UPDATE

Using the evidence base on genital herpes: optimising the use of diagnostic tests and information provision

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There have been several important advances in the range of available diagnostic tests for genital herpes simplex virus (HSV) infection in recent years; polymerase chain reaction (PCR) is emerging in routine clinical use and the potential role of type specific serological tests is currently under debate. Several large trials of prophylactic vaccines, subsequently proved to be ineffective, have expanded knowledge of the transmission and epidemiology of HSV infection. This article discusses optimal application of recent research evidence to clinical care, structured around the key issues for patients and their partners. These include acquisition and transmission of genital HSV-1 and HSV-2 infection, the natural history of genital herpes, and the role of partner notification.

Genital infection with herpes simplex virus (HSV) is highly prevalent and the annual number of symptomatic cases continues to increase.[1] Despite the substantial burden of disease created by this common viral infection, its management may not be as effective as it could be. Symptomatic infection remains underdiagnosed[2] and anecdotal experience suggests that patients commonly receive conflicting information from healthcare professionals. All this appears surprising, given the rate at which clinical research into genital herpes has proliferated over the past two decades. Significant recent advances have been made in our understanding of the epidemiology and transmission of HSV, and new diagnostic methodologies have been intensively developed and commercially promoted. The challenge for specialists in sexual health (and colleagues in the other healthcare settings where patients with genital herpes frequently present), is consistent translation of all this research evidence into high quality clinical care.

This article reviews recent clinically important developments in diagnosis and information provision, structured around the key issues for patients and their partners.

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DIAGNOSIS: HOW BEST SHOULD WE USE THE AVAILABLE DIAGNOSTIC TESTS?

Viral detection and characterisation

Culture

Virus isolation in cell culture has been the mainstay of HSV diagnosis over the past two decades, used by 97% of genitourinary medicine (GUM) clinics in the UK.[3] Virus culture requires a laboratory with tissue culture facilities and is highly dependent on the clinical lesions stage. Although HSV can be isolated from over 90% of vesicular or pustular lesions, the isolation rate from ulcerative lesions is only 70% and falls to 27% at the crusting stage.[4] Transport of live virus to the laboratory within a short period is mandatory, requiring maintenance of the cold chain at 4°C. The characteristic cytopathic effect of HSV generally appears within 24 to 72 hours, but may take up to five days. Virus isolation is therefore slow and labour intensive, but has the advantage of demonstrating active infection within a clinical lesion and also allows virus typing and antiviral sensitivity testing.

PCR

Polymerase chain reaction (PCR) is a well characterised method for rapid and sensitive diagnosis of HSV, but, largely because of its cost and the requirement for appropriately trained technical staff, its role has hitherto been confined to investigation of suspected HSV encephalitis.[5] However, with recent advances in automated PCR, the potential to apply molecular diagnosis to routine clinical diagnosis is enhanced and is likely to ultimately prove cost effective. Eight recent large studies have compared PCR with cell culture for detection of HSV, demonstrating consistently superior detection rates with PCR[6–13]; the sensitivity of cell culture compared with PCR in these studies varied between 59% and 89% (table 1). As with application of new, highly sensitive molecular tests to diagnosis of other infections, there is no "gold standard" method against which PCR can be compared, so there is a theoretical risk of false positive results. However, in several of the above studies, discrepant samples—that is, those which were positive on PCR and negative on culture—were confirmed by a second PCR directed to a different gene, which endorses the specificity of PCR.

The clinical importance of typing

HSV-1 has become an important cause of genital herpes in industrialised regions.[14] This may be partly attributable to changing host susceptibility and also to changing sexual behaviour; the age specific population seroprevalence of HSV-1 is

Abbreviations: EIA, enzyme immunoassay; gG, glycoprotein G; GUM, genitourinary medicine; HSV, herpes simplex virus; PN, partner notification; PCR, polymerase chain reaction

Table 1 Virus isolation compared with PCR for diagnosis of herpes simplex virus infection: summary of recent large* studies

First author	Year of publication	Setting	Sample characteristics	Number of specimens analysed	Sensitivity (virus isolation *cf* PCR) (%)
Orle[6]	1996	Laboratory	Genital ulcers	298	72%
Safrin[7]	1997	STD clinic	Oral & genital lesions	246	79%
Slomka[8]	1998	GUM clinic	Anogenital lesions	194	81%
Waldhuber[9]	1999	Sexual health centre	Genital ulcers	131	67%
Coyle[10]	1999	Laboratory (various clinical settings)	Mucocutaneous lesions	134	59%
Espy[11]	2000	Laboratory (various clinical settings)	Genital & dermal	500	76%
Marshall[12]	2001	Laboratory	Anogenital swabs	100	89%
Scoular[13]	2002	GUM clinic	Anogenital lesions	236	81%

*>100 clinical specimens.

progressively declining in prepubertal children in the UK.[15] However, the age specific incidence of HSV-1 infection rises rapidly (5–10% per year) in adolescents, increasing numbers of whom are now acquiring HSV-1 infection in association with sexual activity.[16] As genital tract reactivation of latent HSV-1 infection is infrequent and of short duration, orogenital transmission is considered likely to account for most new cases of genital HSV-1 infection.

