

# Management and prevention of recurrent genital herpes infection

**NATHAN RYDER** MB BS, MPH, FACHSHM

**BASIL DONOVAN** MD, FACHSHM, FAFPHM, FRCPI

Genital herpes is one of the most common sexually transmitted infections in Australia and a diagnosis of the condition can cause significant emotional distress. Affected patients require both pharmacological and psychological treatment.

About 12% of adults in Australia are infected with herpes simplex virus type 2 (HSV-2), making it one of the most common sexually transmissible infections in Australia.<sup>1</sup> However, 75% of adults in Australia harbour type 1 (HSV-1) infection;<sup>1</sup> an unknown proportion of these adults with HSV-1 infection have acquired it sexually and all could potentially sexually transmit the infection to others, particularly through oral sex. It is therefore likely that more than 85% of marriages in Australia include at least one person who harbours the potentially sexually transmissible herpes virus, resulting in genital herpes being common even in 'low-risk' populations.

First-episode genital herpes is increasingly likely to be due to infection with

HSV-1, particularly in young women and men who have sex with men.<sup>2</sup> However, genital HSV-1 infection causes fewer clinical recurrences than HSV-2 infection. The management and prevention of genital herpes relies on both patient education, with expert counselling if required, and selective use of antiviral medications according to individual patient needs.

## Diagnosis

With the widespread availability of polymerase chain reaction (PCR) testing of



Figure. Primary penile herpes simplex virus and syphilis, which was acquired simultaneously.

lesion swabs, the diagnosis of genital herpes is now much easier and more reliable than in the past.

Although screening for HSV-1 or 2 infection is not recommended, type-specific herpes serology can be useful in certain situations, such as in patients who repeatedly present too late for reliable PCR results, for the exclusion of herpes infections in patients with repeatedly negative PCR results and, after careful discussion, for partners of those with genital herpes.

## Case study 1 - Dealing with patient misconceptions

Jane, a 30-year-old woman, presented upset and confused because her husband of five years had recently been diagnosed with genital herpes simplex virus type 2 (HSV-2) infection. Jane had never had any symptoms of genital herpes and was angry and concerned about where her husband had contracted the condition. Her doctor explained that herpes was common and was often contracted years before the first symptomatic episode. He explained that it was possible that her husband had contracted genital herpes from a previous partner or even from Jane herself if she had had partners before him, because asymptomatic transmission was very common. Type-specific herpes serology would determine if Jane had asymptomatic infection. After further discussion Jane decided that there would be limited benefit to her in discovering her herpes status because she was asymptomatic, so she decided not to have the test performed.

Jane then asked her doctor what the chance of her catching herpes from her husband was, assuming she did not already have the virus. She was advised that avoiding sex during symptomatic recurrences was likely to reduce the risk of transmission, as would consistently using condoms, but that transmission was always possible and the average risk of transmission from men to women was about one in 1000 sexual acts.

Dr Ryder is a Postgraduate Fellow, Sydney Sexual Health Centre, Sydney Hospital and Conjoint Lecturer with the School of Public Health and Community Medicine, University of New South Wales. Professor Donovan is Conjoint Professor, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, and Senior Staff Specialist, Sydney Sexual Health Centre, Sydney Hospital, Sydney, NSW. Series Editor: Professor Basil Donovan.

**Table 1. Pharmacological management of recurrent genital herpes**

First-episode treatment	
Aciclovir	200 mg five times a day for 10 days OR 400 mg three times a day for five to 10 days <sup>3*</sup>
Valaciclovir	500 mg twice a day for five to 10 days
Episodic treatment	
Aciclovir	200 mg five times a day for five days 800 mg three times a day for two days <sup>4*</sup>
Famciclovir	125 mg twice a day for five days OR 500 mg stat then 250 mg twice a day for three doses OR 1 g twice a day for one day <sup>5*</sup>
Valaciclovir	500 mg twice a day for five days 500 mg twice a day for three days <sup>6*</sup>
Suppressive treatment	
Aciclovir	200 mg three times a day 400 mg twice a day <sup>7*</sup>
Famciclovir	250 mg twice a day
Valaciclovir	500 mg once a day (1000 mg once a day if 10 or more recurrences per year)

\* Off-label use. TRADE NAMES: aciclovir – Acihexal, Acyclo-V, Lovir, Ozvir, Zovirax Tablets, Zyclir Tablets; famciclovir – Famvir; valaciclovir – Valtrex.

