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Recurrent Genital Herpes Treatments and Their Impact on Quality of Life

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Contents

Abstract

Herpes genitalis is one of the most common viral sexually transmitted diseases in the world, with an estimated seroprevalence in the US of greater than 20%. Two viruses of the same family cause herpes genitalis: herpes simplex virus 1 and 2. After the resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, often causing recurrent (though generally less severe) outbreaks. These outbreaks, as well as the infectious potential to the patient's sexual partners, results in significant psychological stress on the patient, and has a tremendous negative impact on QOL. Current treatment modalities may result in a reduction in the number of outbreaks and viral shedding, but no cure exists.

Although studies have clearly demonstrated the negative impact of recurrent genital herpes on QOL, an assessment scale specific to herpes was not developed until recently. Earlier studies indicated that patients did not perceive a significant benefit from episodic treatment with antivirals, but studies using the Recurrent Genital Herpes Quality of Life Questionnaire (RGHQoL) have now demonstrated that suppressive antiviral therapy improves quality of life in patients with frequent recurrences of genital herpes. However, not all patients with recurrent genital herpes need suppressive therapy, and proposed factors to consider include frequency of recurrence, physical and psychological distress caused by recurrences, and the potential for transmission to the patient's sexual partner.

Newer therapeutic modalities, including the topical immune response modifier resiquimod and herpes vaccines, may eventually be shown to further decrease the psychological morbidity of recurrent genital herpes.

Herpes genitalis, one of the most common viral sexually transmitted diseases in the world,[1] is caused by one of two viruses: herpes simplex 1 or 2 (HSV-1 or HSV-2). HSV-2 infection occurs more commonly than HSV-1 infection, with HSV-2 being responsible for up to two-thirds of cases of genital herpes.[2-5] Genital infection with HSV-2 has an estimated prevalence rate of 21.7% in the US[6] with over 600 000 new cases of HSV-2 diagnosed in the US each year.[7] Genital herpes occurs more frequently in women than men and more frequently in African Americans compared with Caucasians.[8] Additional factors associated with increased rates of HSV-2 infection include lifetime number of sexual partners and low socioeconomic status.[8] After primary infection, the virus persists in the body, often causing recurrences. Due to the persistence of the virus after primary infection, patients remain a source of potential infection to their sexual partners.

Treatment modalities currently available are directed at blocking viral replication. These antiviral therapies may limit the severity and duration of outbreaks (if used acutely), or prolong the interval between outbreaks and reduce asymptomatic viral shedding (if used as suppressive therapy) [see section 2]. Newer treatments aimed at enhancing immune response to herpes viruses are currently undergoing clinical trials. Preventive and therapeutic vaccines are also being studied.

The burden of genital herpes lies not only with physical symptoms but also with psychological complications of the disease. Patients often report decreased self-esteem, anger, guilt and difficulty with personal relationships as a consequence of herpes infection.[9] Psychological complications may in fact have a greater impact on patient well-being than the physical manifestations of infection. Therefore, the impact of treatment on a patient's QOL may be as important as its ability to decrease the signs and symptoms of the disease. Although the psychological impact of herpes has been well described in the literature, a QOL questionnaire specific for genital herpes infection was not developed until recently. Moreover, the psychological effect of available treatments has only recently been addressed. This paper reviews the impact of genital herpes on patients and the effect of currently available treatments on QOL.

1. Genital Herpes

HSV-1 and HSV-2 are enveloped linear double-stranded DNA viruses that belong to a family of eight viruses that also includes varicella zoster virus and Epstein-Barr virus. HSV-2 is the more common aetiological agent of genital herpes.[2-5] While this virus is the causative agent in up to two-thirds of patients with genital herpes,[2-5] it is also responsible for more than 90% of recurrent lesions, indicating increased recurrence rates for those with genital HSV-2 rather than HSV-1 infections.[3,10,11] Transmission of HSV occurs through close personal contact with infected bodily fluids, including saliva, semen, vaginal secretions, or vesicular fluid from active lesions. After contact with abraded mucosal surfaces, the virus replicates and initiates infection.

Symptoms of primary infection typically occur between 3 days to 2 weeks after exposure.[12,13] Constitutional symptoms including headaches, fever, myalgias, lymphadenopathy and fatigue may occur. Lesions are typically more severe during the primary outbreak.[14] They can form anywhere on the external genitalia (and vaginal canal or cervix in women), perianal area and also on the thighs and buttocks. The classic description of herpetic lesions includes grouped vesicles on an erythematous base that subsequently erode and form a crust. On mucosal surfaces, lesions may simply appear as ulcerations. However, as many as 90% of individuals seropositive for HSV-2 do not report a history of

genital herpes,[15,16] implying that the majority of infections are asymptomatic or unrecognised.