Knowledge of the causative type has important implications for patient management. Firstly, the natural history of first episode genital HSV-1 infection is more favourable than that of HSV-2.[17–19] Three cohort studies have compared the natural history of genital HSV-1 with HSV-2 infection; the first of these demonstrated that 180 days following the resolution of a primary episode, 40% of 14 patients with HSV-1 primary infection and 90% of 123 patients with HSV-2 infection, experienced a symptomatic recurrence.[17] Two subsequent studies observed that the mean monthly recurrence frequency following primary genital infection with HSV-1 was 0.02 to 0.08 months, compared with 0.33 to 0.34 months for HSV-2.[18 19]

Secondly, the frequency of subclinical viral shedding following initial genital infection with HSV-1 is consistently lower than for HSV-2; this is likely to be associated with a reduced the risk of future sexual transmission but no prospective studies have yet attempted to quantify this. Koelle *et al* conducted a large cohort study in 306 women with first episode genital herpes.[20] Genital samples were cultured for HSV every four to six weeks, at times when genital symptoms and signs were absent, with a median follow up period of 63 weeks. The rate of asymptomatic genital tract shedding in 43 women with primary HSV-1 infection, was 11.9%, approximately half of the rate found with HSV-2 infection. Viral shedding was detected from the genital tract in 18.3% of 36 women with non-primary HSV-2 infection and 22.9% of 227 with primary HSV-2 infection.[20] A more intensive study of asymptomatic shedding in 110 women with a history of genital herpes attending a research clinic, scheduled participants to collect daily anogenital specimens for a median follow up period of 105 days (range 5 to 799). Subclinical shedding occurred in 29% of 14 women with HSV-1 infection only, 55% of 65 women with HSV-2 infection, and 52% of 31 women with both types. The overall duration of subclinical shedding was also substantially lower for women with HSV-1 infection, occurring on 0.7% of days, compared with 2.0% for those with HSV-2.[21]

Type specific serology

Serological tests detect antibodies to HSV in blood and are indicative of past infection. Older, classical serological tests are vulnerable to cross reactivity between HSV-1 and HSV-2. Several type specific serological tests, developed over the last 20 years, can differentiate antibody responses to the two types and have been extensively applied both to epidemiological surveys and to studies of the transmission of genital herpes. Type specific tests are based on either western blot (which tests for a range of type specific antigens) or glycoprotein G (gG) assays. Western blot tests are expensive, take 2–5 days to complete the screening and confirmatory steps, and require expert interpretation. Therefore, they are unlikely to be commercially developed for use in routine clinical practice. Glycoprotein G assays detect antibodies to the type specific proteins gG-1 and gG-2. Very little sequence homology exists between gG-1 and gG-2, allowing differentiation between established infection with HSV-1 and HSV-2 respectively. A number of gG based tests have been commercially marketed, using a variety of test formats, most often using enzyme immunoassay (EIA) methods. Type specific tests have been used in epidemiological surveys for many years, but their diagnostic performance in individual patients is still a matter for debate and demands critical examination.

A diagnosis of genital herpes may have significant psychosocial consequences for the patient and their partners; it is therefore essential that any diagnostic methods used are accurate, reproducible, and appropriate to the clinical situation to which they are applied. A recent review of commercial type specific antibody tests for HSV-1 and HSV-2 estimated their median sensitivity at 95% (range 81 to 100%) and specificity at 98% (range 97 to 100%).[22] HSV-2 prevalence in two recent surveys among unselected UK GUM clinic attendees was estimated at 22.7% in a central London clinic[23] and 14.3% in a district general hospital in Trafford.[24] However, the general UK population prevalence is probably closer to 4–5%.[15] Dependent on local population characteristics and variations in accessibility and case mix between GUM clinics, the HSV-2 prevalence in GUM settings across the UK may therefore vary between 5 and 20%. Numerous seroprevalence studies have been conducted in various populations worldwide, with widely varying rates of HSV-2 infection reflecting differences in population characteristics, notably in respect of sexual behaviour and socioeconomic attributes. There are few well conducted general population serosurveys. The NHANES III study was an important exception, this study rigorously conducted survey estimated that 22% of the US general population was infected with HSV-2, with higher rates in women and among black ethnic subgroups.[25]

