

MANAGEMENT OF CLINICAL EPISODES OF GENITAL HERPES

Management of First Clinical Episode

KEY POINTS

- First clinical episode may, but does not always, reflect recent infection.
- The '72 hour' herpes zoster rule does not apply to first episode herpes.

The first clinical episode of genital HSV-1 or HSV-2 may, but does not always, reflect recent acquisition of infection. It may represent a primary HSV infection or a new non-primary infection or a first recognised clinical expression of a previously acquired infection. It is not possible to reliably distinguish between these on clinical grounds alone. Nonetheless, as the first episode genital herpes is generally more severe and/or more prolonged, **treatment should always be offered regardless of time of symptom onset.**

Valaciclovir prescriptions do not require specialist authorisation and the medication is available through any pharmacy. Patients are often very unwell and **therapy should be initiated regardless of how long the lesions have been present and before virological confirmation.** This is based on evidence that the virus is shed from the infected area for a median of 11 days, with systemic and local symptoms lasting 2–3 weeks if untreated. Oral antiviral therapy substantially reduces the duration and intensity of symptoms.^{18,19} **GRADE A**

Management for patients presenting with a first episode of genital herpes should encompass the following:

1. History.
2. Examination.
3. Tests:
 - (a) Virus swab for PCR for diagnosis.
 - (b) Consider screening for other STIs if appropriate, although this may be deferred to a follow-up visit, as it is often too painful.
4. Treatment involving:
 - (a) Oral antiviral therapy.
 - (b) Symptomatic treatment.
 - (c) Provide patient information with written material or refer to www.herpes.org.nz
 - (d) Acknowledgement of the psychosocial impact of the disease.
 - (e) Referral to support systems – Herpes Helpline tollfree **0508 11 12 13**.
5. Appropriate follow-up arrangements.

It is not necessary or desirable to attempt to cover all these issues at the initial clinical assessment. However, recognition of the psychosocial impact of the diagnosis, and the provision of adequate information and/or referral to the Herpes Helpline, is important.

It may be helpful to discuss how results will be given, e.g. in person, over the phone. If giving results over the phone, check the person is in an appropriate situation to receive the call.

History of primary genital herpes

Symptoms may appear 2–20 days following exposure to infection with the virus. However, initial symptoms of genital herpes may not be recognised or may not occur until months to years later. Symptom severity differs markedly with severe cases having lesions lasting up to 3 weeks.

The prodrome (if experienced) is signalled by flu-like symptoms of fever, headache and general myalgia, accompanied by local tingling, irritation and/or pruritus or pain in the genital region. Rapidly, pruritic erythematous papules appear, followed by multiple small vesicles that contain clear to cloudy fluid. These vesicles rupture within 1–2 days to form painful, sloughy, shallow ulcers with irregular margins, which may become confluent. The area may be oedematous and can be extremely tender. Pain on urination is typical, particularly in women and spontaneous urination may be impossible. The ulcers dry to form crusts and later heal, leaving a transient red macule with minimal scarring (if any). Less commonly, lesions can pass through the blister phase quickly and blisters may not be noticed. Involvement of the cervix occurs but speculum examination may not be possible. Lesions may also appear extra-genitally, commonly on thighs and buttocks and less commonly on hands, lips, face and breasts. Local lymph nodes, i.e. inguinal nodes with genital infection, are usually enlarged and tender.

Women are more severely affected than men. Immunosuppressed people may develop very extensive disease.