During primary infection, the virus enters nerve axons and is transported via retrograde axonal flow to the sacral sensory ganglia, where it establishes latency. Reactivation of HSV can occur with the proper stimulus. Factors associated with recurrent herpes outbreaks include exposure to ultraviolet light, local trauma, extremes of temperature, and menstruation in women.[17,18] Recurrence rates after primary infection vary widely among individuals. In general, patients with genital herpes caused by HSV-1 have fewer recurrences and milder symptoms than patients infected with HSV-2.[3,5,10,11,19] Patients with more severe primary infections are more likely to have recurrences and a shorter time to first recurrence than those with mild primary infections.[2] Nearly 90% of patients have at least one outbreak during the first year after primary infection and 20% of patients have more than ten outbreaks per year.[2] Men also tend to have more frequent recurrences than women.[2] Recurrent genital herpes is typically less severe and shorter in duration than the primary infection.

Individuals with genital herpes are capable of infecting their sexual partners during periods when virus is shed on the skin surface. The greatest amount of viral shedding occurs around the time of symptomatic outbreaks. However, viral shedding also occurs during asymptomatic periods. One recent study estimated that shedding occurs on around 3% of days when patients do not describe symptoms of herpes outbreaks as measured by viral culture.[16] Polymerase chain reaction (PCR) studies resulted in an even higher estimated rate of viral shedding (28% of asymptomatic days).[20] Since many people abstain from sexual contacts in the presence of symptomatic lesions, it has been estimated that more than 70% of HSV transmission to uninfected partners occurs during periods when patients are shedding asymptomatically.[21]

The diagnosis of genital herpes is most frequently made on the basis of its clinical presentation. It may also be made by means of viral culture (the current gold standard of laboratory diagnosis), although cultures are not able to differentiate between HSV-1 and HSV-2. PCR testing of swabs obtained from anogenital lesions may soon become commercially available, allowing for rapid identification of herpes infection as well as herpes typing. Finally, serum antibodies to herpes viruses may be suggestive of genital herpes, although other infections such as herpes labialis cannot be ruled out. This may lead to considerable confusion for patients and clinicians alike. A negative antibody test for HSV-2 does not exclude a diagnosis of genital herpes (around one third of primary genital herpes outbreaks are caused by HSV-1).[2-5] Similarly, HSV-2 antibodies do not confirm a diagnosis of genital herpes since this virus may also (rarely) be found in herpes labialis. The role of type-specific antibody testing in diagnosing genital herpes therefore remains undefined.

2. Treatment of Genital Herpes

Currently, the only commercially available treatments for recurrent genital herpes are the antiviral agents aciclovir, famciclovir and valaciclovir. These agents act to prevent viral replication, and thereby limit viral spread to other cells. They may be used for the primary outbreak, on an episodic basis for recurrences, or chronically as suppressive therapy.

2.1 Aciclovir

Aciclovir is a purine nucleoside analogue that acts to prevent viral DNA replication by means of inactivating viral DNA polymerase. Intravenous (IV), oral and topical forms are commercially available. However, IV aciclovir is not frequently used in immunocompetent patients because of the necessity of hospitalisation, and topical aciclovir has demonstrated only limited effect in the primary infection and no effect in recurrent outbreaks.[22-24]

Oral aciclovir is the oldest (and best studied) genital herpes treatment available. It has been found effective for primary herpes outbreaks as well as recurrences (see table I for dosage recommendations). Oral aciclovir has been shown to reduce the duration of both lesions and viral shedding in primary herpes outbreaks.[25,26] The duration and severity of recurrent episodes are also reduced after oral

Table I. Dosage recommendations for oral antiviral medications for the treatment of genital herpes

Medication	Primary episode	Recurrent episodes	Suppressive therapy
Aciclovir	200mg five times daily for 10 days[25,26]	200mg five times daily for 5 days[27,33]	400mg twice daily[31,32,34-36]
Valaciclovir	1000mg twice daily for 10 days[37]	500mg twice daily for 3 days[38]	500mg once daily (≤10 outbreaks a year)[39,40] 1000mg once daily (>10 outbreaks a year)[39]
Famciclovir	250mg three times daily for 10 days[41]	125mg twice daily for 5 days[42-44]	250mg twice daily[45,46]

aciclovir treatment.[27] Finally, aciclovir has also been approved for chronic suppressive treatment of frequent recurrences. Suppressive aciclovir has proven to be effective and have a good safety profile.[28] Five-year follow up of 389 patients with recurrent genital herpes treated with suppressive aciclovir therapy has been described. Mean annual recurrences in these patients decreased from 12.9 before the study to 1.7 after the first year of suppression to 0.8 after the fifth year.[29] Oral treatment was well tolerated and aciclovir resistance was not observed. Suppressive therapy with aciclovir also reduces the frequency of asymptomatic viral shedding.[30] However, suppressive therapy does not show any protective effects after cessation of aciclovir treatment.[28,31,32]

2.2 Valaciclovir

Valaciclovir is a prodrug of aciclovir. After absorption, valaciclovir is metabolised to aciclovir in the liver.[47,48] Following oral administration of valaciclovir, the serum levels achieved are comparable to IV aciclovir.[47] Valaciclovir has greater oral bioavailability than oral aciclovir, resulting in a less frequent dosage schedule (see table I).