Table 2 quantifies the impact of population HSV-2 prevalence on performance of commercial type specific tests, assuming the sensitivity and specificity values above. Even in a clinic population with a very high prevalence of 20%, 10% of positive results would be false positives, rising to a 29% false positive rate in populations with a prevalence of 5%. Should the "real world" performance of currently available gG assays fall short of the sensitivity and specificity values quoted above, the likelihood of false positive results would increase considerably. In the case of investigations for other serious medical conditions, the risk of a false positive test is minimised by use of a second confirmatory test, however, this strategy is

Table 2 Diagnostic performance of commercial type specific serological tests* related to population prevalence

Prevalence	PPV (%)	NPV (%)	% False positive tests	% False negative tests
5%	71%	100%	29%	0%
10%	83%	100%	17%	0%
15%	88%	99%	12%	0%
20%	90%	99%	10%	1%

*Assumes test sensitivity of 95% and specificity of 98%.[22]
PPV, positive predictive value; NPV, negative predictive value.

currently not easily available in the context of HSV serology and absence of a contributory test remains a fundamental barrier to widespread application of type specific tests.

Clearly, the prevalence of HSV-2 infection is likely to be higher in specific subgroups of patients at higher risk of infection, such as those presenting with genital symptoms suggestive of herpetic infection and partners of patients with a known diagnosis of genital herpes. In these groups, test accuracy would be higher than in the clinic population as a whole. A final issue to bear in mind when interpreting gG based tests is the influence of time. Seroconversion following initial infection may take up to six months and, secondly, the phenomenon of "seroreversion" (spontaneous reversal from seropositive to seronegative status), raises some concerns about the long term reliability of tests based on antibodies to a single protein, such as gG tests.[22]

In summary, in assessing the merits of type specific serological testing for genital herpes, the crucial elements must include: firstly, knowledge of the prevalence of HSV infection in the population being offered testing, secondly, an appreciation of variation in test accuracy from one application to another and, most importantly, a strategy for pretest discussion, interpretation of the results, and communication of the meaning of the results to patients. Assuming that a valid, reproducible type specific test were available for use in individual patients, there are a number of potential clinical applications, which include assessment of pregnant women, evaluation of monogamous couples in a discordant relationship and investigation of symptomatic patients. The potential for offering HSV-2 screening as part of a sexual health "check up" also exists.

Type specific testing has been suggested as a means of identifying women at risk of acquiring HSV-1 or HSV-2 infections close to term, a setting in which there is a high risk (30–50%) of neonatal herpes. In theory, the couple could be counselled on avoiding the risk of transmission during the third trimester. However, partners would also require testing to identify serodiscordant couples. As the majority of pregnant women are at risk of acquiring of HSV-1 and/or HSV-2 during their pregnancy, this would be an enormous task. Even if it were feasible to identify women most at risk, no reliably effective intervention is available to prevent HSV transmission from infected partners. A recent decision analysis model concluded that the low absolute incidence of neonatal herpes, the unknown effectiveness of preventive strategies and a minimum estimated cost of $891 000 per case of neonatal infection prevented did not support a programme of HSV type specific antibody screening.[26]

Management of discordant couples in a monogamous relationship, where one partner has documented HSV-2 infection and is concerned about potential transmission risks to the other partner, is a frequent scenario in GUM practice. If a reliable blood test were available to show that the asymptomatic partner is already infected with HSV-2, the couple could be reassured that further transmission between them cannot take place. In theory, the expected prevalence of HSV-2 in long term partners of individuals with proven genital herpes would be higher than that of the wider GUM clinic population, so the performance of type specific assays in this context may be somewhat better than in unselected GUM clinic attendees, however, this has not been formally researched. A retrospective study by Munday *et al* explored the role of type specific serology for HSV-1 and HSV-2 in 29 partners of individuals diagnosed with genital herpes.[27] The test was useful for diagnosis in six, for counselling in nine, and non-contributory in 14 (48%). The consequences of giving a false positive result in this context are potentially disastrous and further research is desirable before adoption of type specific assays in this clinical situation.