Complications of primary genital herpes

- Neurological complications are more common with genital herpes than is often recognised. Acute, generally benign, lymphocytic meningitis may occur; HSV-2 is associated with aseptic meningitis in up to 36% of adult women and 13% of men with primary HSV-2 infection. Symptoms include neck stiffness, low-grade fever and severe headache. Diagnostic features include photophobia with CSF findings of positive HSV-2 PCR, increased white cell count and raised protein.²⁰
- Similarly, a diagnosis of acute radiculitis (herpetic lumbosacral radiculoneuropathy or Elsberg syndrome) tends to be overlooked, yet may cause acute urinary retention, constipation and sacral neuralgia. Referred pain can affect the saddle area distribution, S3 and 4, of the sacral nerve and the bladder detrusor muscle. Erectile dysfunction, dull or severe burning pain in the anogenital region, loss of sensation and hypersensitivity can occur down the thighs and the lower legs. The condition is usually self-limiting and tends to resolve in 1–2 weeks; in the meantime, supportive cares should be offered. Symptoms may sometimes persist for weeks and rarely severe intractable pain may require opiate analgesia.
- HSV-2 myelo-radiculitis, associated with advanced immunosuppression and AIDS, may be associated with a fatal outcome.²¹
- Bells Palsy is probably caused by either VZV, HSV-1 and rarely HSV-2. Early treatment with oral steroids is effective.^{22,23} A recent Cochrane review suggests that, compared with steroids alone, antiviral treatment increases the proportion of patients who recover at 3- and 12-month follow-up, albeit the quality of evidence is limited.
- Sporadic herpes simplex encephalitis is an acute necrotising viral encephalitis that is more usually caused by primary infection with HSV-1. Clinical features are often nonspecific, as is common with all forms of encephalitis, and include headache, signs of meningeal irritation, altered mental status, and seizures. Because prompt treatment of HSV encephalitis may minimise residual neurologic damage and prevent death, early consideration of this diagnosis is important.
- HSV (especially Type 1) is a common predisposing trigger for erythema multiforme, a hypersensitivity condition most often caused by infections and sometimes drugs. Many cases have no obvious precipitating cause. It develops 3–14 days following HSV infection. Mild forms of this condition are common and start and present as macules, papules and urticarial lesions which reach up to 3cm on extremities. They especially affect the hands and feet, dorsum of elbows and knees, and less often the trunk. Some lesions develop into the classical “target” lesion with three colour zones: central dusky erythema, surrounded by a paler oedematous zone and an outer erythematous ring with a well-defined border. Resolution within 7–10 days is the norm.
- Infrequently, HSV viraemia may result in infection of visceral organs. In most cases of disseminated infection, lesions are confined to the skin, but hepatitis, pneumonitis and other organ involvement may occur, with or without vesicular skin lesions.

A relevant specialist should review any patient with complications.

Examination

Examination should include inspection of the genital region; speculum examination should be considered, but may need to be delayed if discomfort is anticipated.