## Management Education and counselling

The diagnosis of genital herpes is often associated with significant anxiety and relationship difficulties, so the optimal management of genital herpes requires both psychological and pharmacological input. Many patients will have inaccurate information about genital herpes, particularly about disease transmission, and education can have a large therapeutic effect by reducing anxiety. As with most sexually transmitted infections, the diagnosis of herpes is often associated with guilt and blame. Efforts should be made to explore these feelings and correct any misconceptions. Case study 1 on page 71 provides an example of how to deal with this situation.

Simple counselling strategies are

generally sufficient; however, formal counselling may at times be required, particularly in the context of serious relationship issues and underlying anxiety disorders. Specialist sexual health services throughout Australia accept direct referrals from GPs for counselling. Providing access to accurate sources of information can be helpful and convenient for both patient and doctor. There are numerous sources of reliable information. The Australian Herpes Management Forum has comprehensive information for both health professionals and patients ([www.ahmf.com.au](http://www.ahmf.com.au)). Two other useful online sources of information for patients are the Facts website sponsored by Glaxo-SmithKline ([www.thefacts.com.au](http://www.thefacts.com.au)) and the herpes website sponsored by Novartis ([www.herpes.com.au](http://www.herpes.com.au)).

## Drug treatment

Over the past 20 years the oral nucleoside analogues (aciclovir, famciclovir [Famvir] and valaciclovir [Valtrex]) have proven to be effective, well tolerated and safe in the management of genital herpes. Resistance to antiviral drugs is almost entirely limited to severely immune compromised patients, and is rare even in that setting. For recurrent genital herpes the nucleoside analogues can be used interchangeably with equal efficacy; however, the cost of treatment varies from \$5 to \$13 per day, so it is useful to consult the PBS to minimise the cost.

Two strategies are used in the management of recurrent genital herpes – episodic and suppressive treatment – and the choice for any individual patient usually varies over time. Most patients opt for no ongoing treatment or occasional episodic management of recurrent lesions. Suppressive treatment is usually reserved for patients with frequent or severe recurrences, or as a temporary adjunct to counselling.

## First-episode treatment

All patients with a first episode of anogenital ulceration consistent with genital herpes should be treated urgently with a five to 10-day course of oral nucleoside analogue therapy, without waiting for the PCR results (Table 1).<sup>3-7</sup> Although treatment of a first episode of genital herpes has no effect on the development of latency and subsequent recurrences, it is important to prevent the common complications of primary herpes, such as aseptic meningitis, urinary retention and labial adhesions.

For both first and recurrent episodes of genital herpes, there is also a role for general measures such as the use of analgesics, rest and bathing lesions in saline solution, with oral analgesia often required for true primary genital herpes episodes.

## Episodic treatment

Episodic treatment refers to the use of short courses of treatment taken at the first

## Table 2. Relative indications for suppressive treatment

- Frequent symptoms, as defined by the patient
- Severe 'collateral' symptoms, e.g. malaise, lethargy, headache, regional neuropathy, lesion pain
- Late stage of pregnancy with patient anxiety
- Start of a new relationship, to help prevent transmission of herpes simplex virus (HSV) infection – preferably combined with condom use
- Presence of HSV-2 infection, rather than HSV-1 infection, making recurrences more likely
- Severe sequelae, e.g. erythema multiforme, recurrent meningitis, eczema herpeticum
- Recently infected, making recurrences more likely
- Socially valuable suppression, e.g. going on honeymoon
- Not reconciled to the condition, e.g. recent diagnosis, in need of counselling
- Concurrent conditions confusing the symptomatology, e.g. recurrent candidiasis, lichen sclerosis
- Little or no prodrome, undermining episodic therapy
- Concurrent HIV infection

suggestion of a recurrence to either stop the formation of visible lesions or shorten the duration of symptoms. In recent years there has been a shift towards very short courses of treatment (one to three days) for episodic therapy. Short-course treatment is approved by the TGA for famciclovir, but this is an off-label use for aciclovir and valaciclovir. Viral replication and cellular destruction occur immediately before and during the initial 24 hours of a recurrent episode, so there is little rationale for longer courses of antiviral drugs.

A variety of short-course regimens have

## Case study 2 – Suppressive treatment for recurrent genital herpes

Thomas presented complaining of monthly recurrences of genital herpes since he was first diagnosed six months ago. He asked whether there was any medication that may help him deal with his symptoms, particularly because he had a new sexual partner and his avoidance of sex during his frequent recurrences was causing relationship difficulties.