Patients frequently present with recurrent genital eruptions, with a history suggestive of genital herpes, but no lesions present at the time of presentation. A reliable blood test could confirm a diagnosis of HSV-2 and appropriate management could be initiated. The performance of type specific assays in this context is under researched and formal evaluation studies are urgently required. Munday *et al's* retrospective study concluded that investigation of patients with undiagnosed recurrent genital ulceration was the most useful application of type specific serology in their practice, being diagnostically useful in 31 of 39 such patients and non-contributory in eight.[27] The complete absence of seropositivity is potentially useful in excluding a diagnosis of genital herpes; with the currently available commercial tests, the likelihood of a false negative result is very low (table 2). However, caution is required in interpretation of a seropositive result, as symptoms in HSV-2 seropositive patients may not be caused by their herpes infection. Ideally, other diagnostic techniques (such as culture or PCR) should be used to confirm the presence of active HSV infection within visible lesions.

Finally, the concept of offering HSV-2 screening to asymptomatic individuals is an area of very active debate. In this situation, the impact of lower population prevalence on the likelihood of false positive results is greater. Potentially large numbers of asymptomatic individuals may receive a diagnosis of a chronic infection, with substantial transmission potential, but no proven strategies to reduce the risk. The potential harm, healthcare burden, and costs of screening need to be weighed against its uncertain benefits; there is currently no evidence to guide practice in this area, but if an effective intervention for reduction of transmission became available, it would become an urgent priority.

INFORMATION PROVISION TO PATIENTS: HOW BEST CAN WE ANSWER OUR PATIENTS' QUESTIONS?

Several keynote studies have transformed our understanding of the epidemiology and natural history of genital herpes over the past five years. If well translated, the evidence they provide has great potential to enhance consultations with patients and optimise provision of high quality information. Four of the commonest initial questions asked by patients are addressed below, using evidence from the recent literature on the epidemiology, transmission, and natural history of genital HSV infection.

How did I get this ?

An initial diagnosis of genital herpes is often associated with substantial psychological distress. Information about its relatively high incidence and prevalence may help patients begin to adjust to the diagnosis. Between 1972 and 1999, diagnoses of genital herpes in GUM clinics in the UK increased fourfold in males and fourteenfold in females[1]; similar patterns have been observed in many other regions of the world. In the United States, a well conducted seroepidemiological survey of the general population showed that HSV-2 seroprevalence rose

by 32% during the 1980s, from 16.4% in 1976–80 to 21.7% in 1988–94.[25] HSV-1 is an increasingly important cause of genital infection.[14 16] In Glasgow, the ratio of HSV-1:HSV-2 isolates in patients with genital herpes has risen progressively over the past 15 years; genital HSV-1 infection is independently associated both with being female and being young (aged ⩽25 years).[28]

As risk factors for acquisition of HSV-1 and HSV-2 differ, it is crucially important that knowledge of the causative type informs counselling and information given to patients. Risk factors for HSV-1 infection are heterogeneous. In economically deprived populations, seroconversion occurs early in life, with around 70–80% of the population infected by late adolescence, many in the first few years of life. In more advantaged populations, acquisition of HSV-1 shows a more linear relationship with age; about 20% of individuals seroconvert in childhood, a further 20–40% in early adulthood and by the age of 50, a high proportion of the general population is usually infected.[16] The rapid increase in age specific seroprevalence rates in early adulthood (occurring at an earlier age in females than males[15]), together with the observed increase in the proportion of clinically manifest genital herpes attributable to HSV-1,[28] suggest that sexual transmission of HSV-1 is progressively assuming a more important role. The majority of genital HSV-1 infection is presumed to be acquired as a result of orogenital contact, but no evidence is available to quantify this more precisely. Only a third of HSV-1 antibody positive individuals have a known diagnosis of oral herpes, but most regularly shed HSV-1 from the oral cavity.[29 30] Overall, acquisition of HSV-1 in sexually active people occurs with ease. In a cohort study of 7046 pregnant women, 2033 of whom were initially HSV-1 and HSV-2 negative, the estimated mean risk of HSV-1 acquisition during pregnancy, adjusted for length of gestation, was 2.3 % (SE 0.4).[31] Another prospective study in a population at high risk of HSV-2 acquisition (two randomised controlled trials of a prophylactic HSV-2 vaccine which was subsequently shown to be ineffective), estimated an overall incidence rate of new HSV-1 infection at 1.6 per 100 patient years, which was similar for men and women.[32]

HSV-2 infections are usually sexually transmitted. The principal risk factors for acquisition are gender (women are at substantially greater risk than men),[32 33] sexual behaviour,[23 34] and socioeconomic deprivation.[16] Asymptomatic shedding and unrecognised symptomatic infection in source partners play a major role in the acquisition of genital herpes. In Mertz's well conducted, prospective study of discordant couples, nine of 14 (70%) of transmissions occurred when the source partner was asymptomatic,[33] strengthening the evidence in this regard from older retrospective studies.[35]