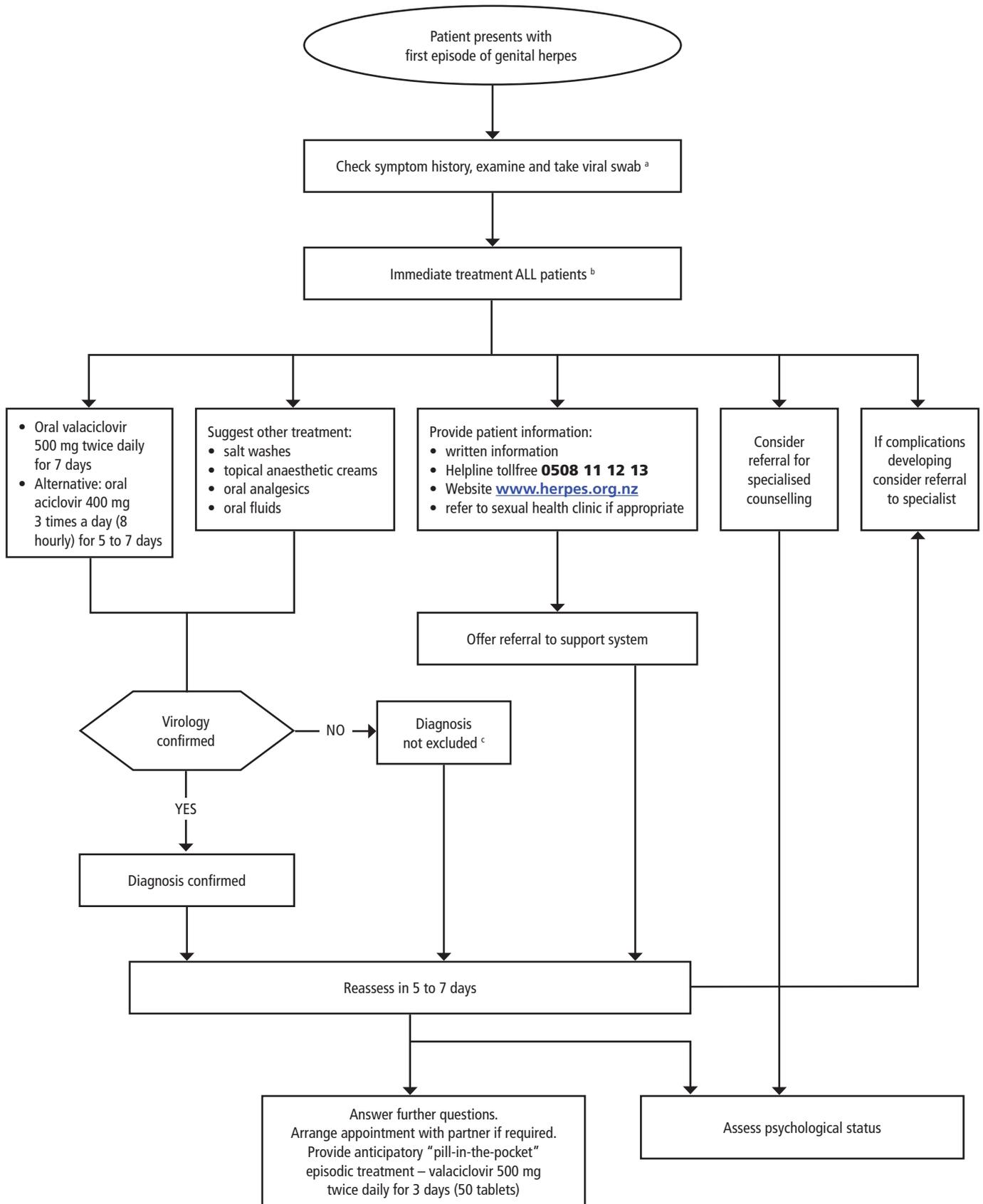
Diagnosis

Laboratory confirmation of the diagnosis is important, but should not delay the initiation of treatment. A negative result does not necessarily exclude a diagnosis of HSV (see [page 8-9](#)).

Differential diagnosis

- Aphthous ulcers. There are fewer and larger lesions with no preceding vesicles.
- Steven Johnson syndrome. This is usually but not always associated with skin lesions. (HSV infection can cause this condition.)
- Autoimmune blistering disorders such as pemphigus and cicatricial pemphigoid, which are chronic.
- Other genital infections lack the preceding vesicular stage, apart from varicella zoster infection which is unilateral.
- Candidiasis and folliculitis produce pustules, which must be differentiated from HSV infection.

Management of First Episode of Genital Herpes



a In cases of immunocompromised patients or herpes proctitis, refer to specialist.
 b Specialist consultation is recommended for use of antivirals in pregnancy.
 c Recommend early presentation for viral swab if recurrence.

Treatment of First Episode Genital Herpes

A. Pharmacological treatment

If there is a possibility of pregnancy, please refer to **page 18**. Refer immunocompromised patients, or those with herpetic proctitis, to an appropriate specialist, e.g. infectious diseases, sexual health.

1. Oral antiviral treatment

Recommended treatment for first episode genital herpes:

- **Valaciclovir 500mg BD for 7/7.**
- **Alternative: oral aciclovir 400mg 3 times daily (8-hourly) for 7 days.**

Lesions may not completely heal over during the course of drug treatment; similarly, mild neurological symptoms may not yet have fully resolved. Nonetheless, a further course of therapy is not usually indicated unless new lesions continue to appear.

2. Intravenous antivirals

Intravenous (IV) aciclovir therapy could be considered for patients who have severe disease or complications that necessitate hospitalisation.²⁴

- For patients with severe disease requiring hospitalisation the dose for intravenous aciclovir is 5–10 mg/kg 8 hourly for 2–7 days followed by oral treatment to complete at least 10 days of antiviral therapy.

3. Topical antivirals

Topical aciclovir creams are not recommended because they offer minimal clinical benefit (see **page 16**).