Studies have shown that oral valaciclovir is as effective as aciclovir for the treatment of primary and recurrent genital herpes.[37,39] Moreover, suppressive therapy with valaciclovir has also proven to be effective and have a good safety profile. One study showed that 69% of patients with recurrent genital herpes were recurrence-free after 16 weeks of suppressive therapy with valaciclovir.[40] Another study demonstrated that 65% of women and 69% of men with recurrent genital herpes remained recurrence-free after 1 year of valaciclovir therapy.[49]

2.3 Famciclovir

Finally, famciclovir, a prodrug of penciclovir, demonstrates a similar mechanism of action to aciclovir, inhibiting viral replication by blocking viral DNA polymerase. Oral famciclovir exhibits similar efficacy to aciclovir and valaciclovir for the treatment of genital herpes and has a similar safety profile (see table I for dosage recommendations).[45,50] It may also be used for suppression of recurrent genital herpes. One study found that 79–86% of patients with recurrent genital herpes remained free of recurrences after 1 year of suppressive treatment with famciclovir.[45]

2.4 Investigational Treatments

Two promising new treatment modalities for recurrent genital herpes are currently being studied in clinical trials: an immune response modifier and therapeutic vaccines.

Resiquimod is a topical gel currently undergoing phase III clinical trials for recurrent genital herpes. As opposed to currently available antiviral therapies, resiquimod acts by locally increasing cytokine production, thereby enhancing an individual's immune response. Early trials suggest that episodic administration of resiquimod significantly increases the time to recurrence in patients. A recent phase II double-blind placebo-controlled trial involving 52 patients showed that the average time to recurrence was increased to a mean of 169 days with resiquimod compared with 57 days for placebo recipients.[51] Adverse effects were typically mild, and were limiting only at higher concentrations.[51]

At least one therapeutic vaccine has undergone clinical trials. Replication-incompetent viral mutant vaccines based on disabled infectious single cycle

HSV-1[52,53] or HSV-2[54] viruses have demonstrated immunogenicity and protection against HSV-2 disease and recurrence after application to mucosal surfaces in animal models. However, the results of phase II trials have not demonstrated therapeutic efficacy.[55] The development of a therapeutic vaccine remains a goal of herpes research and other vaccine candidates currently under study may prove effective for the treatment of recurrent genital herpes.[56]

3. Psychological Impact of Recurrent Genital Herpes

Although genital herpes does not typically result in severe physical disability in immunocompetent patients, it can have a devastating psychological impact. The relationship between recurrent genital herpes and psychological morbidity has been well documented in the literature. Patients frequently worry about the social implications of having a chronic sexually transmitted disease. Furthermore, the risk of transmitting herpes to partners or loved ones and the fear of revealing their condition to new partners often leads to depression and social isolation.[57-59] Patients also experience a loss of self-esteem and feel less sexually desirable.[57,60,61] Finally, one study suggests that many patients feel that the disease significantly hampers their performance at school or at work.[60]

Although these studies clearly demonstrate the negative impact of genital herpes on QOL, an assessment scale specific to herpes was not developed until recently (section 4).

4. Assessment of QOL in Recurrent Genital Herpes

Quantitative assessment of the impact of recurrent genital herpes on QOL has, until recently, been problematic. Early attempts at measuring the effects of recurrent genital herpes used many different assessment tools (table II). Anxiety, social support, coping styles, personality characteristics and emotional difficulties have all been associated with genital herpes recurrences.[62-66] Although widely reported in the literature, studies have not conclusively demonstrated an association between acute stressors and recurrent genital herpes.[66-68] However, chronic stress has been associated with frequency of genital herpes recurrence in some studies.[65,69]

The assessment tools used in the above studies all have the disadvantage of being generic instruments and frequently do not address QOL issues specific to recurrent genital herpes. In particular, generalised QOL scales do not assess the impact of transmission anxiety on QOL for those with recurrent genital herpes. As mentioned earlier, this is one of the greatest areas of concern for patients and can have a tremendous impact on a patient's sense of well-being.[57-59]

At least four herpes-specific assessment instruments have been developed,[60,61,71,74] but only one, the Recurrent Genital Herpes Quality of Life Ques-

Table II. Selected scales used to measure psychological impact and/or QOL in recurrent genital herpes