The advent of type specific serology has been immensely helpful in prospective evaluation of new infections with HSV-1 and HSV-2 infections, of which 37% and 63% respectively are asymptomatic.[32] Finally, 10–17% of patients who present with clinical features of initial episodes of genital herpes can be serologically confirmed as having recurrent disease.[36 37]

In summary, patients who present with an initial episode of genital herpes can be advised that they may not necessarily have acquired their infection within the recent past, that the infection is highly prevalent among the general population, the partner from whom they acquired infection was unlikely to be aware of their infection, and the most likely acquisition route would depend on the viral type, HSV-1 or HSV-2. The availability of diagnostic tests to further define the HSV status of partners is limited by the factors discussed in the previous section.

Can I pass it on?

A major concern for patients with genital herpes is fear of transmission to sexual partners. In general, transmission of HSV infections occurs by close contact with an individual who is shedding virus at a mucocutaneous surface and/or in oral or genital secretions. Infection occurs by inoculation of susceptible mucosal surfaces or through breaches in skin that are invisible to the naked eye. Since HSV is readily inactivated at room temperature and by drying, transmission by means other than direct contact is rare.

Research into transmission of genital herpes has focussed virtually exclusively on HSV-2 infection in heterosexual people. Limited indirect evidence on shedding patterns suggests that the advice we should be giving to patients about risk of transmission following a diagnosis of genital HSV-1 may differ substantially. Similarly, some information is available on HSV shedding frequency and patterns in a small study of 30 HIV negative gay men,[38] but not on absolute transmission rates within gay partnerships.

As detailed above, both the proportion of patients who asymptomatically shed HSV from the anogenital region and the duration of shedding following initial genital infection with HSV-1 are consistently lower than that for HSV-2.[20 21] Although these observations are likely to translate into a reduced risk of genital transmission, no prospective studies have yet been conducted to investigate this and the advice we give to patients must therefore be based on biological plausibility combined with a summary of the above data on shedding rates. Much better data are urgently required to inform the advice and counselling process we provide in this respect, particularly in view of the increasing predominance of genital HSV-1 infection.

In contrast, several large prospective studies of HSV-2 transmission have been published in recent years (table 3), which followed on from an early couple study of 29 HSV-2 seronegative partners; this had reported a male to female transmission rate of 14% (23% in HSV-1 seronegative susceptible partners and 6% in those who were HSV-1 seropositive).[39] Of the large prospective studies shown in table 3, two studied HSV discordant couples,[33 34] one a population at high risk of HSV acquisition,[32] and the fourth a lower risk population, comprising 7046 pregnant women receiving routine antenatal care in Seattle.[31] The first three of these studies were designed and powered to investigate the efficacy of prophylactic HSV-2 vaccines, not the determinants of transmission. Brown *et al's* study of HSV acquisition in pregnant women has the advantage of reflecting more closely the situation in the general population. In this study, the estimated mean risk of HSV-1 acquisition during pregnancy, adjusted for length of gestation, was 2.3 % (0.4), with a risk of 1.4 % (0.3) for HSV-2 acquisition in women with no serological evidence of pre-existent HSV infection and 1.7% (0.3) in those with pre-existent HSV-1 antibodies.[31]

Mertz *et al* studied 144 heterosexual couples in whom each source partner had symptomatic, recurrent genital herpes (97% due to HSV-2) and each susceptible partner was HSV-2 antibody negative. Transmission occurred in 14 couples, 11 with male source partners and three with female source partners. In nine couples, transmission occurred when the source partner was asymptomatic. Only 15% of couples in the study used condoms; in this subgroup, there was a 5.7% risk of transmission, compared with 13.6% in those who did not ($p = 0.19$). Overall, pre-existent HSV-1 infection in the susceptible partner did not protect against HSV-2 infection, but subgroup analysis by gender suggested a protective effect in women.[33]

Useful data on HSV acquisition have recently been generated from two parallel phase three trials of an ineffective HSV-2 vaccine. One trial enrolled 531 HSV-2 seronegative individuals, each of whom was in a monogamous relationship with a partner with HSV-2 infection. The second enrolled 1862 STD clinic attendees at high risk of HSV-2 acquisition. Langenberg *et al* used combined data from both trials to describe the acquisition rate of HSV-1 and HSV-2 and describe the characteristics of new infection. In contrast to the much

Table 3 Summary of recent large prospective studies of herpes simplex virus transmission