Thomas was an ideal candidate for suppressive therapy, so his doctor started him on daily antiviral therapy and also counselled him about the risk of transmission to his partner and the partial protection offered by condoms. Initially Thomas was reluctant to inform his partner of his diagnosis due to anxiety about her response, but after a detailed discussion of the pros and cons of disclosure he decided that, given that she may contract herpes at any time, an honest disclosure was probably the best course of action to avoid future mistrust in the relationship.

Two years later he returned for another prescription for suppressive therapy. After his disclosure his partner was very supportive, they had used condoms most of the time since then and she had not developed symptoms as yet. His doctor explained that he may not require suppressive treatment any longer and suggested a treatment break to see what would happen. Thomas stopped his medication, and although he had a recurrence one week later he had no other recurrences for the next nine months. Thomas decided to continue with short-course episodic treatment as needed and to keep a supply of medication on hand to use as soon as he noticed the prodromal tingling sensation that he had learnt to recognise.

been shown to be at least as effective as the standard five-day course, with the benefit of increased convenience for the patient. It is important that the patient begins treatment as soon as possible, ideally at the first hint of the prodrome: this is characterised by local or regional tingling or itching, or generalised symptoms such as headache or rapid-onset lethargy. To avoid delay in initiating therapy, the patient should be advised to have the first dose of medication readily available.

In contrast to with oral herpes, topical therapies have not been shown to be effective for genital herpes.<sup>3</sup> As the treatment of recurrences has no effect on the future course of the disease, patients should be advised to only treat recurrences if they perceive a net benefit when balancing the reduction in symptoms against the inconvenience and cost of treatment.

### Suppressive treatment

Continuous daily medication suppresses viral replication and prevents the vast majority of both symptomatic and asymptomatic recurrences (See Table 1 for dosing

regimens).<sup>8</sup> In fact, ongoing symptoms while taking suppressive medication is an indicator that HSV infection may not be the cause of the patient's symptoms. Use of suppressive therapy is limited to patients with frequent or severe recurrences; however, the meaning of 'frequent' and 'severe' is subjective and will vary depending on each patient's situation (Table 2).

By reducing asymptomatic viral shedding, in addition to symptomatic recurrences, suppressive therapy significantly reduces herpes transmission, but its use for the reduction of transmission alone is not an indication for treatment on the PBS. The frequency of recurrences naturally varies over time, so a patient may wish to try a treatment break after six to 12 months to determine whether suppression is still required. An early breakthrough recurrence after stopping treatment is common and re-initiation of suppressive treatment should not be rushed. Case study 2 on this page provides an example of the use of suppressive treatment for recurrent genital herpes.

**Table 3. Prevention of transmission of genital herpes**

Strategy	Effectiveness
Abstinence	Excellent in theory, but in practice compliance is problematic
Avoiding sexual contact when lesions present	Unknown. Some benefit likely, especially if abstinence begins during the prodromal phase
Condoms	Depends on how often they are used. They are about 50% effective when used at least 75% of the time <sup>14</sup>
Antiviral therapy	Suppressive valaciclovir therapy leads to a 50% reduction in transmission to a regular partner <sup>8</sup>
Vaccines	No vaccine currently available
Microbicide	Encouraging laboratory results but nothing commercially available at present <sup>17</sup>

In the long term and on an individual basis, patients may opt to vary their self-management of recurrences with a mixture of suppressive, episodic and no therapy. There are no contraindications to adopting this strategy provided the patient feels that they are in control.

### Prevention

Short of the unpopular method of sexual abstinence, it is impossible to completely prevent the transmission of genital herpes. It is also important to note that as the majority of people with genital herpes are undiagnosed, no actions by those with known genital herpes are likely to affect herpes transmission in the population as a whole. Despite that, newly diagnosed patients are often concerned about transmission to a sexual partner, and there is evidence available to guide the advice they should be given (Table 3).

Traditionally, patients have been advised to avoid sexual contact during symptomatic recurrences, but the effectiveness of this strategy is unknown. We now know that at least 80% of herpes viral shedding occurs when the person has no lesions<sup>9</sup> and that most transmission from a person who is known to be infected occurs when he or she is asymptomatic.<sup>10</sup> The frequency of asymptomatic shedding is unrelated to the frequency of symptomatic recur-

rences, so even those who rarely have a recurrence will shed virus frequently.<sup>11</sup> Studies have found that asymptomatic shedding occurs between 8 and 27% of the time, with the frequency tending to decrease with an increase in the length of time since infection.<sup>8,12</sup>

Condom use has been shown to reduce the acquisition of genital herpes in both men and women,<sup>13,14</sup> with more frequent use associated with greater protection. However, even with 100% reported condom use some transmission still occurs, probably reflecting the fact that a large area of genital skin is not covered by a condom.

