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Mini review

New developments in the epidemiology, natural history and management of genital herpes

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Abstract

The prevalence of genital herpes is increasing in several populations worldwide. Factors that may be contributing to this increase include greater numbers of sexual partners, the high frequency of asymptomatic infections, poor use of safe sexual practices, and possibly the decreased incidence of childhood oral herpes simplex virus infection. Transmission occurs via skin-to-skin or mucous membrane contact during periods of viral shedding when lesions are present but may also occur when the patient is unaware of the lesions or when lesions are not clinically apparent. This has important implications for strategies to prevent transmission of the disease. The introduction of the antiherpes agent, acyclovir, and more recently famciclovir and valacyclovir, facilitates the management of genital herpes. Treatment of first-episode genital herpes reduces the severity and duration of symptoms, time to lesion healing, and

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cessation of viral shedding. Episodic treatment of recurrences as they occur may be of benefit to some patients. Daily suppressive therapy significantly reduces the frequency of recurrences and asymptomatic viral shedding. Accordingly, patients who experience frequent or severe recurrences, those particularly troubled by their disease, and those who wish to reduce the frequency of asymptomatic infection generally prefer suppressive therapy. The possibility that suppressive therapy may have an impact on transmission of the disease is currently under investigation. Antiviral treatments have important implications for public health and may help reduce the psychological and psychosocial impact of genital herpes on individual patients.

Keywords: Herpes simplex virus; Genital herpes; Herpes epidemiology; Herpes treatment

1. Introduction

Genital herpes is one of the most widespread sexually transmitted diseases in the developed world. It most commonly results from infection with the herpes simplex virus (HSV) type 2 (HSV-2), or sometimes with HSV type 1 (HSV-1). Genital herpes may be associated with symptoms ranging from mild irritation to severe pain. In the majority of cases, the symptoms of genital herpes are mild or absent and the infected individual may not seek medical help. Most people are intermittently infectious (irrespective of the severity of symptoms, frequency of recurrences, or whether medical help is sought). Therefore, all patients require advice on how to prevent transmission. This risk of transmitting the disease to sexual partners makes genital herpes an important public health issue as well as a medical condition that may cause significant pain and social and psychological distress to individuals.

Over recent years, we have seen important changes in our understanding of the epidemiology, transmission dynamics and clinical manifestations of genital herpes. In addition, our diagnostic and treatment options have improved. This article reviews these changes and how this improved understanding of the disease and its treatment should be used to improve patient care. The review is the outcome of a meeting that was held in Avon, Colorado between 6 and 8 April 1997, to examine new information and developments concerning genital herpes.

2. Epidemiology

The past 10–20 years have seen a significant increase in the prevalence of genital herpes in several different communities worldwide. For example, there has been a 30% increase in HSV-2 seropositivity in the USA between 1978 and 1992 with a marked shift toward younger ages of acquisition (Johnson et al., 1989; Fleming et al., 1997). Similar trends have been reported in other countries (Cowan et al., 1994; Forsgren et al., 1994). The factors responsible for the increase in prevalence are not clearly understood. Possible contributing factors include increasing numbers of sexual partners, the high frequency of asymptomatic infections, the failure to utilize safer sexual practices, and possibly a reduction in the prevalence of prior HSV-1 infection among youth. HSV-1 seropositivity may provide partial protection against HSV-2 infection (Mertz et al., 1992). Thus the decrease in prevalence of the HSV-1 infection in some populations could increase susceptibility to the HSV-2 infection.

HSV-1 as a cause of genital herpes is increasing worldwide (Wald et al., 1994; Christie et al., 1997). In the UK, for example, it is now estimated that 50% of cases of primary genital herpes result from HSV-1 infection (Ross et al., 1993; Tayal and Pattman, 1994; Government Statistical Service, 1995; Rodgers and O'Mahony, 1995). This may be due to declining HSV-1 seropositivity among adolescents and possibly increased oral–genital contact and lack of use of barrier methods to prevent oral–genital HSV-1 transmission. Genital HSV-1 infections recur far less often than genital HSV-2 infections with greater than 95% of the episodes of recurrent genital herpes resulting from HSV-2 infection (Benedetti et al., 1994).

The increase in prevalence of genital herpes in some countries is particularly worrisome as it has occurred despite educational programmes aimed at

promoting safer sexual practices to prevent HIV infection. This suggests that the practices recommended for reducing HIV transmission may be ineffective for the prevention of transmission of genital herpes infection, or that people at risk of HSV-2 are not sufficiently motivated to adopt safer practices. Alternative strategies to prevent transmission may therefore be required.

3. Transmission

Advances in our understanding of the transmission of HSV-1 and HSV-2 may help in the development of better strategies. It has long been recognized that transmission occurs via direct skin-to-skin or mucous membrane contact and occurs when lesions are clinically apparent (Mertz et al., 1985). Transmission may also occur when the patient is unaware of lesions (atypical/unrecognized lesions) or when lesions are not clinically apparent (asymptomatic shedding) (Mertz et al., 1985, 1992). Wald has conducted several studies to investigate asymptomatic shedding in women with recurrent genital herpes. In a study involving 110 patients (Wald et al., 1995), HSV-2 could be detected in the genital tract on at least 1 day without reported lesions in 65% of patients. In 11% of patients, viral shedding in the absence of detectable lesions occurred on over 5% of days. The risk of asymptomatic shedding was greater in patients infected with HSV-2 than HSV-1 and in those experiencing frequent recurrences. In addition, patients with newly acquired infections were more likely to shed the virus than those who had been infected for more than 1 year. Transmission studies show that most transmission to sexual partners occurs when the person who is the source of infection is not aware of genital herpes lesions (Mertz et al., 1985, 1992).

In the light of these results, the recommendations for reducing the risk of transmission need to be reviewed. When lesions are present, the patient is almost certainly infectious and should therefore abstain from sexual intercourse. However, even when the patient is apparently asymptomatic, some risk of transmission exists. Both symptomatic and asymptomatic transmission risks need to be discussed with patients so that they can make informed decisions regarding how they might reduce their risk of disease transmission. Condom use should be recommended during sexual intercourse when lesions or symptoms are not present. However, the data supporting condom use for prevention of genital herpes transmission are weak (Oberle et al., 1989; Mertz et al., 1992). Antiviral therapy has been shown to reduce viral shedding (Wald et al., 1996; Sacks et al., 1997; Sacks and Shafran, 1998; Wald et al., 1998) and thus may also reduce the risk of transmission. However, antiviral therapy should not be a substitute for safer sexual practices, especially for persons with multiple sexual partners.

4. Impact of genital herpes on the patient

The psychological and psychosocial effects of genital herpes have been under-appreciated. For many persons these effects may well be more troublesome than the physical manifestations.

