct recovery of herpes simplex virus (HSV)-specific T lymphocyte clones from recurrent genital HSV-2 lesions. *J Infect Dis* 1994;**169**:956–961.
- Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002;**185**:45–52.
- Mbizvo EM, Msuya S, Sia E, Stray-Pedersen B, Chirenje MZ, Munjoma M, Hussain A. Association of herpes simplex virus type 2 with the human immunodeficiency virus among urban women in Zimbabwe. *Int J STD AIDS* 2002;**13**:343–348.
- Schacker T, Zeh J, Hu HL, Hill E, Corey L. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* 1998;**178**:1616–1622.
- Krone MR, Wald A, Tabet SR, Paradise M, Corey L, Celum CL. Herpes simplex virus type 2 shedding in human immunodeficiency virus-negative men who have sex with men: frequency, patterns, and risk factors. *Clin Infect Dis* 2000;**30**:26–267.
- Holmberg SD, Stewart JA, Gerber AR, Byers RH, Lee FK, O'Malley PM *et al*. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA* 1988;**259**:1048–1050.
- Keet IP, Lee FK, van Griensven GJ, Lange JM, Nahmias A, Coutinho RA. Herpes simplex virus type 2 and other genital ulcerative infections as a risk factor for HIV-1 acquisition. *Genitourin Med* 1990;**66**:330–333.
- Kingsley LA, Armstrong J, Rahman A, Ho M, Rinaldo CR, Jr. No association between herpes simplex virus type-2 seropositivity or anogenital lesions and HIV seroconversion among homosexual men. *J Acquir Immune Defic Syndr* 1990;**3**:773–779.
- Renzi C, Douglas JM, Foster M, Critchlow CW, Ashley-Morrow R, Buchbinder SP *et al*. Herpes simplex virus type 2 infection as a risk factor for human immunodeficiency virus acquisition in men who have sex with men. *J Infect Dis* 2003;**187**:19–25.
- McFarland W, Gwanzura L, Bassett MT, Machezano R, Latif AS, Ley C *et al*. Prevalence and incidence of herpes simplex virus type 2 infection among male Zimbabwean factory workers. *J Infect Dis* 1999;**180**: 1459–1465.
- Kamali A, Nunn AJ, Mulder DW, Van Dyck E, Dobbins JG, Whitworth JA. Seroprevalence and incidence of genital ulcer infections in a rural Ugandan population. *Sex Transm Infect* 1999;**75**: 98–102.
- del Mar Pujades Rodriguez M, Obasi A, Mosha F, Todd J, Brown D, Changalucha J *et al*. Herpes simplex virus type 2 infection increases HIV incidence: a prospective study in rural Tanzania. *AIDS* 2002;**16**:451–462.
- Reynolds SJ, Risbud AR, Shepherd ME, Zenilman JM, Brookmeyer RS, Kulkarni SV *et al*. Recent herpes simplex virus type 2 infection and the risk of HIV acquisition in Pune, India. *XIV International AIDS Conference*, Barcelona, Spain, 2002; Abstract MoOrC1012.
- Reynolds SJ, Risbud AR, Shepherd ME, Zenilman JM, Brookmeyer RS, Paranjape RS *et al*. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. *J Infect Dis* 2003;**187**:1513–1521.
- Kucera LS, Leake E, Iyer N, Raben D, Myrvik QN. Human immunodeficiency virus type 1 (HIV-1) and herpes simplex virus type 2 (HSV-2) can coinfect and simultaneously replicate in the same human CD4+ cell: effect of coinfection on infectious HSV-2 and HIV-1 replication. *AIDS Res Hum Retroviruses* 1990;**6**:641–647.
- Heng MC, Heng SY, Allen SG. Co-infection and synergy of human immunodeficiency virus-1 and herpes simplex virus-1. *Lancet* 1994;**343**: 255–258.
- Golden MP, Kim S, Hammer SM, Ladd EA, Schaffer PA, DeLuca N *et al*. Activation of human immunodeficiency virus by herpes simplex virus. *J Infect Dis* 1992;**166**:494–499.
- Albrecht MA, DeLuca NA, Byrn RA, Schaffer PA, Hammer SM. The herpes simplex virus immediate-early protein, ICP4, is required to potentiate replication of human immunodeficiency virus in CD4+ lymphocytes. *J Virol* 1989;**63**:1861–1868.