	Brown *et al*[31]	Langenberg *et al*[32]	Mertz *et al*[33]	Wald *et al*[34]
Year of publication	1997	1999	1992	2001
Setting	Two antenatal clinics (University Hospital Seattle and Madigan Army Hospital, Tacoma)	Two multicentre randomised controlled trials of an ineffective HSV-2 vaccine	Two university research clinics	Multicentre randomised controlled trials of an ineffective HSV-2 vaccine
Participants	7046 pregnant women at risk for HSV acquisition	2393 sexually active adults at high risk of HSV-2 acquisition	144 heterosexual couples discordant for genital HSV infection (97% had HSV-2)	528 monogamous couples discordant for HSV-2 infection
Duration of follow up	Duration of pregnancy	18 months	Median 334 days	18 months
Outcome measure(s)	Type specific seroconversion	Culture proven HSV infection or type specific seroconversion in susceptible partner	Culture proven HSV infection or type specific seroconversion in susceptible partner	Acquisition of HSV-2 infection by susceptible partner
Transmisson rate	HSV-1 : 2.3 % (± SE 0.4)	HSV-1 : 1.0/100 person years	16.9%	9.7%
(Male to female)	HSV-2 : 1.6% (± SE 0.4)	HSV-2 : 6.8/100 person years		
Transmisson rate		HSV-1 : 1.9/100 person years	3.8%	1.9%
(Female to male)		HSV-2 : 4.4/100 person years		
Effect of pre-existing HSV-1 antibodies on risk of acquisition	No protective effect demonstrated	No protective effect demonstrated	Protective for female susceptible partners only	No protective effect demonstrated
Effect of pre-existing HSV-1 antibodies on risk of transmission	–	–	No effect demonstrated	Increased risk of transmission in HSV-1 and HSV-2 coinfected source partners
Effect of condoms on risk of transmission	–	–	No effect demonstrated	Use in >25% of sex acts protective for female susceptible partners
Other determinants of transmission	–	–	–	Age, frequency of sexual activity, duration of relationship

HSV, herpes simplex virus

smaller study conducted by Mertz *et al*, pre-existent HSV-1 infection did not reduce the rate of HSV-2 acquisition, but it did increase the likelihood of asymptomatic seroconversion. Sixty three per cent and 37% of newly acquired HSV-1 and HSV-2 infections respectively were symptomatic. The sensitivity and specificity of a clinical diagnosis of genital herpes was 39% and 99% respectively.[32]

Wald *et al* evaluated a wide range of risk factors for HSV-2 acquisition in 528 HSV-2 seronegative individuals whose partners had recurrent genital HSV-2 infection. Twenty six women (9.7%) and five men (1.9%) acquired HSV-2. Condom use during more than 25% of sex acts was associated with protection against HSV infection for women, but not for men. Risk of HSV-2 transmission declined from 8.5 per 100 person years in the initial 150 day interval to 0.9 per 100 person years in the final 150 day interval ($p=0.002$ for trend). Caution should be used in interpretation of these observations, however, as some may be an artefact of extrapolating data on transmission from a vaccine efficacy trial. Younger age and more frequent sexual activity were associated with higher risk of HSV-2 acquisition, as was pre-existent HSV-1 infection in the source partner.[34]

In summary, patients can be advised that the risks of subsequent transmission depend on a number of factors, including the infecting viral type, HSV-1 or HSV-2, gender, and (possibly) duration of relationship. New data suggest that there may be a protective effect from consistent use of condoms, but the effect appears to be confined to male to female transmission. There is no evidence that prior HSV-1 infection protects against HSV-2 acquisition, but it may modify the natural history of HSV-2 infection.

Will it keep coming back for ever?

The long term natural history of genital herpes has been poorly studied. The Seattle research group has conducted several short term studies and one longer term observational study over the past two decades.[17–19 40] The findings of the shorter studies, which had median follow up periods of six to 12 months, are described in the section above (the clinical importance of typing).

Benedetti *et al* described the longer term natural history of genital herpes in an observational study of 664 patients recruited to their research clinic between 1974 and 1991. Three hundred and six patients had first episode genital herpes (60 had primary HSV-1 infection, 205 primary HSV-2 infection, and 41 non-primary initial HSV-2 infection). The remaining 358 patients had recurrent HSV-2 infection at enrolment. In the 169 patients who were followed up for more than 6 years, clinically significant reductions in recurrence frequency occurred in the majority of patients. However, 25% had an increase in recurrence frequency.[40]

In summary, the expected course of genital HSV infection is strongly dependent on the infecting viral type. Although the long term natural history of genital HSV-2 infection is very variable, reductions in recurrence frequency can be expected in the majority of patients

Should my partner come in for a test?