The diagnosis of genital herpes is usually unexpected, especially for those in monogamous relationships. This can lead to feelings of shock, embarrassment, depression, anger, diminished self-esteem and isolation (Catotti et al., 1993; Longo and Koehn, 1993; Carney et al., 1994). Depression is thought to result from the permanency of the disease and fear of social or sexual rejection. Many people feel unable to discuss the diagnosis of genital herpes with their partner, fearing rejection or accusations of infidelity. Others feel unable to form new relationships and may even retreat into celibacy (Sacks, 1997; Stanberry, 1998a). Fear of discovery and of transmission to new sexual partners are common anxieties for many patients (Limandri, 1989). The fear of discovery may largely be due to the social stigma associated with the disease and the fear of transmission may lead to withdrawal from sexual relationships.

Various studies have investigated the psychological and psychosexual impact of genital herpes (Mindel, 1996). Patients who experience frequent recurrences may experience more severe psychological and psychosexual problems. However, re-

ports have largely investigated highly selected patient groups, which may not be representative of patients in general. Some studies have compared the psychosocial morbidity associated with genital herpes with that of other genital conditions. For example, Stronks et al. (1993) found that patients with genital herpes were more anxious, sexually inhibited and angry towards their sexual partners than were subjects with gonorrhoea. This suggests that the chronic nature of genital herpes, rather than the sexual nature of the disease, may be an important factor in the associated psychological morbidity. Another study (Carney et al., 1993) compared psychological morbidity in patients with first-episode genital herpes, patients attending the Genitourinary Medicine Department who did not have genital herpes and young patients with chronic dermatoses, and found that psychosocial morbidity was higher in the group of patients with genital herpes.

Stress has been linked to the development of recurrent genital herpes. It has been suggested that stress may trigger the onset of recurrences, possibly via effects on the production of adrenergic substances or neurohormonal mediators. Results supporting this hypothesis come from retrospective studies where patients were asked to identify whether stressful events proceeded the recurrences (Bierman, 1985; Luby and Klinge, 1985; Manne et al., 1986). However, the results of prospective studies do not support this hypothesis (Vuchinich and Tucker, 1988; Hoon et al., 1991). It is possible that the development of recurrences causes stress; individuals who experience frequent recurrences may be more likely to feel anxious than those with infrequent recurrences. This hypothesis is supported by two prospective studies (Rand et al., 1990; Carney et al., 1994).

Carney et al. (1994) investigated how the psychosocial impact of genital herpes changes over time, after the primary infection. Not surprisingly, at the time of diagnosis patients were found to have profound emotional problems. Anxiety levels and concern decreased in patients who did not suffer recurrent episodes but remained high in patients who did, suggesting that the psychosocial impact is related to either the presence or frequency of recurrent episodes, or both. Furthermore, patients with frequent episodes who had psychosexual dysfunction, showed a marked improvement when treated with suppressive acyclovir.

The results of these studies and the experience of clinicians treating patients with genital herpes show that patients need strong support to deal with their disease. Sensitive counselling and, where necessary, antiviral therapy to reduce the severity of symptoms and frequency of recurrences are measures that clinicians can take to help their patients.

5. Diagnosis of genital herpes

The diagnosis of genital herpes is often established on clinical grounds alone, without laboratory confirmation. While the presence of bilateral vesicles or shallow ulcerations with an erythematous base in the genital area of a sexually active person is characteristic of primary genital herpes, the most common presentations are atypical and easily missed. Even when the presentation is considered typical, laboratory studies are important not only for confirming the diagnosis (often an aid in counselling) but for providing prognostic information since genital HSV-2 infection recurs much more frequently than HSV-1 (Benedetti et al., 1994). Atypical presentations of genital herpes include cervicitis without external genital ulcers, dysuria mimicking urinary tract infection or folliculitis (Barton et al., 1981). Often a history of similar problems is elicited, usually with previous resolution within a few days. In addition, several other conditions can mimic genital herpes, including scabies, fixed drug eruptions and yeast vulvovaginitis (Stanberry, 1996). In the developed countries, herpes is the most common cause of genital ulcers but syphilis and chancroid can also occur and appropriate tests for these infections should also be obtained (DiCarlo, 1997; Centers for Disease Control and Prevention, 1998). There is a wide overlap in the clinical manifestations of these infections, especially in patients with HIV infection (Morse et al., 1997), so that the diagnosis based on morphology of the lesions is often inaccurate.

The optimal method for diagnosis of genital herpes in the presence of genital lesions is viral culture with identification of viral type (Ashley, 1993). Viral recovery is highest from vesicular and ulcerative lesions and when the specimen is obtained by firmly rubbing the base of the lesions with a swab. However, the appropriate laboratory facilities may not be available and viral recovery is rarely $>60\%$, even when the specimen is collected and transported appropriately. Antigen detection tests are also available and the performance characteristics are similar to viral culture (Cone et al., 1993).

Recently, there has been renewed interest in the development of serologic tests for HSV. Historically, serological tests have not been able to distinguish accurately between HSV-1 and HSV-2 infections (Ashley et al., 1991, 1993; Ashley, 1994). In particular, the diagnosis of HSV-2 infection in persons with prior HSV-1 antibody was often inaccurate. The Western blot is the current gold standard for serological diagnosis. Up to date and less expensive commercial tests appear to have high sensitivity and specificity (Slomka et al., 1995; Ashley et al., 1998), although false negative or false positive results do occasionally occur. When there is significant doubt regarding the results of one of the new diagnostic tests the results should be confirmed by Western blot analysis. Serology can be very helpful in supporting the diagnosis of typical clinical presentations where cultures are not available or persistently negative. Moreover, serological tests can be used to support the diagnosis of typical clinical presentation when culture is not available or persistently negative, and to diagnose persons with atypical presentations or subclinical infection.

The settings in which the serological assays will be useful have not been well studied. However, these tests can potentially be used in high prevalence settings such as an STD clinic or to determine persons at risk of acquisition (Ashley and Corey, 1997). As women who acquire genital HSV in late pregnancy are at high risk of perinatal transmission of the infection to the newborn, type-specific serologies can be used to identify women who are at risk of acquiring the infection from their partners (Brown et al., 1997). The development of antibodies to HSV may take 2–12 weeks after the initial infection. As a result, serologic assays are not particularly useful in confirming diagnosis in recently infected persons. Because these assays are just becoming commercially available, their optimal use remains to be determined.