- Mosca JD, Bednarik DP, Raj NB, Rosen CA, Sodroski JG, Haseltine WA *et al*. Activation of human immunodeficiency virus by herpesvirus infection: identification of a region within the long terminal repeat that responds to a trans-acting factor encoded by herpes simplex virus 1. *Proc Natl Acad Sci U S A* 1987;**84**:7408–7412.
- Cunningham AL, Turner RR, Miller AC, Para MF, Merigan TC. Evolution of recurrent herpes simplex lesions. An immunohistologic study. *J Clin Invest* 1985;**75**:226–233.
- Fauci AS. The human immunodeficiency virus: infectivity and mechanisms of pathogenesis. *Science* 1988;**239**:617–622.
- Mole L, Ripich S, Margolis D, Holodniy M. The impact of active herpes simplex virus infection on human immunodeficiency virus load. *J Infect Dis* 1997;**176**:766–770.
- Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. *J Infect Dis* 2002;**186**:1718–1725.
- Suligoi B, Dorrucchi M, Volpi A, Andreoni M, Rezza G. No protective effect of acyclovir on HIV disease progression in a cohort of HSV-2-HIV-infected individuals. *Antivir Ther* 2002;**7**:289–291.
- Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F *et al*. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. *Lancet* 2001;**357**: 1149–1153.
- Kreiss JK, Coombs R, Plummer F, Holmes KK, Nikora B, Cameron W *et al*. Isolation of human immunodeficiency virus from genital ulcers in Nairobi prostitutes. *J Infect Dis* 1989;**160**:380–384.
- Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. *JAMA* 1998;**280**:61–66.
- Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M *et al*. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000;**182**:1090–1096.
- Zhu T, Wang N, Carr A, Nam DS, Moor-Jankowski R, Cooper DA *et al*. Genetic characterization of human immunodeficiency virus type 1 in blood and genital secretions: evidence for viral compartmentalization and selection during sexual transmission. *J Virol* 1996;**70**:3098–3107.
- Schacker T, Hu HL, Koelle DM, Zeh J, Saltzman R, Boon R *et al*. Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med* 1998;**128**:21–28.
- Augenbraun M, Feldman J, Chirgwin K, Zenilman J, Clarke L, DeHovitz J *et al*. Increased genital shedding of herpes simplex virus type 2 in HIV-seropositive women. *Ann Intern Med* 1995;**123**: 845–847.
- Mostad SB, Kreiss JK, Ryncarz AJ, Mandaliya K, Chohan B, Ndinya-Achola J *et al*. Cervical shedding of herpes simplex virus in human immunodeficiency virus-infected women: effects of hormonal contraception, pregnancy, and vitamin A deficiency. *J Infect Dis* 2000;**181**:58–63.
- McClelland RS, Wang CC, Overbaugh J, Richardson BA, Corey L, Ashley RL *et al*. Association between cervical shedding of herpes simplex virus and HIV-1. *AIDS* 2002;**16**:2425–2430.
- Posavad CM, Koelle DM, Shaughnessy MF, Corey L. Severe genital herpes infections in HIV-infected individuals with impaired herpes simplex virus-specific CD8+ cytotoxic T lymphocyte responses. *Proc Natl Acad Sci U S A* 1997;**94**:10289–10294.
- Palella FJ, Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;**338**:853–860.
- Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN *et al*. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. *Lancet* 1989;**2**:403–407.
- Dickerson MC, Johnston J, Delea TE, White A, Andrews E. The causal role for genital ulcer disease as a risk factor for transmission of human immunodeficiency virus. An application of the Bradford Hill criteria. *Sex Transm Dis* 1996;**23**:429–440.

46. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC *et al.* Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. AIDS CAP Malawi Research Group. *Lancet* 1997;**349**: 1868–1873.
47. Grosskurth H, Moshafir F, Todd J, Mwijarubi E, Klokke A, Senkoro K *et al.* Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995;**346**:530–536.
48. Wawer MJ, Sewankambo NK, Serwadda D, Quinn TC, Paxton LA, Kiwanuka N *et al.* Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomised community trial. Rakai Project Study Group. *Lancet* 1999;**353**:525–535.
49. Grosskurth H, Gray R, Hayes R, Mabey D, Wawer M. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet* 2000;**355**:1981–1987.
50. Ballard RC. Syndromic case management of STDs in Africa. *Afr Health* 1998;**20**: 13–15.

Interaction between HSV and HIV • **HERPES** 11 Supplement 1 2004

FORTHCOMING SUPPLEMENTS TO HERPES IN 2004

Two further supplements representing the combined experience and knowledge of the many physicians and healthcare professionals involved with the IHMF are planned for publication in *Herpes* during 2004:

These supplements present comprehensive summaries of presentations and discussions held at the *IHMF Management Strategies Workshops* held in April 2002, Denver, USA and May 2003, Seattle, USA and at the *10th Annual Meeting of the IHMF* in Paris, February 2003.

To be published in print and on-line at www.ihmf.org

Herpesvirus infections of the CNS

Expected publication spring 2004

Detailing the broad spectrum of CNS diseases and complications that are associated with herpesvirus infections, to include:

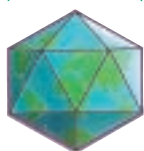
- ◆ Diagnosis of Herpesvirus Infections of the CNS
- ◆ HSV Infections of the CNS: Encephalitis and Meningitis, including Mollaret's
- ◆ HSV Meningitis and Encephalitis in Neonates
- ◆ HSV-1 and Alzheimer's Disease
- ◆ Viruses and Schizophrenia: A Focus on HSV
- ◆ VZV and CNS Syndromes
- ◆ CMV Infection of the CNS
- ◆ HHV-6 and HHV-7 Infections of the CNS
- ◆ HHV-6 and Multiple Sclerosis
- ◆ EBV and HHV-8 Infections of the CNS

Interrupting the transmission of genital and neonatal herpes

Expected publication spring 2004

Discussing a variety of ways in which these diseases can be monitored and controlled, to include:

- ◆ Risk Factors for and the Importance of Virus Shedding in the Transmission of HSV-2
- ◆ Modelling the Genital Herpes Epidemic
- ◆ Condoms and Microbicides
- ◆ Educational Interventions
- ◆ Clinical Trials of Prophylactic and Therapeutic HSV Vaccines
- ◆ Prevention of HSV-2 Transmission with Antiviral Therapy
- ◆ Preventing HSV Transmission to the Neonate



Global Epidemiology of Genital Herpes and the Interaction of Herpes Simplex Virus with HIV

An *IHMF Management Strategies Workshop* was held on 25–26 September 2002 to formulate strategies to interrupt the transmission of genital HSV infection. Articles that outlined the recommendations developed at the workshop were discussed, amended and ratified by delegates at the *10th Annual Meeting of the IHMF* on 28 February–2 March 2003.

The articles were then submitted to the Editors of *Herpes* for publication in this supplement and were independently peer-reviewed, amended if necessary, and accepted for publication in accordance with standard scientific journal practices.

Contents

1A Editorial

Lawrence Corey

2A Epidemiology of Genital Herpes Simplex Virus Infection in Developed Countries

Jean-Elie Malkin

24A Epidemiology of Herpes Simplex Virus Type 2 Infection in the Developing World

Helen Weiss

36A The Interaction between Herpes Simplex Virus and Human Immunodeficiency Virus

Connie L Celum