B. Symptomatic treatment

In addition to oral antivirals, other measures to control symptoms should be suggested. Paracetamol 4-hourly is usually adequate, but stronger pain relief may be necessary. Drinking fluids hourly produces dilute urine that is less painful to void. Female patients can be advised to sit in a bath or bowl of warm water to pass urine. Advice about drying lesions with the lowest setting of a hair dryer may be helpful. Bathing in salt water (e.g. half a cup of household salt in the bath or 2 teaspoons per litre of warm water for topical application) may help relieve pain and promote healing. Adequate pain relief should be provided. Topical anaesthetic jelly such as lignocaine (Xylocaine) gel applied 5 minutes before micturition helps relieve the pain. As lignocaine is a potential skin sensitizer, patients should be warned to use it for the shortest possible time (usually 1 or 2 days maximum). **GRADE C**

C. Education

It is important to ensure that patients receive accurate up-to-date information about genital herpes. A range of printed materials can be downloaded from the NZHF website, or ordered at no cost (please refer to resources listed on the **inside front cover**). Primary care practitioners should have access to these resources or be able to advise their patients on how to obtain them, e.g. www.herpes.org.nz. There is also a Herpes Helpline **0508 11 12 13**, a telephone service which is free to all New Zealanders.

Informing the patient of the diagnosis can be a delicate matter. **Health providers may find it helpful to review the 3 minute PowerPoint resource on the NZHF website www.herpes.org.nz which provides information on what patients tell us they want to know at this point in their management.** Although initial counselling can be provided at the first visit, it may be preferable to wait until the initial outbreak settles to discuss chronic aspects of the infection. Written materials, such as the NZHF **Myth vs Facts** leaflet and **The Facts** booklet, should be offered to patients at the first visit with discussion and further questions encouraged at the follow-up and subsequent visits.

See **Key Information for Health Professionals to Give Patients in Counselling** on **page 34**. **GRADE C**

D. Follow-up

Follow-up is important for those with first episode herpes. For most patients, one visit is insufficient to properly manage the impact of genital herpes. Counselling and advice often form the major part of a follow-up appointment and time should be allowed for this. The practitioner should be alert to the possibility of further psychological problems manifesting after a diagnosis of genital herpes.

At the initial visit, a follow-up appointment should be offered for 5–7 days later, to evaluate symptoms, their psychological status, complete a full STI screen if appropriate, discuss results and answer any questions they may have. It should be noted that it might take longer than 5 days for skin lesions to heal completely. Further therapy is not usually required unless new lesions continue to appear.

Anticipatory episodic therapy is recommended. Episodic antiviral therapy is more effective when patients start therapy themselves at the first signs of a recurrence. **GRADE A**

Suppressive antiviral therapy can be considered for those with frequent and/or severe recurrences or associated psychosocial morbidity. It is suggested that either a minimum of two recurrences or approximately 3 months without suppressive therapy is required to establish the pattern.

Management of Recurrent Episodes of Genital Herpes

KEY POINTS

- Most recurrent herpes is mild and infrequent.
- There is effective oral antiviral treatment for frequent, severe, problematic genital herpes.
- Treatment/management options should be discussed with the patient. No treatment is also a common and acceptable option.
- Individualised treatments and increased emphasis on prompt initiation of episodic treatment.
- Suppressive therapy can be considered for those with frequent and/or severe recurrences, and/or associated psychological morbidity and those associated with erythema multiforme.
- 20–25% of patients may have 'recurrences' despite being on suppression. If the patient is compliant with suppressive therapy, it is important to consider other genital conditions that mimic or coexist. A positive HSV DNA result in a patient who is compliant with suppression suggests ACV-resistant virus which is very rare.
- Withdrawal of therapy should be for a sufficient length of time to establish whether the pattern of recurrence has changed (3 months).
- Reduced dose of valaciclovir or aciclovir should be considered in the presence of severe renal failure.
- Education and counselling are an extremely important part of management (refer to www.herpes.org.nz or Herpes Helpline tollfree **0508 11 12 13** or from a mobile 09 433 6526).

Management of recurrent herpes depends on whether there is prior virological confirmation of infection. Management of patients presenting with recurrent herpes should encompass the following:

1. History
2. Examination
3. Tests:
 - (a) Viral swab for PCR for diagnosis; confirmation of diagnosis at least once is strongly recommended.
 - (b) Consider exclusion of other STIs if appropriate.
4. Treatment involving:
 - (a) Either episodic therapy or suppressive therapy where appropriate.
 - (b) Symptomatic treatment.
 - (c) Education concerning transmission, epidemiology, etc; provide written material.
 - (d) Acknowledgement of the psychosocial impact of the disease.
 - (e) Referral to support systems – Herpes Helpline tollfree **0508 11 12 13** or visit www.herpes.org.nz.
5. Appropriate follow-up arrangements.