6. Management of genital herpes—antiviral therapy

Antiviral agents assist in the management of genital herpes in patients who seek medical intervention for their symptoms, and may also offer the potential to reduce the risk of transmission. There are now three antiviral agents available for the treatment of genital herpes: acyclovir, valacyclovir and famciclovir. Acyclovir was the first oral antiherpes agent to be developed. Although acyclovir is very effective, it is poorly bioavailable following oral administration (10–20%) (O'Brien and Campoli-Richards, 1989). Valacyclovir, a prodrug that is metabolized to yield acyclovir, was developed to overcome the poor bioavailability of acyclovir (bioavailability, 57%) (Burnette et al., 1995; Perry and Faulds, 1996). Famciclovir is a distinct antiviral agent that is a prodrug of penciclovir (Hodge and Cheng, 1993). Famciclovir also has a high bioavailability (77%) (Pue and Benet, 1993; Perry and Wagstaff, 1995). Penciclovir and acyclovir both require viral thymidine kinase for initial phosphorylation and act by inhibiting viral DNA polymerase, but there are a number of pharmacological differences in the two drugs. For example, penciclovir triphosphate has a significantly longer intracellular half-life (10–20 h) compared with acyclovir triphosphate (<1 h) (Bacon et al., 1996) and penciclovir has a greater affinity for thymidine kinase than acyclovir but a lower affinity for the viral DNA polymerase. In vitro, penciclovir and acyclovir have comparable inhibitory activity against HSV replication (Weinberg et al., 1992).

Data from studies in mice (Field et al., 1995a; Field and Thackray, 1995b; Thackray and Field, 1996, 1998) suggest that famciclovir, but not acyclovir or valacyclovir, can reduce the overall viral burden of latency when used to treat the initial

HSV infection. Studies using the guinea pig model of genital herpes (Bourne and Stanberry, 1999) suggest a direct relationship between the burden of latent infection and the frequency of recurrent genital infections (Stanberry, unpublished data). The question of whether early famciclovir administration in the course of first episode infection can have an impact on recurrence rates in humans is being investigated in an ongoing multicenter clinical trial. This study compares famciclovir and valacyclovir in patients presenting within 72 h onset of first-episode genital HSV-2 infection.

The role of antiviral therapies will now be discussed for the three main clinical settings.

6.1. Treatment of first episode

Patients who present with suspected or proven first-episode genital herpes, irrespective of whether it is the primary infection or not, should be offered antiviral therapy at the time of initial evaluation (Centers for Disease Control and Prevention, 1998). For many patients, the first episode is associated with severe symptoms, pain and systemic illness. The severity of the disease, which may develop over the first 1–2 weeks of illness, cannot necessarily be predicted at first presentation. Antiviral therapy is most effective when initiated early in the course of infection. Therapy should not be delayed pending laboratory confirmation. The excellent safety profiles of all available medications suggest that empirical treatment is a preferable strategy in patients whose diagnosis is unclear; if an alternative diagnosis is established, antiviral therapy can be discontinued.

All three antiviral agents have been shown to be beneficial. Symptoms are reduced both in duration and severity and these agents significantly reduce time to lesion healing and duration of viral shedding (Corey et al., 1983a; Loveless et al., 1995; Fife et al., 1997). Antiviral therapy may also prevent the development of neurologic complications such as aseptic meningitis and urinary retention which are common, especially among women (Bryson et al., 1983; Corey et al., 1983b).

Although very effective, acyclovir was approved at a dosing schedule of 200 mg five times a day. Many patients find this regimen burdensome. As a result, many physicians in the United States prescribe a three times a day regimen (400 mg t.i.d.) which is thought to be effective but has not been evaluated in a clinical trial (Centers for Disease Control and Prevention, 1998). If the initial infection is very severe, with neurological complications such as urinary retention or aseptic meningitis, the physician may consider intravenous administration three times a day (Mindel et al., 1982).

The improved bioavailability of famciclovir and valacyclovir allows these agents to be administered less frequently. The recommended regimens for first episode infection are: famciclovir, 250 mg t.i.d. for 5–10 days, and valacyclovir, 1 g b.i.d. for 10 days (Centers for Disease Control and Prevention, 1998). The less frequent regimens are likely to be more acceptable to patients than five times a day dosing and may lead to better compliance. The duration for which therapy is required is unclear but treatment may be continued beyond 5–10 days for patients still experiencing symptoms.

Treating the first episode helps the patient overcome the initial symptoms but most patients, especially those with genital HSV-2, are likely to have recurrences. At present, there is no compelling clinical evidence that any of the currently available therapies for first episode disease affects the subsequent frequency or severity of recurrences in humans (Corey et al., 1985).

6.2. Treatment of recurrences

Most patients with genital HSV-2 experience recurrences for years after the initial infection. Following a clinically apparent first episode of genital HSV-2 infection, patients typically experience four to five recurrences per year. However, approximately 20% of patients experience more than six recurrences per year, and even as many as ten per year. Patients with particularly prolonged primary infections (>34 days) are more likely to experience frequent recurrences (Benedetti et al., 1994). Strategies for management of recurrences will depend on a number of factors including recurrence frequency and severity, and relationship and lifestyle issues of the individual.

6.3. Episodic treatment

Episodic treatment of each recurrence as it arises might be considered in circumstances where the frequency of recurrences is low, the recurrences are not very bothersome to the patient, the individual typically has a well defined prodrome that allows early self-initiation of therapy, or where asymptomatic shedding is not especially relevant (e.g. both partners have herpes). If treatment is to be used, it should begin as early as possible in the course of the outbreak to maximize efficacy. Therefore, it is best initiated by the patient at the first sign or symptom (Reichman et al., 1984; Sacks et al., 1996; Spruance et al., 1996; Bodsworth et al., 1997). Patients should have a supply of medication to keep at home and should start treatment at the first indication of prodrome or other early signs of a recurrence. Therapy aims to relieve symptoms and to hasten healing of lesions. In addition, therapy can decrease the duration of symptomatic viral shedding.

Acyclovir, valacyclovir and famciclovir have all been shown to reduce the duration of viral shedding and time to lesion healing (Nilsen et al., 1982; Reichman et al., 1984; Goldberg et al., 1986; Sacks et al., 1996; Spruance et al., 1996). Valacyclovir, dosed at 500 or 1000 mg twice daily for 5 days, has also been shown to shorten the duration of pain and speed up the resolution of the episode (an efficacy endpoint combining all symptoms and signs of the episode) (Spruance et al., 1996). Sacks et al. (1996) reported that famciclovir, at a dose of 125 mg b.i.d. administered for 5 days from the start of symptoms significantly reduced time to healing, time to cessation of viral shedding and the duration of lesion compared with placebo. Times to cessation of all symptoms were also reduced by about 20%. Episodic therapy typically reduces the duration of the episode by only 1–2 days.