Generic QOL scales
General Health Questionnaire (GHQ)[62,63,70]
Life Events Questionnaire (LEQ)[62]
Eysenck Personality Questionnaire (EPQ)[62,63,65]
Rotter Internal/External Locus of Control Scale (LOC)[64]
Life Experiences Survey[64,65,69]
Ways of Coping Checklist[64]
Social Support Index[64]
Symptom Checklist 90 (SCL-90)[64]
Schedule of Recent Events[66]
State-Trait Anxiety Inventory (STAI)[66]
Hospital Anxiety and Depression Scale (HAD)[65,70]
Illness Attitude Scale (IAS)[70]
Illness Concern Questionnaire[70]
Health-Related Quality of Life Scale (HRQOL)[71]
Wallston and Wallston Multidimensional Health Beliefs Questionnaire[65]
Medical Outcomes Study Short Form 36-item health survey (SF-36)[65,72,73]
Weekly Stress Log[69]
Mood Questionnaire[69]
Taylor Manifest Anxiety Scale[69]
Life Orientation Test of Scheier and Carver[69]
Herpes-specific QOL scales
Quality of Life with Herpes (QLH) Scale[71]
Genital Herpes Questionnaire[60]
Herpes Research Center Questionnaire[61]
Recurrent Genital Herpes Quality of Life Questionnaire[72-76]

tionnaire (RGHQoL) has become widely used and reported in the literature. The RGHQoL was developed in 1997 after extensive interviews with patients with recurrent genital herpes.[74] In these interviews, patients described feelings of loss of intimacy, fear of discovery and starting new relationships. A series of 20 items specific to QOL for patients with herpes were then developed relating to concerns expressed in these interviews. In particular, the fear of transmitting the virus to sexual partners and consequent loss of intimacy are specifically addressed with questions such as 'I feel insecure about personal (intimate) relationships because of herpes', 'Because of herpes, I become tense when someone touches me', and 'I worry about giving my herpes to someone'. Items are all scored from 0–3, and the RGHQoL is therefore scored from 0–60 with a higher score indicating a better QOL.

The RGHQoL measure has been validated in numerous languages, including English, Danish, Italian, German, French, and Dutch.[72,74] Initial validation studies are described in Doward et al.[74] They found a significant relationship between perceived severity of herpes outbreaks and RGHQoL scores. Furthermore, test-retest comparisons showed a very high level of correlation, demonstrating that scores remain constant through time. The RGHQoL may therefore be used to measure the effects of therapy on QOL over time. The popularity of this measure also derives from the fact that the test is easily self-administered in a matter of a few minutes. At least five recently published studies have used the RGHQoL as the primary tool for assessing QOL in patients with recurrent genital herpes.[72-76]

Spencer et al. described a French population sample assessed for follow-up after validation of the RGHQoL.[75] A group of 150 individuals with recurrent genital herpes were assessed. Results indicated that QOL scores are lowest in younger patients. Internal consistency was judged to be good and test-retest correlations also supported the validity of the measure (0.85 Spearman rank correlation coefficient). Finally, the RGHQoL was found to correlate very well with subjective perception of the burden of recurrent genital herpes.

Two studies used the RGHQoL in combination with the Medical Outcomes Study Short Form 36-item health survey (SF-36), a generic QOL measure, to assess differences in QOL between patients with genital herpes and the general population. Taboulet et al. compared 150 patients with genital herpes with 200 individuals who were herpes-free in France.[73] They found that patients with genital herpes had a significantly higher degree of emotional distress (nervousness, dejection and depression), increased sense of isolation, difficulty with concentration and attentiveness, and a trend towards increased problems with interpersonal relationships. Furthermore, those with genital herpes indicated concern with spreading the disease, difficulty with sexual relationships and fear of rejection. A high number of patients with genital herpes (50%) felt that it is difficult to live with the disease. Finally, those with genital herpes made significantly greater use of healthcare resources. Another study by Patel et al. assessed QOL using the same measures.[72] This study found significantly decreased scores on the SF-36 for patients with recurrent genital herpes compared with population norms in the areas of physical functioning, bodily pain, general health, vitality, social functioning, emotional state and mental health. Furthermore, the study evaluated RGHQoL scores with respect to frequency of herpes recurrence and severity of pain during recurrences. They found significantly lower RGHQoL scores for those with more frequent outbreaks and those who rated their outbreaks as more painful/uncomfortable.

5. Effect of Suppressive Treatments on QOL

Current therapeutic modalities for genital herpes are very limited. As noted in section 2, only episodic or suppressive treatment with the antivirals aciclovir, valaciclovir, or famciclovir are available. Additionally, some psychological treatments have also been assessed, with very limited data suggesting benefit (measured by reduced number of herpes outbreaks) for psychoanalysis, cognitive restructuring, hypnotherapy, psychotherapy, biofeedback, cognitive restructuring and psychosocial interven-

tions such as stress management[77] (see also Longo and Koehn[78] for a more detailed review of psychological therapy for genital HSV infections). Very little has been published regarding improved QOL with these treatments.

The efficacy of suppressive antiviral treatment has been well established in patients with recurrent genital herpes, but only a few publications address the significance of such therapy on QOL issues. Although early episodic antiviral treatment of primary and recurrent genital herpes has proven effective in reducing new lesion formation, the time to lesion healing, and duration of viral shedding, patients often do not perceive any benefits from therapy.[31,79] The appropriate patient population for suppressive therapy remains a source of discussion, and several factors need to be considered before starting patients on daily suppressive doses of antiviral medications, as discussed later in this section.