Sufficient time should be allowed to address all these aspects.

History, examination and diagnosis

- Only 10–25% of persons who are HSV-2 seropositive report a diagnosis of genital herpes, which suggests that most have unrecognised symptomatic or completely asymptomatic infections.²⁵ However, once told they are HSV-2 seropositive, more than 50% are able to identify clinically symptomatic recurrences that may have previously been thought to be due to other conditions.
- In straightforward cases with a prior laboratory-confirmed diagnosis, the clinical history is often the principal means of determining that the patient has a recurrent episode, but other genital conditions may mimic and/or coexist with recurrent herpes, and careful examination of the genitalia should always form part of the diagnostic procedure.
- Common differential diagnoses include lichen sclerosus, fissuring due to candidiasis, folliculitis, bacterial skin infections, dermatitis and any other skin conditions that cause itching and fragility of the skin.
- Uncommon conditions include erythema multiforme, hidradenitis suppurativa, scabetic nodules, fixed drug eruption, trauma (self-inflicted or accidental) and autoimmune blistering disease (rare). Other infections may cause genital ulcers, although not necessarily recurrent, e.g. other herpes viruses such as herpes zoster virus and Epstein-Barr virus, primary syphilis and chancroid.
- All these examples serve to underpin the importance of taking a detailed history and thorough physical examination of the whole skin, including oral mucosa. Atypical presentation is not unusual and HSV should be considered in any recurrent intermittent inflammatory genital lesions regardless of appearances. **Any recurring lesion of 1–2mm in size, occurring in the same genital area, is strongly suggestive of HSV-2 infection.**

- All genital lesions not previously diagnosed should have a swab taken with an explanation to the patient why this has been done. **GRADE B**
- It is highly desirable, but not always possible, to obtain virological confirmation. Typically, the viral load is reduced in recurrences compared with the first episode. There is a significant false-negative rate in the laboratory tests for HSV, although this is less for PCR. The best method of obtaining confirmation during a recurrence is to take a swab for PCR within 24 hours of symptoms developing. **GRADE B**
- An option is to instruct patients how to take a swab themselves and deliver direct to the laboratory. Other causes of recurrent genital lesions should be considered, but in the event of continuing recurrent lesions and HSV PCR remaining negative, type-specific herpes serology testing may aid diagnosis.

Complications of recurrent genital herpes

- Recurrent herpes lesions can occur on the hands, arms, shoulders and other areas of the body, commonly around the buttocks; the diagnosis is often overlooked.
- Benign headaches.
- Lumbar sacral radiculopathy can recur, but usually with less severe symptoms than in primary infection. Recurrent, benign, aseptic meningitis, known as Mollaret's meningitis, may occur with HSV-2. Patients should be offered long-term suppressive antiviral management, which may need to be continued indefinitely.
- HSV is a common predisposing trigger for erythema multiforme. Mild forms of this condition are common and present with mildly itchy, pink-red blotches, starting on the extremities. Some of the skin patches take on the classical 'target lesion' appearance, with a dark centre surrounded by a pale oedematous circle and a red periphery. Resolution within 7–10 days is the norm. Recurrent episodes may be managed with continuous antiviral suppression treatment.
- Erythema multiforme major is a more severe condition with mucosal involvement affecting mouth, eyes and genital mucosae. It may become recurrent with each episode of HSV infection and requires suppressive therapy.

A specialist should review any patient with complications.

Treatment of Recurrent Genital Herpes

Episodic antiviral therapy

The aim of episodic treatment is to reduce symptoms and duration of viral shedding during recurrences, rather than reduce the frequency of recurrences. Further, early therapy may abort episodes, that is, lesions may be prevented from progressing beyond the papular stage.^{26,27} In situations where patients have well recognised prodromes and/or have less frequent recurrences, some may find episodic treatment preferable to continuous suppressive therapy.

Effective episodic antiviral treatment of recurrent herpes requires initiation of therapy during the prodrome that precedes some outbreaks or within one day of lesion onset.^{26,27} Beyond this timeframe there is no clear benefit, so it is important that a prescription is readily available. In consultation with the patient, sufficient quantities of medication may be prescribed with instructions to start treatment as soon as symptoms begin. **GRADE A**

Recommended dosage regimen

If the patient is pregnant, specialist consultation is recommended (see [page 18](#)). In cases of immunocompromised patients, refer to appropriate specialist.