Which of the three agents is the most effective for episodic therapy is unknown since the studies have different designs. One study has shown acyclovir and valacyclovir to be equivalent (Bodsworth et al., 1997; Tyring et al., 1998), but famciclovir has not been compared directly with acyclovir or valacyclovir. However, twice-daily therapy with famciclovir or valacyclovir may be more convenient than three times daily acyclovir therapy. The recommended regimens in this setting are: famciclovir, 125 mg b.i.d. for 5 days, or valacyclovir, 500 mg b.i.d. for 5 days. Acyclovir is approved at a dose of 200 mg five times a day but is often prescribed at 400 mg t.i.d. (Centers for Disease Control and Prevention, 1998), although this regimen has not been tested in clinical trials.

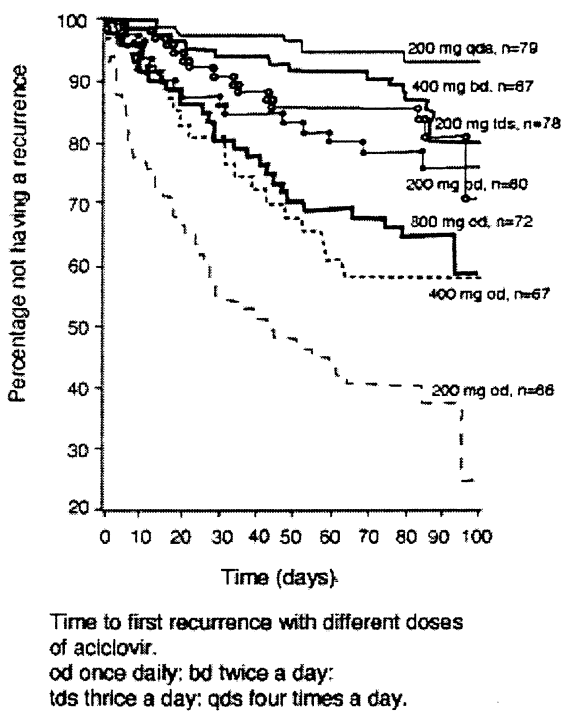
6.4. Chronic suppressive therapy

Chronic suppressive therapy is more appropriate than episodic therapy for most patients who suffer frequent recurrences. This may also apply to patients who experience less frequent but severe recurrences, who are psychologically distressed by their recurrences, or who are particularly concerned about preventing a recurrence. Chronic suppressive antiviral therapy can reduce the frequency of recurrences and severity of the associated symptoms. It may also improve psychosexual well-being early in the infection (Carney et al., 1993). New evidence suggests that continuous antiviral therapy also decreases asymptomatic shedding and hence could theoretically decrease the risk of transmission, although this benefit has not yet been demonstrated.

7. Impact on recurrences

The impact of daily antiviral therapy on the frequency of recurrences has been studied extensively for both acyclovir and the new antiviral agents. Mindel (Mindel et al., 1988) showed that the efficacy of acyclovir in suppressing recurrences is markedly influenced by the frequency of administration (Fig. 1). Of the patients receiving acyclovir twice a day or more frequently, at least 80% remained recurrence-free at 3 months. This decreased to 40% recurrence-free when acyclovir was administered once a day. The most effective regimen was acyclovir 200 mg taken four times a day. Although somewhat less effective, acyclovir 400 mg taken twice daily has become the standard regimen in North America since it balances efficacy and convenience.

Famciclovir and valacyclovir have both been investigated as once-and twice-daily regimens for suppression of recurrences. Mertz et al. (1997) found that famciclovir, 250 mg b.i.d., given for 16 weeks suppressed recurrences in 90% of patients, while only 48% of patients receiving placebo were recurrence-free after 4 months. Patients receiving lower doses or less frequent dosing (125 mg o.d. or b.i.d., 250 mg o.d. or 500 mg o.d.) were more likely to experience recurrences than those receiving famciclovir, 250 mg b.d. All famciclovir regimens were more effective than placebo. In another study (Diaz-Mitoma et al., 1998), famciclovir, 250 mg b.i.d., was compared with famciclovir, 125 mg t.i.d. or 250 mg t.i.d. given for 1 year. All three regimens were significantly more effective than placebo and the twice-daily regimen was as effective as both of the three times a day regimens in suppressing clinically confirmed recurrences. The median time to first recurrence was 47 days for placebo recipients and 336 days for famciclovir 250mg b.i.d. recipients. In particular, 22% of patients treated with placebo remained without a recurrence after 1 year of therapy compared to 72% of patients treated with famciclovir 250 mg b.i.d.



Time to first recurrence with different doses of aciclovir.
od once daily; bd twice a day;
tds thrice a day; qds four times a day.

Fig. 1. Influence of frequency of administration on the efficacy of acyclovir to suppress recurrences (Mindel et al., 1988).

Valacyclovir, 500 mg o.d., has also been compared with placebo in a study involving 16 weeks of treatment (Patel et al., 1997). At the end of the treatment period, 69% of patients receiving valacyclovir were recurrence-free, compared with 9.5% in the placebo group. In a second study, once-and twice-daily regimens of valacyclovir were compared with placebo and acyclovir, 400 mg b.i.d. (Reitano et al., 1998). The once-daily regimens (250, 500 and 1000 mg) showed a significant dose-response. Overall, the proportion of patients free of recurrence at 1 year was 50% for the valacyclovir 250 mg b.i.d., 49% for acyclovir 400 mg b.i.d., 48% for 1000 mg o.d. and 40% for valacyclovir 500 mg o.d. Analyses of subgroups according to frequency of recurrences prior to the trial revealed that patients with very frequent recurrences were more likely to recur during therapy with valacyclovir 500 mg o.d. than with either 250 mg b.i.d. or 1000 mg o.d. As a result, valacyclovir can be given at a dose of 500 mg once daily for suppression of recurrences for patients with fewer than ten recurrences per year but, in patients with more frequent recurrences, 250 mg twice daily or 1000 mg once daily is recommended. Because the patient population differed in the famciclovir and valacyclovir studies, the results do not yield to direct comparisons of the efficacy of the two new agents. These studies cannot be directly compared with prior acyclovir studies as the severity of disease in patients in clinical trials has decreased. Patients with severe genital herpes may be unwilling to enter placebo-controlled studies, as effective therapy is available.