The first article specifically addressing the effect of suppressive therapy on QOL in patients with genital herpes was published in 1993.[70] In an open-label study in 102 patients with at least eight recurrences of genital herpes per year, the researchers assessed change in QOL after starting the study participants on suppressive doses of aciclovir. As assessment tools, the General Health Questionnaire (GHQ), the Hospital Anxiety and Depression scale (HAD), Illness Attitude Scales (IAS), and an Illness Concern Questionnaire were used. Patients were followed for 1 year, with a 3-month follow-up period after therapy. The study found a significant decrease in GHQ scores from baseline during the course of suppressive therapy (indicating an improved perception of general health in these patients). HAD scores also showed a corresponding decrease, as did Illness Concern scores. No significant improvement was found in patients' IAS scores. Suppressive therapy was very well tolerated. The study concluded that suppressive therapy with aciclovir has a significant beneficial impact on QOL in those with frequent recurrences of genital herpes.[70]

The most recent QOL study used the RGHQoL scale to assess the impact of suppressive valaciclovir versus aciclovir therapy in patients with six or more recurrences of genital herpes per year.[76] This study was double-blind and placebo-controlled, and found that there was a sustained beneficial impact on QOL as measured by the RGHQoL for all treatment groups as compared with placebo over a 52-week timeframe. Additionally, the evidence suggested that those with more than ten herpes recurrences per year at baseline had marginally greater benefit from the use of suppressive therapy. No significant differences in improvements in QOL were noted between treatment groups, and the antiviral treatment was as well tolerated as placebo.[76]

The RGHQoL was also used in a limited study to judge the effects of suppressive therapy on patients' QOL during the initial assessment of the RGHQoL questionnaire in Denmark.[74] They found that there was a significant improvement in QOL for those patients with recurrent genital herpes who decided to undergo suppressive therapy.[74]

Given the perceived improvements in QOL in patients with recurrent genital herpes who receive antiviral suppressive therapy, the question of who should receive this treatment modality becomes paramount. Not all patients with recurrent genital herpes need suppressive therapy. For example, although those who were placed on suppressive therapy in the Denmark study had a significant improvement in their QOL, those who chose to continue with episodic therapy had better baseline RGHQoL scores (mean baseline scores 42.9 for those continuing episodic therapy versus 34.6 for those choosing suppressive therapy), and suppressive therapy only served to narrow the margin (mean end score 43.1 for those with episodic therapy versus 40.1 for those undergoing suppressive therapy).[74] Clearly, those with very frequent recurrences of genital herpes deserve serious consideration for suppressive therapy. However, the severity of prodromes and outbreaks, the psychological impact of the disease and the serological status of a patient's sexual partner should also be considered in determining whether or not to begin suppressive therapy with antivirals.

6. Future Directions

Although current treatment strategies for recurrent genital herpes have proven both well tolerated and effective, they are not ideal treatments. Episodic antiviral therapy does reduce the duration of lesions, but patients perceive no benefit. Suppression limits the number of herpes recurrences and has a demonstrable benefit on QOL in patients (see section 5). However, the need for daily (or twice daily) therapy may reduce patient adherence, and the cost of treatment may be prohibitive.[80] Two new therapeutic options are currently being studied that may represent improved clinical options for the treatment of genital herpes – therapeutic vaccines and resiquimod.

A therapeutic vaccine against genital herpes may have the greatest potential for improving QOL in patients with recurrent genital herpes. Although no vaccine has demonstrated efficacy in treating recurrent genital herpes to date, several vaccine candidates are being studied both as preventive and therapeutic modalities.

Episodic treatment with the topical immune response modifier, resiquimod, has been shown to significantly increase the time to next recurrence in one published study.[51] Furthermore, longitudinal QOL assessments using the RGHQoL are being studied in ongoing phase III trials of resiquimod. Resiquimod has the advantage of being topically applied and used only episodically for recurrent lesions. Resiquimod was applied at bedtime three times weekly for 3 weeks in the study protocols. This may make it much more attractive as a therapeutic option than currently available agents.

7. Conclusion

Although the physical symptoms of recurrent genital herpes are typically mild to moderate, recent studies have convincingly demonstrated significant psychosocial morbidity as a result of this disease. QOL issues in relation to recurrent genital herpes have still not adequately been addressed, and a clinically acceptable, reproducible, herpes-specific QOL scale has only recently been developed. This scale has been used to demonstrate significant improvements in QOL for patients after starting suppressive therapy with antivirals to treat frequent outbreaks of genital herpes. Older studies showed a lack of perceived benefit for patients undergoing episodic antiviral therapy.

Despite the potential for improved QOL, the indications for initiating suppressive therapy with antivirals in patients with recurrent genital herpes have not yet been adequately developed. The decision to start suppressive therapy relies on the frequency of recurrent lesions, but should also depend on the views of the patient regarding physical discomfort of prodromes and outbreaks, psychological sequelae of their disease and the potential of transmission of the virus from the patient to their sexual partners.