This is essentially a question about the value of partner notification in patients recently diagnosed with genital herpes, up to 20% of whom have established infection and are presenting with a first symptomatic recurrence at a variable time interval following asymptomatic seroconversion.[36 37] The aims of partner notification (PN) are to break the chain of transmission of STIs and reduce the population rates of infections, firstly through identifying, counselling, and offering treatment if appropriate and, secondly, by educating and promoting sexual health on an individual basis.[41] The effectiveness of PN in managing genital herpes has not been studied, but, returning to basic principles, the effectiveness of PN depends on the characteristics shown by the disease: existence of a symptomatic phase of infection in a substantial proportion of affected individuals, a short incubation period, a high transmission rate to partners, and availability of treatment which offers clear benefit to partners and/or in prevention of onward

transmission. Availability of an accurate diagnostic test to offer asymptomatic individuals is an essential element of PN for viral STIs, as antimicrobial therapy does not have the potential to eliminate the disease. Finally, in evaluating any clinical intervention, the potential for harm must be weighed against any perceived benefits. Few, if any, of the above criteria would support a systematic strategy of PN for asymptomatic partners of individuals recently diagnosed with genital herpes. However, as a high proportion of partners of newly diagnosed individuals have symptomatic but undiagnosed disease,[35] there is some evidence to support an offer to see partners for a general sexual health consultation, to identify any symptoms suggestive of previously unrecognised HSV infection, leading towards a formal diagnosis (currently, this should ideally be made by direct confirmation of HSV—see type specific serology) and appropriate counselling and information provision about transmission.

CONCLUSION

There have been several major advances in the range of available diagnostic tests for genital HSV infection in recent years, as well as substantially improved understanding of its epidemiology and transmission. In reviewing the recent literature, this article demonstrates the application of some of this new evidence to clinical care, focussing on the issues which are most important to patients and their partners.