8. Impact on asymptomatic viral shedding

In addition to reducing the frequency of recurrences, antiviral therapy can also reduce asymptomatic shedding. Wald (Wald et al., 1996) has shown that twice-daily therapy with acyclovir 400 mg can significantly suppress viral shedding in

women with recurrent genital herpes. In this study involving 34 patients, viral shedding on days without lesions was observed in 15 of the 17 patients receiving placebo, compared with only 3 of the 17 patients receiving acyclovir over the 10-week study period. The percentage of days where subclinical viral shedding occurred decreased from 6.9 (on placebo) to 0.3% (on acyclovir therapy). However, when a more sensitive test such as HSV DNA polymerase chain reaction assay was used, the virus could be detected on 8% of days of acyclovir therapy (Wald et al., 1997). Preliminary data show that famciclovir and valacyclovir are also effective in reducing subclinical shedding of HSV (Sacks et al., 1997; Sacks and Shafran, 1998; Wald et al., 1998). Famciclovir has been studied in both men and women at 125, 250 mg t.i.d., and 250 mg b.i.d. Valacyclovir has been studied at 500 mg b.i.d. in men and women; studies of once daily valacyclovir are in progress.

9. Impact on psychological well-being

Chronic suppressive therapy may also improve psychological well-being. Evidence supporting this comes from a study of the impact of acyclovir on 102 patients with frequently recurring genital herpes (Carney et al., 1993). A questionnaire was completed before therapy and every 3 months for 1 year to assess psychological morbidity. A significant improvement in all three measures of psychological morbidity used in the study was noted during acyclovir therapy. Further studies are required to confirm this impact on psychological well-being. However, the results do suggest that psychological morbidity should be a major consideration when assessing patients for chronic suppressive therapy.

10. Recommended therapy

The results of these studies of suppressive antiviral therapy suggest that both once- and twice-daily regimens are effective in the suppression of recurrences, depending on the agent administered. Regardless of the drug chosen, it is crucial that treatment adequately controls the patients' disease. Several concerns exist about once-daily regimens for suppressive therapy. Firstly, based on the pharmacokinetic profiles of antiherpes agents, once-daily regimens may be more likely to allow breakthrough recurrences than twice-daily regimens. This risk of breakthrough increases as the baseline frequency of recurrences increases. Secondly, if a patient misses one dose of a once-daily regimen, they will be without adequate antiviral cover for a substantially longer period than if a patient misses one dose of a twice-daily regimen. This may not lead to a symptomatic breakthrough but may allow viral reactivation to occur thus increasing the risk of asymptomatic viral shedding and, potentially, transmission of the disease. For these reasons, twice-daily dosing of antiviral agents may be appropriate for many patients who may be concerned about asymptomatic shedding and disease transmission. However, a study to evaluate the efficacy of once-daily valacyclovir in reducing sexual transmission of HSV-2 is ongoing.

At present, suppressive therapy is prescribed infrequently. This may well be due to a lack of physician knowledge of the benefits and an undue concern about side-effects. The results of many studies show that the latter concern is clearly unfounded. For example, in a study by Mindel et al. (1988) of acyclovir suppressive therapy administered for 1 year, no significant side-effects were observed. Studies of daily acyclovir for up to 10 years have demonstrated that even long-term therapy is not associated with any clinical or laboratory toxicity (Goldberg et al., 1993; Fife et al., 1994). Similarly, famciclovir and valacyclovir have been reported to be well-tolerated when given for up to 12 months as continuous suppressive therapy (Mertz et al., 1997; Patel et al., 1997; Diaz-Mitoma et al., 1998; Reitano et al., 1998). Many clinicians and patients express concern about the potential for development of resistance of HSV to antiviral drugs after prolonged therapy. However, neither in vivo nor in vitro emergence of resistance has been noted in chronically treated immunocompetent patients (Fife et al., 1994). Concern about cost, in the absence of a cost-benefit analysis, may also contribute to un-

derprescription. However, the more profound benefits of suppressive therapy, compared with episodic therapy, make this the treatment of choice for many patients. The availability of generic acyclovir has also made it more affordable.

Chronic antiviral therapy, given at the optimum dose, can be highly effective for suppressing recurrences. Usually patients perceive benefits of suppressive therapy after 3–6 months of daily dosing. However, some patients do not respond to therapy. The most common reason for this is that the diagnosis of genital herpes is incorrect. In situations where breakthrough herpes lesions occur, the patients may not be receiving an adequate dose of the antiviral agent, either because they are not compliant, are not absorbing the drug, or because the physician is not prescribing the correct dose. It may be helpful in such situations to increase the dosing frequency or to try an alternative antiviral. Occasionally, higher than standard doses are required for suppression of recurrences. Because of the large margin of safety of antiviral drugs, increase in dose is usually possible without adverse effects.

11. Patient perspective

It is important to communicate information about options in antiviral therapy to the patient. Clinicians can make clear recommendations to their patients regarding the optimum management of their disease, the advantages and disadvantages of the various options, and the issues that patients should consider. However, each patient should be considered individually and the management programme should be tailored to his or her specific situation and needs. The patient's views of the disease and how it should be controlled are important considerations. Social circumstances and sexual behaviour may also influence the decision. For instance, an individual starting a new relationship is likely to need greater support, and possibly more active management than someone who is not in a relationship.

An essential part of the therapeutic decision is to provide the patient with information on how to control symptoms and reduce the risk of transmission. During the patient's first visit, the shock of the diagnosis often means that the patient fails to retain most of the information they are given. It is, therefore, essential to provide the patient with written information that they can read at home. This may also help them pass on the relevant information to a partner. Scheduling a return visit is an essential part of the management of the first episode of genital herpes. During the second visit, questions regarding the natural history of the disease can be addressed more comprehensibly.

The patient's view of genital herpes is likely to be very different to that of the physician. This, together with an incomplete understanding of a patient's needs, can lead to patient dissatisfaction with the care offered by physicians (Catotti et al., 1993). A non-judgemental approach that does not trivialize the disease is likely to help the patient cope with the social and psychological implications of the disease. For some patients, these are more important than treatment of the physical symptoms. Patients may also benefit from additional skilled counselling or peer support. Counselling can help patients overcome feelings of anger, depression, isolation and helplessness so that they can live a full and normal life. It may be particularly important in helping patients discuss the disease with their partners.

Both the physician and patient in partnership should make the decisions regarding long-term management. To make informed decisions the patient requires information about available options. This is unlikely to be made during the initial visit. A follow-up visit should thus be arranged once the patient has been able to think rationally about the disease and the possible options. Later follow-up is also necessary as both the disease and the patient's lifestyle and acceptance level significantly evolve with time, especially over the first few years of infection. Some individuals may choose not to treat the disease even though they experience frequent recurrences. Others may want to use antiviral therapy, even though their symptoms may be relatively mild and occur infrequently. Cost considerations may influence some patients' and physicians' decisions.

12. Summary

Increases in the incidence and prevalence of HSV genital infections in many countries and populations are being accompanied by a greater recognition of the psychological impact of the disease and the need for counselling and support, as well as a better understanding of its transmission.