The greatest potential reduction of herpes-related morbidity involves the prevention of transmission of HSV-2. Our experience at the University of Texas Medical Branch (UTMB) Center for Clinical Studies suggests that a majority of patients with genital herpes are unaware of the potential for transmitting the disease during periods of asymptomatic viral shedding (the greatest source of spread of the disease[21]) prior to education at our clinic. Patient education remains a mainstay of prevention. All patients need to be educated about standard prevention of sexually transmitted diseases and recommended guidelines regarding safe sexual practices. The potential for transmission of HSV during periods of asymptomatic viral shedding should also be discussed, especially with patients with recurrent genital herpes.

Newer therapies are under development that may further decrease the psychological morbidity associated with recurrent genital herpes. Episodic topical treatment with the immune response modifier resiquimod appears promising. Preventive vaccines (including DNA vaccines and adjuvant subunit vaccines) are currently undergoing clinical trials. A phase I trial for a preventive DNA vaccine is underway.[56] Also, recent phase III trials of a recombinant subunit HSV vaccine demonstrated protection in women who were HSV-1 and HSV-2 seronegative,

but not in women with HSV-1 antibodies or in men.[81]

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References

1. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological and -sociological patterns of herpes simplex virus infection in the world. Scand J Infect Dis Suppl 1990; 69: 19-36
2. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. Ann Intern Med 1994; 121 (11): 847-54
3. Lafferty WE, Downey L, Celum C, et al. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. J Infect Dis 2000; 181 (4): 1454-7
4. Langenberg AG, Corey L, Ashley RL, et al. A prospective study of new infections with herpes simplex virus type 1 and type 2. Chiron HSV Vaccine Study Group. N Engl J Med 1999; 341 (19): 1432-8
5. Tyring SK, Carlton SS, Evans T. Herpes: atypical clinical manifestations. Dermatol Clin 1998; 16 (4): 783-8, xiii
6. Johnson RE, Nahmias AJ, Magder LS, et al. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. N Engl J Med 1989; 321 (1): 7-12
7. Nadelman CM, Newcomer VD. Herpes simplex virus infections: new treatment approaches make early diagnosis even more important. Postgrad Med 2000; 107 (3): 189-95, 199-200
8. 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 (16): 1105-11
9. Swanson JM, Chenitz WC. Psychosocial aspects of genital herpes: a review of the literature. Public Health Nurs 1990; 7 (2): 96-104
10. 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 (23): 1444-9
11. 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 (6): 315-9
12. Severson JL, Tyring SK. Viral disease update. Curr Probl Dermatol 1999; 11 (2): 37-72
13. Whitley RJ, Roizman B. Herpes simplex viruses. Edinburgh: Churchill Livingstone, 1997
14. Adams HG, Benson EA, Alexander ER, et al. Genital herpetic infection in men and women: clinical course and effect of topical application of adenine arabinoside. J Infect Dis 1976; 133 Suppl.: A151-9
15. Furman PA, St Clair MH, Spector T. Acyclovir triphosphate is a suicide inactivator of the herpes simplex virus DNA polymerase. J Biol Chem 1984; 259 (15): 9575-9
16. Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. N Engl J Med 2000; 342 (12): 844-50
17. Buchman TG, Roizman B, Nahmias AJ. Demonstration of exogenous genital reinfection with herpes simplex virus type 2 by restriction endonuclease fingerprinting of viral DNA. J Infect Dis 1979; 140 (3): 295-304
18. Snoeck R, Andrei G, Gerard M, et al. Successful treatment of progressive mucocutaneous infection due to acyclovir- and foscarnet-resistant herpes simplex virus with (S)-1- (3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC). Clin Infect Dis 1994; 18 (4): 570-8
19. Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. N Engl J Med 1995; 333 (12): 770-5
20. Wald A, Corey L, Cone R, et al. Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. J Clin Invest 1997; 99 (5): 1092-7
21. Mertz GJ, Benedetti J, Ashley R, et al. Risk factors for the sexual transmission of genital herpes. Ann Intern Med 1992; 116 (3): 197-202
22. Chen XS, Han GZ, Guo ZP, et al. A comparison of topical application of penciclovir 1% cream with acyclovir 3% cream for treatment of genital herpes: a randomized, double-blind, multicentre trial. Int J STD AIDS 2000; 11 (9): 568-73
23. Barton IG, Kinghorn GR, Rowland M, et al. Recurrences after first episodes of genital herpes in patients treated with topical acyclovir cream. Antiviral Res 1984; 4 (5): 293-300
24. Luby JP, Gnann Jr JW, Alexander WJ, et al. A collaborative study of patient-initiated treatment of recurrent genital herpes with topical acyclovir or placebo. J Infect Dis 1984; 150 (1): 1-6
25. Bryson YJ, Dillon M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. N Engl J Med 1983; 308 (16): 916-21
26. Mertz GJ, Critchlow CW, Benedetti J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. JAMA 1984; 252 (9): 1147-51
27. Ruhnek-Forsbeck M, Sandstrom E, Andersson B, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. J Antimicrob Chemother 1985; 16 (5): 621-8
28. Kinghorn GR, Jeavons M, Rowland M, et al. Acyclovir prophylaxis of recurrent genital herpes: randomised placebo controlled crossover study. Genitourin Med 1985; 61 (6): 387-90
29. Baker DA. Long-term suppressive therapy with acyclovir for recurrent genital herpes. J Int Med Res 1994; 22 Suppl. 1: 24A-31A
30. Wald A, Zeh J, Barnum G, et al. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. Ann Intern Med 1996; 124 (1 Pt 1): 8-15
31. Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. N Engl J Med 1984; 310 (24): 1551-6
32. Straus SE, Takiff HE, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled double-blind trial of oral acyclovir. N Engl J Med 1984; 310 (24): 1545-50
33. Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. JAMA 1984; 251 (16): 2103-7
34. Mertz GJ, Eron L, Kaufman R, et al. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. Am J Med 1988; 85 (2A): 14-9
35. Mertz GJ, Jones CC, Mills J, et al. Long-term acyclovir suppression of frequently recurring genital herpes simplex