Episodic treatment

- Valaciclovir 500mg bd for 3/7.
- Alternative: oral aciclovir 800mg 3 times daily for 2 days.

Prescribe enough tablets for patients to be able to self-initiate treatment at onset of symptoms.

Note: Famciclovir is not subsidised or marketed in New Zealand.

Suppressive antiviral therapy

Suppressive therapy is an oral antiviral taken continuously over a given period of time that effectively reduces the frequency of recurrences.^{28,29} **GRADE A**

The main aims of suppressive therapy are:

- As an effective strategy for improving the quality of life of patients with recurrent genital herpes.^{30,31}
- To allow the patient to have a break from experiencing recurrences of the disease.
- To reduce the risk of transmission.
- Reduced dose of valaciclovir or aciclovir should be considered in the presence of severe renal failure.

Aciclovir, famciclovir and valaciclovir all suppress symptomatic and asymptomatic shedding, by up to 80–95%.¹⁵ Suppressive once-daily valaciclovir has been shown to reduce transmission to an uninfected partner with a 48% reduction in acquisition of HSV infection and a 75% reduction in clinical symptomatic genital herpes.¹⁶ Other antivirals may be similarly effective, but this has not been proven in clinical trials. Patients may wish to consider this as a useful adjunct to safer sex behaviour and the use of condoms for the prevention of genital herpes transmission.

Indications for suppressive therapy

KEY POINTS

- Frequent and/or severe recurrences or associated psychological morbidity. Consider suppressive therapy in conjunction with other management. **GRADE B**
- For HSV-2 positive male partners of pregnant women (see [page 21](#)).

With long-term suppressive therapy it is strongly advisable to have virological confirmation of the diagnosis before commencing treatment. **Patients who have suggestive symptoms but do not have virological confirmation of recurrences, or who have complications or ongoing issues relating to their herpes, should see a specialist.**

Recommended dosage regimen

If the patient is pregnant, specialist consultation is recommended (see [page 18](#)).

In cases of immunocompromised patients, refer to appropriate specialist.

Recommended treatment regimens for suppressive therapy include:

- Valaciclovir 500mg daily. Increase to 500mg bd on individual basis of clinical presentation and/or having breakthrough recurrences on 500mg daily.
- Alternative: oral aciclovir 400mg twice daily.

Suggest prescribing for 12 months, followed by a break of 3 months to see if recurrences are still frequent. **GRADE C**

20–25% of patients may experience recurrent episodes whilst on suppressive therapy.^{28,32} Other genital conditions may mimic and/or coexist and, even if symptoms are suggestive of breakthrough recurrences, such patients are advised to see a specialist. The usual recommended dose of valaciclovir may need to be altered if breakthrough episodes are confirmed; suppressive therapy does not alter the natural history of recurrences long term and it is common to have a recurrence soon after withdrawal of therapy. It is helpful to anticipate this and to provide sufficient medication to allow prompt self-initiated treatment of any early recurrences. It is suggested that either a minimum of two recurrences or approximately 3 months without suppressive therapy is necessary to establish the new pattern.

Some patients may need to be on suppressive therapy for years. Valaciclovir is well tolerated and safety and efficacy data are supportive of longer-term use.³³ Neurotoxicity (lethargy, confusion, hallucinations and involuntary movements) has been reported in those with renal impairment.

Topical antiviral therapy

Topical aciclovir creams are less effective than oral aciclovir.³⁴ Hence, use of topical treatment is not recommended. Topical antiviral creams are available over the counter, but are no longer subsidised on the pharmaceutical schedule.

Newer topical agents such as immune modulators are currently in clinical trials.