The new antiviral agents, famciclovir and valacyclovir, offer more convenient treatment schedules thus facilitating the management of patients. Of particular importance is the recognition of the value of continuous suppressive therapy for appropriate patients as this significantly reduces the risk of recurrences and impacts viral shedding. Because of the risk of viral shedding during the presence of lesions and when no lesions are apparent, a patient may be infectious even when they are not aware of lesions. Since continuous suppressive therapy can reduce asymptomatic shedding it might also reduce the risk of transmission, although proof of this concept awaits the results of an ongoing clinical trial.

Advances in our understanding of genital herpes, including transmission, disease manifestations, and psychological/psychosexual impact should help improve the management of this disease. Antiviral therapies can effectively diminish physical and psychological suffering. We await data on the effect of suppressive therapy on transmission, itself. Any medical intervention must be accompanied by counselling that empowers patients to help manage their disease, including the social and psychological aspects. Better management also has important public health implications as it should in turn lead to lower risks of transmission and hence a lower incidence of the disease.

Widespread availability of tools to diagnose patients with atypical or subclinical infection is likely to facilitate management of sexual partners and pregnant women. Development of vaccines against HSV may provide new strategies for reducing transmission (Stanberry, 1998b). The preliminary data on the establishment of latency is exciting as it suggests that early antiviral therapy may offer the possibility of preventing or reducing subsequent recurrences. The clinical implications of these strategies offer important opportunities to improve public health and the health of the individual.

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References

Ashley, R., 1993. Laboratory techniques in the diagnosis of herpes simplex infection. Genitourin. Med. 69, 174–183.

Ashley, R., Cent, A., Maggs, V., Corey, L., 1991. Inability of enzyme immunoassays to discriminate between infections with herpes simplex virus type 1 and 2. Ann. Intern. Med. 115, 520–526.

Ashley, R.L., 1994. Progress and pitfalls in serologic testing for genital herpes. Herpes 2, 49–51.

Ashley, R.L., Corey, L., 1997. HSV type specific antibody tests: patients are ready, are clinicians? Genitourin. Med. 73, 235–236.

Ashley, R.L., Dalessio, J., Dragavon, J., Koutsky, L.A., Lee, F.K., Nahmias, A.J., Steven, C.E., Holmes, K.K., Corey, L., 1993. Underestimation of HSV-2 seroprevalence in a high-risk population by microneutralization assay. Sex. Transm. Dis. 20, 230–235.

Ashley, R.L., Wu, L., Pickering, J.W., Tu, M.C., Schnorenberg, L., 1998. Premarket evaluation of a commercial glycoprotein-G based enzyme immunoassay for herpes simplex virus type-specific antibodies. J. Clin. Microbiol. 36, 294–295.

Bacon, T.H., Gilbart, J., Howard, B.A., Standing-Cox, R., 1996. Inhibition of varicella-zoster virus by penciclovir in cell culture and mechanism of action. Antiviral Chem. Chemother. 7, 71–78.

Barton, I.G., Kinghorn, G.R., Walker, M.J., Al-Omer, L.S., Potter, C.W., Turner, E.B., 1981. Association of HSV-1 with cervical infection. Lancet 2, 1108.

Benedetti, J., Corey, L., Ashley, R., 1994. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann. Intern. Med. 121, 847–854.

Bierman, S.M., 1985. Recurrent genital herpes simplex infection: a trivial disorder. Arch. Dermatol. 121, 513–517.

Bodsworth, N.J., Crooks, R.J., Borelli, S., Vejlsgarrd, G., Paavonen, J., Worm, A.-M., Uexkull, N., Esmann, J., Strand, A., Ingamells, A.J., Gibb, A. and the International Valaciclovir HSV Study Group, 1997. Valaciclovir versus acyclovir in patient-initiated treatment of recurrent genital herpes: a randomized, double-blind clinical trial. Genitourin. Med. 73, 110–116.

Bourne, N., Stanberry, L.R., 1999. Animal models of herpes virus genital infection: Guinea pig. In: Zak, O., Sande, M. (Eds.), Experimental models in antimicrobial chemotherapy. Academic Press, London (in press).

Brown, Z.A., Selke, S.A., Zeh, J., Kopleman, J., Maslow, A., Ashley, R.L., Watts, D.H., Berry, S., Herd, M., Corey, L., 1997. Acquisition of herpes simplex virus during pregnancy. N. Engl. J. Med. 337, 509–515.

Bryson, Y.J., Dillon, M., Lovett, M., Acuna, G., Taylor, S., Cherry, J.D., Johnson, B.L., Wiesmeier, E., Growdo, W., Creagh-Kirk, T., Keeney, R., 1983. Treatment of first episodes of genital herpes simplex virus infections with oral acyclovir: a randomized double-blind controlled trial in normal subjects. N. Engl. J. Med. 308, 916–920.

Burnette, T.C., Harrington, J.A., Reardon, J.E., Merrill, B.M., de Miranda, P., 1995. Purification and characterization of a rat liver enzyme that hydrolyzes valaciclovir, the L-valyl ester prodrug of acyclovir. J. Biol. Chem. 270, 15827–15831.

Carney, O., Ross, E., Bunker, C., Ikkos, G., Mindel, A., 1994. A prospective study of the psychological impact on patients with a first episode of genital herpes. Genitourin. Med. 70, 40–45.

Carney, O., Ross, E., Ikkos, G., Mindel, A., 1993. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. Genitourin. Med. 69, 457–459.

Catotti, D.N., Clarke, P., Catoe, K.E., 1993. Herpes revisited: still a cause of concern. Sex. Transm. Dis. 20, 77–80.

Centers for Disease Control and Prevention, 1998. CDC 1998 Guidelines for Treatment of Sexually Transmitted Diseases. Morb. Mortal. Wkly. Rep. 47, 1–118.

Christie, S.N., McCaughey, C., McBride, M., Coyle, P.V., 1997. Herpes simplex type 1 and genital herpes in Northern Ireland. Int. J. STD AIDS 8, 68–69.

Cone, R.W., Swenson, P.D., Hobson, A.C., Remington, M., Corey, L., 1993. Herpes simplex virus detection from genital lesions: a comparative study using antigen detection (HerpChek) and culture. J. Clin. Microbiol. 31, 1774–1776.

Corey, L., Benedetti, J., Critchlow, C., Mertz, G., Douglas, J., Fife, K., Fahnlander, A., Remington, M.L., Winter, C., Dragavon, J., 1983. Treatment of primary first-episode genital herpes simplex virus infections with acyclovir: results of topical, intravenous and oral therapy. J. Antimicrob. Chemother. 12, 79–88.

Corey, L., Fife, K., Benedetti, J.K., Winter, C., Fahnlander, A., Connor, J.D., Hintz, M.A., Holmes, K.K., 1983. Intravenous acyclovir for the treatment of primary genital herpes. Ann. Int. Med. 98, 914–921.