virus infection. A multicenter double-blind trial. JAMA 1988; 260 (2): 201-6
36. Mindel A, Faherty A, Carney O, et al. Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes. Lancet 1988; I (8591): 926-8
37. Fife KH, Barbarash RA, Rudolph T, et al. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection: results of an international, multicenter, double-blind, randomized clinical trial. The Valaciclovir International Herpes Simplex Virus Study Group. Sex Transm Dis 1997; 24 (8): 481-6
38. Leone PA, Trottier S, Miller JM. A comparison of oral valacyclovir 500mg twice daily for three or five days in the treatment of recurrent genital herpes [abstract 22.012]. International Congress of Infectious Diseases; 1998 May 15-18; Boston (MA)
39. Reitano M, Tyring S, Lang W, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. International Valaciclovir HSV Study Group. J Infect Dis 1998; 178 (3): 603-10
40. Patel R, Bodsworth NJ, Woolley P, et al. Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy. International Valaciclovir HSV Study Group. Genitourin Med 1997; 73 (2): 105-9
41. Loveless M, Sacks SL, Harris JR. Famciclovir in the management of first-episode genital herpes. Infect Dis Clin Prac 1997; 6 (1 Suppl.): S12-6
42. Sacks SL, Aoki FY, Diaz-Mitoma F, et al. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes: a randomized, double-blind multicenter trial. Canadian Famciclovir Study Group. JAMA 1996; 276 (1): 44-9
43. Chosidow O, Drouault Y, Leconte-Veyriac F, et al. Famciclovir vs aciclovir in immunocompetent patients with recurrent genital herpes infections: a parallel-groups, randomized, double-blind clinical trial. Br J Dermatol 2001; 144 (4): 818-24
44. Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. Clin Infect Dis 1998; 26 (3): 541-53
45. Diaz-Mitoma F, Sibbald RG, Shafran SD, et al. Oral famciclovir for the suppression of recurrent genital herpes: a randomized controlled trial. Collaborative Famciclovir Genital Herpes Research Group. JAMA 1998; 280 (10): 887-92
46. Mertz GJ, Loveless MO, Levin MJ, et al. Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women: a multicenter, double-blind, placebo-controlled trial. Collaborative Famciclovir Genital Herpes Research Group. Arch Intern Med 1997; 157 (3): 343-9
47. Soul-Lawton J, Seaber E, On N, et al. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. Antimicrob Agents Chemother 1995; 39 (12): 2759-64
48. Spruance SL. Prophylactic chemotherapy with acyclovir for recurrent herpes simplex labialis. J Med Virol 1993; Suppl. 1: 27-32
49. Baker DA, Blythe JG, Miller JM. Once-daily valacyclovir hydrochloride for suppression of recurrent genital herpes. Obstet Gynecol 1999; 94 (1): 103-6
50. Tyring S, Diaz-Mitoma F, Locke L, et al. Famciclovir for long-term suppression of recurrent genital herpes: a meta-analysis [abstract 22.023]. 8th Annual International Congress of Infectious Diseases; 1998 May 15-18; Boston (MA)
51. Spruance SL, Tyring SK, Smith MH, et al. Application of a topical immune response modifier, resiquimod gel, to modify the recurrence rate of recurrent genital herpes: a pilot study. J Infect Dis 2001; 184 (2): 196-200
52. McLean CS, Ni Challanain D, Duncan I, et al. Induction of a protective immune response by mucosal vaccination with a DISC HSV-1 vaccine. Vaccine 1996; 14 (10): 987-92
53. McLean CS, Erturk M, Jennings R, et al. Protective vaccination against primary and recurrent disease caused by herpes simplex virus (HSV) type 2 using a genetically disabled HSV-1. J Infect Dis 1994; 170 (5): 1100-9
54. Boursnell ME, Entwisle C, Blakeley D, et al. A genetically inactivated herpes simplex virus type 2 (HSV-2) vaccine provides effective protection against primary and recurrent HSV-2 disease. J Infect Dis 1997; 175 (1): 16-25
55. Tyring SK. Viral infections (SYM 342). American Academy of Dermatology 60th Annual Meeting; 2002 Feb 22-27; New Orleans (LA)
56. Stanberry LR, Cunningham AL, Mindel A, et al. Prospects for control of herpes simplex virus disease through immunization. Clin Infect Dis 2000; 30 (3): 549-66
57. Bierman SM. A retrospective study of 375 patients with genital herpes simplex infections seen between 1973 and 1980. Cutis 1983; 31 (5): 548-52, 557, 560-5
58. Lukacs J, Corey L. Genital herpes simplex virus infection: an overview. Nurse Pract 1977; 2 (5): 7-10
59. Nahmias AJ, Norrild B. Herpes simplex viruses 1 and 2: basic and clinical aspects. Dis Mon 1979; 25 (10): 1-49
60. Drob S, Loemer M, Lifshutz H. Genital herpes: the psychological consequences. Br J Med Psychol 1985; 58 (Pt 4): 307-15
61. Luby ED, Klinge V. Genital herpes: a pervasive psychosocial disorder. Arch Dermatol 1985; 121 (4): 494-7
62. Goldmeier D, Johnson A, Jeffries D, et al. Psychological aspects of recurrences of genital herpes. J Psychosom Res 1986; 30 (5): 601-8
63. Goldmeier D, Johnson A, Byrne M, et al. Psychosocial implications of recurrent genital herpes simplex virus infection. Genitourin Med 1988; 64 (5): 327-30
64. Silver PS, Auerbach SM, Vishniavsky N, et al. Psychological factors in recurrent genital herpes infection: stress, coping style, social support, emotional dysfunction, and symptom recurrence. J Psychosom Res 1986; 30 (2): 163-71
65. Cassidy L, Meadows J, Catalan J, et al. Are reported stress and coping style associated with frequent recurrence of genital herpes? Genitourin Med 1997; 73 (4): 263-6
66. VanderPlate C, Aral SO, Magder L. The relationship among genital herpes simplex virus, stress, and social support. Health Psychol 1988; 7 (2): 159-68
67. Rand KH, Hoon EF, Massey JK, et al. Daily stress and recurrence of genital herpes simplex. Arch Intern Med 1990; 150 (9): 1889-93
68. Longo DJ, Clum GA. Psychosocial factors affecting genital herpes recurrences: linear vs mediating models. J Psychosom Res 1989; 33 (2): 161-6
69. Cohen F, Kemeny ME, Kearney KA, et al. Persistent stress as a predictor of genital herpes recurrence. Arch Intern Med 1999; 159 (20): 2430-6
70. Carney O, Ross E, Ikkos G, et al. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. Genitourin Med 1993; 69 (6): 457-9
71. Wild D, Patrick D, Johnson E, et al. Measuring health-related quality of life in persons with genital herpes. Qual Life Res 1995; 4 (6): 532-9