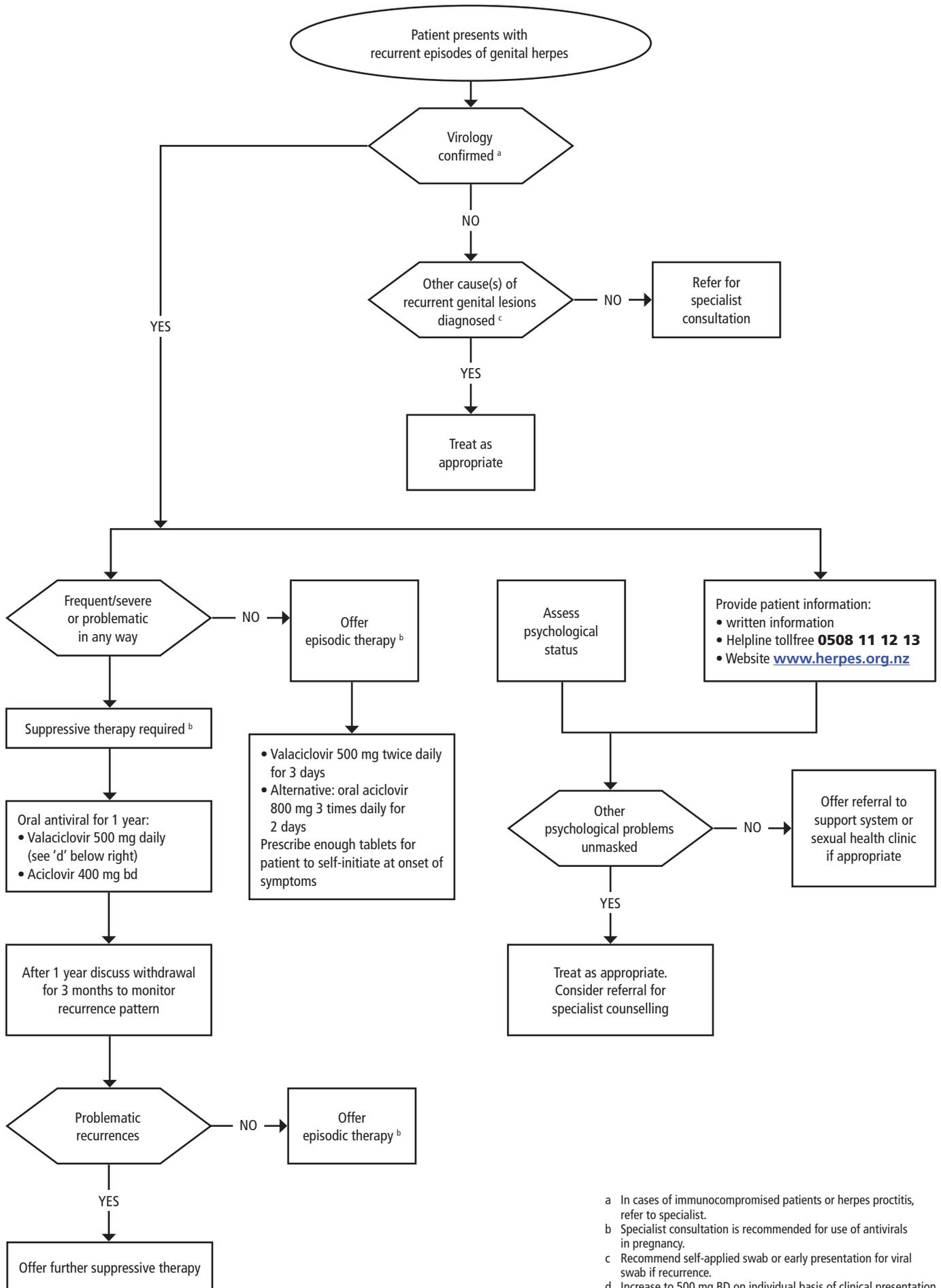
Other therapies

Evidence for other therapies (oral L-lysine, aspirin, liquorice root cream, lemon balm, aloe vera cream, etc.) is absent.

Genital Herpes in Immunocompromised Individuals

Although rare in immunocompetent individuals, clinically refractory (large, severe and sometimes atypical) lesions due to genital HSV may occur in patients with severe immunodeficiency, including late stage HIV disease. Immunocompromised individuals need referral to specialist care.

Management of Recurrent Episodes of Genital Herpes



- a In cases of immunocompromised patients or herpes proctitis, refer to specialist.
- b Specialist consultation is recommended for use of antivirals in pregnancy.
- c Recommend self-applied swab or early presentation for viral swab if recurrence.
- d Increase to 500 mg BD on individual basis of clinical presentation and/or having breakthrough recurrences on 500mg daily.