Corey, L., Mindel, A., Fife, K.H., Sutherland, S., Benedetti, J., Adler, M.W., 1985. Risk of recurrence after treatment of first episode genital herpes with intravenous acyclovir. Sex. Transm. Dis. 12, 215–218.

Cowan, F.M., Johnson, A.M., Ashley, R., Corey, L., Mindel, A., 1994. Antibody to herpes simplex virus type 2 as serological marker of sexual lifestyle in populations. Br. Med. J. 309, 1325–1329.

Diaz-Mitoma, F., Sibbald, R.G., Shafran, S.D., Boon, R., Saltzman, R.L. and the Collaborative Famciclovir Genital Herpes Research Group, 1998. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. J. Am. Med. Assoc. 280, 887–92.

DiCarlo, R.P., Martin, D.H., 1997. Chanchroid surveillance—New Orleans men 1992–996. International Congress of Sexually Transmitted Diseases, Seville, Spain. Abstract p. 370.

Field, H.J., Tewari, D., Sutton, D., Thackray, A.M., 1995. Comparison of efficacies of famciclovir and valacyclovir against herpes simplex virus type 1 in a murine immunosuppression model. Antimicrob. Agents Chemother. 39, 1114–1119.

Field, H.J., Thackray, A.M., 1995. The effects of delayed-onset chemotherapy using famciclovir or valaciclovir in a murine immunosuprression model for HSV-1. Antiviral Chem. Chemother. 6, 210–216.

Fife, K.H., Barbarash, R.A., Rudolph, T., Degregorio, B., Roth, R., 1997. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind randomized clinical trial. Sex. Transm. Dis. 24, 481–486.

Fife, K.H., Crumpacker, C.S., Mertz, G.J., Hill, E.L., Boone, G.S. and the Acyclovir Study Group, 1994. Recurrence and resistance patterns of herpes simplex virus following cessation of ≥ 6 years of chronic suppression with acyclovir. J. Infect. Dis. 169, 1338–41.

Fleming, D.T., McQuillan, G.M., Johnson, R.E., Nahmias, A.J., Aral, S.O., Lee, F.K., St. Louis, M.E., 1997. Herpes simplex virus type 2 in the United States, 1976 to 1994. N. Engl. J. Med. 337, 1105–1111.

Forsgren, M.F., Skoog, E., Jeansson, S., Olofsson, S., Giesecke, J., 1994. 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 5, 113–116.

Goldberg, L.H., Kaufman, R., Conant, M.A., Sperber, J., Allen, M., Illeman, M., Chapman, S., 1986. Oral acyclovir for episodic treatment of recurrent genital herpes: efficacy and safety. J. Am. Acad. Dermatol. 15, 256–264.

Goldberg, L.H., Kaufman, R., Kurtz, T., Conant, M.A., Eron, L.I., Batenhorst, R.I., 1993. Long-term suppression of recurrent genital herpes with acyclovir: a 5-year benchmark. Arch. Dermatol. 129, 582–587.

Government Statistical Service, 1995. Sexually Transmitted Diseases England, 1994, 16.

Hodge, R.A., Cheng, Y.C., 1993. The mode of action of penciclovir. Antiviral Chem. Chemother. 4 (S1), 13–24.

Hoon, E.F., Hoon, P.W., Rand, K.H., Johnson, J., Hall, N.R., Edwards, N.B., 1991. A psycho-behavioral model of genital herpes recurrence. J. Psychosom. Res. 35, 25–36.

Johnson, R.E., Nahmias, A.J., Magder, L.S., Lee, F.K., Brooks, C.A., Snowden, C.B., 1989. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. N. Engl. J. Med. 321, 7–12.

Limandri, B.J., 1989. Disclosure of stigmatizing conditions: the discloser's perspective. Arch. Psychiatr. Nurs. 3, 69–78.

Longo, D., Koehn, K., 1993. Psychosocial factors and recurrent genital herpes: a review of prediction and psychiatric treatment studies. Int. J. Psychiatry Med. 23, 99–117.

Loveless, M., Harris, W., Sacks, S., 1995. Treatment of first episode genital herpes with famciclovir. In: Programs and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California.

Luby, E.D., Klinge, V., 1985. Genital herpes: a pervasive psychosocial disorder. Arch. Dermatol. 121, 494–497.

Manne, S., Sandler, I., Zautra, A., 1986. Coping and adjustment to genital herpes: the effects of time and social support. J. Behavior Med. 9, 163–168.

Mertz, G.J., Benedetti, J., Ashley, R., Selke, S.A., Corey, L., 1992. Risk factors for the sexual transmission of genital herpes. Ann. Intern. Med. 116, 197–202.

Mertz, G.J., Loveless, M.O., Levin, M.J., Kraus, S.J., Fowler, S.L., Goade, D., Trying, S.K., 1997. Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women: a multicenter, double-blind, placebo-controlled trial. Arch. Intern. Med. 157, 343–349.

Mertz, G.J., Schmidt, O., Jourden, J.L., Guinan, M.E., Remington, M.L., Fahnlander, A., Winter, C., Holmes, K.K., Corey, L., 1985. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. Sex. Transm. Dis. 12, 33–39.

Mindel, A., 1996. Psychological and psychosexual implications of herpes simplex virus infections. Scand. J. Infect. Dis. Suppl. 100, 27–32.

Mindel, A., Adler, M.W., Sutherland, S., Fiddian, A.P., 1982. Intravenous acyclovir treatment for primary genital herpes. Lancet 1, 697–700.

Mindel, A., Carney, O., Freris, M., Faherty, A., Patou, G., Williams, P., 1988. Dosage and safety of long term suppressive acyclovir therapy for recurrent genital herpes. Lancet 1, 926–928.

Morse, S.A., Trees, D.L., Htun, Y., Radebe, F., Orie, K.A., Dangor, Y., Beck-Sague, C.M., Schmid, S., Fehler, G., Weiss, J.B., Ballard, R.C., 1997. 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. 175, 001–007.

Nilsen, A.E., Aasen, T., Halsos, A.M., Kinge, B.R., Tjotta, E.A., Wikstrom, K., Fiddian, A.P., 1982. Efficacy of oral acyclovir in treatment of initial and recurrent genital herpes. Lancet 2, 572–573.

Oberle, M.W., Rosero-Bixby, L., Lee, F.K., Sanz chez-Braverman, M., Nahmias, A.J., Guinan, M.E., 1989. Herpes simplex virus type 2 antibodies: high prevalence in monogamous women in Costa Rica. Am. J. Trop. Med. Hyg. 41, 118–224.