72. Patel R, Boselli F, Cairo I, et al. Patients' perspectives on the burden of recurrent genital herpes. Int J STD AIDS 2001; 12 (10): 640-5
73. Taboulet F, Halioua B, Malkin JE. Quality of life and use of health care among people with genital herpes in France. Acta Derm Venereol 1999; 79 (5): 380-4
74. Doward LC, McKenna SP, Kohlmann T, et al. The international development of the RGHQoL: a quality of life measure for recurrent genital herpes. Qual Life Res 1998; 7 (2): 143-53
75. Spencer B, Leplege A, Ecosse E. Recurrent genital herpes and quality of life in France. Qual Life Res 1999; 8 (4): 365-71
76. Patel R, Tyring S, Strand A, et al. Impact of suppressive antiviral therapy on the health related quality of life of patients with recurrent genital herpes infection. Sex Transm Infect 1999; 75 (6): 398-402
77. Cruess S, Antoni M, Cruess D, et al. Reductions in herpes simplex virus type 2 antibody titers after cognitive behavioral stress management and relationships with neuroendocrine function, relaxation skills, and social support in HIV-positive men. Psychosom Med 2000; 62 (6): 828-37
78. Longo D, Koehn K. Psychosocial factors and recurrent genital herpes: a review of prediction and psychiatric treatment studies. Int J Psychiatry Med 1993; 23 (2): 99-117
79. Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. Lancet 1982; II (8298): 571-3
80. Wald A. Beyond efficacy: new issues for HSV antiviral therapy. Genitourin Med 1997; 73 (2): 83-4
81. Tyring SK. Virology for the dermatologist. American Academy of Dermatology, 59th Annual Meeting; 2001 Mar 30; Washington, DC

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