REFERENCES

1 **www**.phls.co.uk/facts/STI/sti_in_uk/epi-herpes.htm (accessed April 2002).
2 **Koutsky LA**, Stevens CE, Holmes KK, *et al*. Underdiagnosis of genital herpes by current clinical and viral isolation procedures. *N Engl J Med* 1992;**326**:1533–9.
3 **Scoular A**, Kinghorn G, on behalf of the MSSVD Special Interest Group on Genital Herpes and the British Cooperative Clinical Group. BCCG national survey on diagnostic issues surrounding genital herpes. *Sex Transm Infect* 1999;**75**:403–5.
4 **Corey L**, Adams HG, Brown ZA, *et al*. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983;**98**:958–72.
5 **Aurelius E**, Johannsson B, Skoldenberg B, *et al*. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. *Lancet* 1991;**337**:189–92.
6 **Orle KA**, Gates CA, Martin DH, *et al*. Simultaneous PCR detection of Haemophilus ducreyi, Treponema pallidum and herpes simplex types 1 and 2 from genital ulcers. *J Clin Microbiol* 1996;**34**:49–54.
7 **Safrin S**, Shaw H, Bolan G, *et al*. Comparison of virus culture and the polymerase chain reaction for diagnosis of mucocutaneous herpes simplex virus infection. *Sex Transm Dis* 1997;**24**:176–80.
8 **Slomka MJ**, Emery L, Munday PE, *et al*. A comparison of PCR with virus isolation and direct antigen detection for diagnosis and typing of genital herpes. *J Med Virol* 1998;**55**:177–83.
9 **Waldhuber MG**, Denham I, Wadey C, *et al*. Detection of herpes simplex virus in genital specimens by type-specific polymerase chain reaction. *Int J STD & AIDS* 1999;**10**:89–92.
10 **Coyle PV**, Desai A, Wyatt D, *et al*. A comparison of virus isolation, indirect immunofluorescence and nested multiplex polymerase chain reaction for the diagnosis of primary and recurrent herpes simplex type 1 and type 2 infections. *J Virol Methods* 1999;**83**:75–82.
11 **Espy MJ**, Ross TK, Teo R, *et al*. Evaluation of LightCycler PCR for implementation of laboratory diagnosis of herpes simplex virus infections. *J Clin Microbiol* 2000;**38**:3116–18.
12 **Marshall DS**, Linfert DR, Draghi ABS, *et al*. Identification of herpes simplex virus genital infection: comparison of a multiplex PCR assay and traditional viral isolation techniques. *Modern Pathology* 2001;**14**:152–6.
13 **Scoular A**, Gillespie G, Carman WF. Polymerase chain reaction for diagnosis of genital herpes in a genitourinary medicine clinic. *Sex Transm Infect* 2002;**78**:21–5.
14 **Lamey P-J**, Hyland PL. Changing epidemiology of herpes simplex virus type 1 infections. *Herpes* 1999;**6**:20–4.
15 **Vyse AJ**, Gay NJ, Slomka M, *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**:183–7.
16 **Nahmias AJ**, Lee FK, Bechman-Nahmias S. Sero-epidemiological and serological patterns of herpes simplex infection in the world. *Scand J Infect Dis* 1990;**69**:19–36.
17 **Reeves WC**, Corey L, Adams HG, *et al*. Risk of recurrence after first episodes of genital herpes. Relation to HSV type and antibody response. *N Engl J Med* 1981;**305**:315–19.
18 **Lafferty WE**, Coombs RW, Benedetti J, *et al*. Recurrences after oral and genital herpes simplex virus infection—influence of site of infection and viral type. *N Engl J Med* 1987;**316**:1444–9.
19 **Benedetti J**, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first episode infection. *Ann Intern Med* 1994;**121**:847–54.
20 **Koelle DM**, Benedetti J, Langenberg A, *et al*. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992;**116**:433–7.
21 **Wald A**, Zeh J, Selke S, *et al*. Virological characteristics of subclinical and symptomatic genital herpes infection. *N Engl J Med* 1995;**333**:770–5.
22 **Ashley RL**. Sorting out the new HSV type specific antibody tests. *Sex Transm Infect* 2001;**77**:232–7.
23 **Cowan FM**, Johnson AM, Ashley R, *et al*. Antibody to herpes simplex virus type 2 as a serological marker of sexual lifestyle in populations. *BMJ* 1994;**309**:1325–9.
24 **Woolley PD**, Chandiok S, Pumphrey J, *et al*. Serological prevalence of herpes simplex virus type 2 amongst GUM clinic attenders in a district general hospital setting. *Int J STD & AIDS* 2000;**11**:379–82.
25 **Fleming DT**, McQuillan GM, Johnson RE, *et al*. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;**337**:1105–11.
26 **Rouse DJ**, Stringer JSA. An appraisal of screening for maternal type-specific herpes simplex virus antibodies to prevent neonatal herpes. *Am J Obstet Gynecol* 2000;**183**:400–6.
27 **Munday PE**, Vuddamalay J, Slomka MJ, *et al*. Role of type specific herpes simplex virus serology in the diagnosis and management of genital herpes. *Sex Transm Infect* 1998;**74**:175–8.
28 **Scoular A**, Norrie J, Gillespie G, *et al*. Fifteen year survey of the changing epidemiology of genital herpes infection: implications for patient management. BMJ 2002 (in press).
29 **Cowan FM**, Johnson AM, Ashley R. Relationship between antibodies to herpes simplex virus (HSV) and symptoms of HSV infection. *J Infect Dis* 1996;**174**:470–5.
30 **Scott DA**, Coulter WA, Lamey PJ. Oral shedding of herpes simplex virus type 1: a review. *J Oral Pathol & Med* 1997;**26**:441–7.
31 **Brown ZA**, Selke S, Zeh J, *et al*. The acquisition of herpes simplex virus during pregnancy. *N Engl J Med* 1997;**337**:509–15.
32 **Langenberg AGM**, Corey L, Ashley RL, *et al*. A prospective study of new infections with herpes simplex virus type 1 and type 2. *N Engl J Med* 1999;**341**:1432–8.
33 **Mertz GJ**, Benedetti J, Ashley R, *et al*. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992;**116**:197–202.
34 **Wald A**, Langenberg AGM, Link K, *et al*. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001;**285**:3100–6.
35 **Mertz GJ**, Schmidt O, Jourden JL, *et al*. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985;**12**:33–9.
36 **Diamond C**, Selke S, Ashley R. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. *Sex Transm Dis* 1999;**26**:221–5.
37 **Löwhagen G-B**, Tunbäck P, Andersson K. First episodes of genital herpes in a Swedish STD population: a study of epidemiology and transmission by use of herpes simplex virus (HSV) typing and specific serology. *Sex Transm Infect* 2000;**76**:179–82.
38 **Krone MR**, Wald A, Tabet SR, *et al*. 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**:261–7.
39 **Bryson Y**, Dillon M, Bernstein DI. Risk of acquisition of genital herpes virus type 2 in sex partners of persons with genital herpes: a prospective couple study. *J Infect Dis* 1993;**167**:942–6.
40 **Benedetti JK**, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreses in frequency over time. *Ann Intern Med* 1999;**131**:14–20.
41 **The Society of Health Advisers in Sexually Transmitted Diseases**. *Partner notification guidelines*. www.shastd.org.uk/professional_interest/partner.htm (accessed April 2002).