O'Brien, J.J., Campoli-Richards, D.M., 1989. Aciclovir: An updated review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. Drugs 37, 233–309.

Patel, R., Bodsworth, N.J., Woolley, P., Peters, B., Vejlsgaard, G., Saari, S., Gibb, A., Robinson, J. and the International Valaciclovir HSV Study Group, 1997. Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once-daily therapy. Genitourin. Med. 73, 105–9.

Perry, C.M., Faulds, D., 1996. Valaciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. Drugs 52, 625–795.

Perry, C.M., Wagstaff, A.J., 1995. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. Drugs 50, 396–415.

Pue, M.A., Benet, L.Z., 1993. Pharmacokinetics of famciclovir in man. Antiviral Chem. Chemother. 4 (S1), 47–55.

Rand, K.H., Hoon, E.F., Massey, J.K., Johnson, J.H., 1990. Daily stress and recurrence of genital herpes simplex. Arch. Int. Med. 150, 1889–1893.

Reichman, R.C., Badger, G.J., Mertz, G.J., Corey, L., Richman, D.D., Connor, J.D., Redfield, D., Savoia, M.C., Oxman, M.N., Bryson, Y., Tyrrell, D.L., Portnoy, J., Creigh-Kirk, T., Keeney, R.E., Ashikaga, T., Dolin, R., 1984. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. J. Am. Med. Assoc. 251, 2103–2107.

Reitano, M., Tyring, S., Lang, W., Thoming, C., Worm, A.M., Borelli, S., Chambers, L.O., Robinson, J.M., Corey, L. and the International Valaciclovir HSV Study Group, 1998. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. J. Infect. Dis. 178, 603–10.

Rodgers, C.A., O'Mahony, C., 1995. High prevalence of herpes simplex virus type 1 in female anogenital herpes simplex. Int. J. STD AIDS 6, 144–146.

Ross, J.D.C., Smith, I.W., Elton, R.A., 1993. The epidemiology of herpes simplex types 1 and 2 infection of the genital tract in Edinburgh 1978–1991. Genitourin. Med. 69, 381–383.

Sacks S.L., 1997. The Truth About Herpes, Gordon Soules Books, West Vancouver, British Columbia, Canada.

Sacks, S.L., Aoki, F.Y., Diaz-Mitoma, F., Sellors, J., Shafran, S.D. and a.t.C.F.S.G., 1996. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. J. Am. Med. Assoc. 276, 44–9.

Sacks, S.L., Hughes, A., Rennie, B., Boon, R., 1997. Famciclovir for suppression of asymptomatic and symptomatic recurrent genital herpes shedding: a randomized, double-blind, double dummy, parallel group, placebo-controlled trial. In: Programs and abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada.

Sacks, S.L., Shafran, S.D., 1998. BID amciclovir suppression of asymptomatic genital herpes simplex virus shedding in men. In: Programs and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California.

Slomka, M.J., Ashley, R.L., Cowan, F.M., Cross, A., Brown, D.W.G., 1995. Monoclonal antibody blocking tests for the detection of HSV-1 and HSV-2 specific humoral responses: comparison with Western blot assay. J. Virol. Methods 55, 27–35.

Spruance, S., Trying, S., Degregorio, B., Miller, C., Beutner, K. and the Valaciclovir HSV Study Group, 1996. A large-scale, placebo-controlled, dose-ranging trial of peroral valacyclovir for episodic treatment of recurrent herpes genitalis. Arch. Int. Med. 156, 1729–35.

Stanberry, L.R., 1996. Genital and Neonatal Herpes. Wiley, West Sussex, 244 pp.

Stanberry, L.R., 1998a. Understanding Herpes, University Press of Mississippi Jackson, Mississippi.

Stanberry, L.R., 1998b. Control of STDs—the role of prophylactic vaccines against herpes simplex virus. Sex. Transm. Infect. 74, 391–394.

Stronks, D.L., Rijpma, S.E., Passchier, J., Verhage, F., Van Der Meijden, W., Stolz, E., 1993. Psychological consequences of genital herpes, an exploratory study with a gonorrhea control-group. Psychol. Rep. 73, 395–400.

Tayal, S.C., Pattman, R.S., 1994. High prevalence of herpes simplex virus type 1 in female anogenital herpes simplex in Newcastle upon Tyne 1983–92. Int. J. STD AIDS 5, 359–361.

Thackray, A.M., Field, H.J., 1996. Differential effects of famciclovir and valacyclovir on the pathogenesis of herpes simplex virus in a murine infection model including reactivation from latency. J. Infect. Dis. 173, 291–299.

Thackray, A.M., Field, H.J., 1998. Famciclovir and valaciclovir differ in the prevention of herpes simplex virus type 1 latency in mice: a quantitative study. Antimicrob. Agents Chemother. 42, 1555–1562.

Tyring, S.K., Douglas, J.M., Spruance, S.L., Esmann, J. and the Valaciclovir International Study Group, 1998. A randomized, placebo-controlled comparison of oral valacyclovir and acyclovir in immunocompetent patients with recurrent genital herpes infections. Arch. Dermatol. 134, 185–91.

Vuchinich, R.E., Tucker, J.A., 1988. Contributions from behavioural theories of choice to an analysis of alcohol abuse. J. Abnorm. Psychol. 97, 181–195.

Wald, A., Benedetti, J., Davis, G., Remington, M., Winter, C., Corey, L., 1994. A randomized, double-blind, comparative trial comparing high and standard dose oral acyclovir for first-episode genital herpes infections. Antimicrob. Agents Chemother. 38, 174–176.

Wald, A., Corey, L., Cone, R., Hobson, A., Davis, G., Zeh, J., 1997. Frequent genital HSV-2 shedding in immunocompetent women. J. Clin. Invest. 99, 1092–1097.

Wald, A., Warren, T., Hu, H., Miller, G., Marr, L., Ryncarz, A., Selke, S., Zeh, J., Vargas, M., Corey, L., 1998. Suppression of subclinical shedding of herpes simplex virus type 2 in the genital tract with valacyclovir. In: Programs and abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California.

Wald, A., Zeh, J., Barnum, G., Davis, L.G., Corey, L., 1996. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann. Int. Med. 124, 8–15.

Wald, A., Zeh, J., Selke, S., Ashley, R.L., Corey, L., 1995. Virologic characteristics of subclinical and symptomatic genital herpes infections. N. Engl. J. Med. 333, 770–775.

Weinberg, A., Bate, B., Masters, H., Schneider, S., Clark, J., Wren, C., Allaman, J., Levin, M., 1992. In vitro activities of penciclovir and acyclovir against herpes simplex virus types 1 and 2. Antimicro. Agents Chemother. 36, 2037–2038.