Encouraging patients with genital

herpes to disclose to their partners has been shown to significantly delay herpes transmission.<sup>15</sup> Whether this delay is due to increased condom use or reduced frequency of sexual contact is not known. There are no data to demonstrate that a decrease in transmission persists in the longer term.

Given the lack of durable and potent prevention methods any substantial reduction in the overall incidence of genital herpes is unlikely to be possible without a vaccine. Despite a number of clinical trials, there have been no effective vaccines produced as yet, with the latest only showing effectiveness in women who were seronegative for both HSV-1 and HSV-2.<sup>16</sup> Topical microbicides are another area of active research, with a recent trial showing a decrease in the viability of HSV following the application of the product,<sup>17</sup> however, none of these products have demonstrated a reduction in transmission as yet.

MT

### References

*A list of references is available on request to the editorial office.*

**COMPETING INTERESTS:** Dr Ryder has received financial support from GlaxoSmithKline and Novartis. Professor Donovan has received financial support from GlaxoSmithKline.

### Share your innocence

Sometimes on our journey of learning we can be enlightened by events that are humorous, surprising or touching. Clarity is invariably sharpened by looking through the retrospectroscope. We'd love to hear about your own experiences and will send a bottle of Moss Wood Margaret River Cabernet Sauvignon 1998 to those who submit contributions that we publish (under a nom de plume if you wish).

Please send your anecdotes to: Medicine Today, PO Box 1473, Neutral Bay, NSW 2089, or [editorial@medicinetoday.com.au](mailto:editorial@medicinetoday.com.au) for consideration.



# Management and prevention of recurrent genital herpes infection

**NATHAN RYDER** MB BS, MPH, FACHSHM **BASIL DONOVAN** MD, FACHSHM, FAFPHM, FRCP

## References

1. Cunningham AL, Taylor R, Taylor J, et al. Prevalence of infection with herpes simplex virus types 1 and 2 in Australia: a nationwide population based survey. *Sex Transm Infect* 2006; 82: 164-168.
2. Ryder N, Jin F, McNulty AM, et al. Increasing role of herpes simplex virus type-1 in first episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992-2006. *Sex Transm Infect* 2009; 8 March [Epub ahead of print].
3. Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infection: an evidence-based review. *Arch Intern Med* 2008; 168: 1137-1144.
4. Wald A, Carrell D, Remington M, Kexel E, Zeh J, Corey L. Two-day regimen of acyclovir for treatment of recurrent genital herpes simplex virus type 2 infection. *Clin Infect Dis* 2002; 34: 944-948.
5. Aoki F, Tyring S, Diaz-Mitoma F. Single-day, patient initiated famciclovir therapy for recurrent genital herpes: a randomised, double-blind, placebo-controlled trial. *Clin Infect Dis* 2006; 42: 8-13.
6. Strand A, Patel R, Wulf HC, et al. Aborted herpes simplex virus lesions: findings from a randomised controlled study. *Sex Transm Infect* 2002; 78: 435-439.
7. Mindel A, Carneya O, Frerisc M, Fahertya A, Patoub G, Williams P. Dosage and safety of long-term suppressive acyclovir therapy for recurrent genital herpes. *Lancet* 1988; 331: 926-928.
8. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004; 350: 11-20.
9. 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: 844-850.
10. Mertz GJ, Benedetti J, Ashley R, et al. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992; 116: 197-202.
11. Wald A, Zeh J, Selke S, et al. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* 1995; 333: 770-775.
12. Gupta R, Wald A, Krantz E, et al. Valacyclovir and acyclovir for suppression of shedding of herpes simplex virus in the genital tract. *J Infect Dis* 2004; 190: 1374-1381.
13. Wald A, Langenberg AG, Link K, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001; 285: 3100-3106.
14. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med* 2005; 143: 707-713.
15. Wald A, Krantz E, Selke S, et al. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis* 2006; 193: 27-35.
16. Stanberry LR, Spruance SL, Cunningham AL, et al. Glycoprotein-D-adjuvant vaccine to prevent genital herpes. *N Engl J Med* 2002; 347: 1652-1661.
17. Keller MJ, Zerhouni-Layachi B, Cheshenko N, et al. PRO 2000 gel inhibits HIV and herpes simplex virus infection following vaginal application: a double-blind placebo-controlled trial. *J Infect Dis* 2006; 194: 42-52.