




## GUIDELINES

# 2024 European guidelines for the management of genital herpes

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### Abstract

Genital herpes is one of the most common sexually transmitted infections worldwide. Using the best available evidence, this guideline recommends strategies for diagnosis, management and follow-up of the condition as well as for minimizing transmission. Early recognition and initiation of therapy is key and may reduce the duration of illness or avoid hospitalization with complications, including urinary retention, meningism or severe systemic illness. The guideline covers a range of common clinical scenarios, such as recurrent genital herpes, infection during pregnancy and coinfection with human immunodeficiency virus.

## INTRODUCTION

First infection with either herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) is termed primary infection and results in either symptomatic disease at the site of viral entry (i.e. on the face or genital area) or asymptomatic, and thus unrecognized, infection. In addition, there may be systemic symptoms, as with other acute viral illnesses. Only 25% of patients

who acquire genital herpes have any recognized clinical features at the time of acquisition.<sup>1</sup> Following infection, the virus becomes latent in the local sensory ganglion, periodically reactivating to cause symptomatic lesions, or undergo asymptomatic, but nonetheless infectious, viral shedding.<sup>2</sup> Genital herpes can be caused by either HSV-1—the usual cause of oro-labial herpes—or by HSV-2—the usual cause of genital herpes. Infection with either virus can cause an

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identical initial illness; however, the actual clinical presentation may depend upon previous HSV-1 or HSV-2 infection and previous sites of infection. Subsequent recurrence frequency is greater for HSV-2 than HSV-1 disease when infection involves the genital area.<sup>3</sup>

## Transmission risk

Risk of transmission appears to be greatest during lesional recurrences or prodrome and patients should be advised to abstain from sexual contact during this time. Transmission can occur in the absence of lesional recurrence as a result of sub-clinical viral shedding.<sup>2</sup> Efficacy of condoms to prevent sexual transmission has not been formally assessed; however, indirect evidence from failed vaccine trials provides strong support for their consistent usage to prevent transmission to both males and females (1, B).<sup>4,5</sup> The efficacy of condoms is easier to demonstrate in male to female transmissions where increasing consistent use results in lower levels of transmission.<sup>6</sup>

## DIAGNOSIS

### Clinical diagnosis

Although classical genital herpes can be recognized by the presence of typical papular lesions progressing to vesicle and ulcer formation, associated with local adenitis and in recurrent cases preceded by prodromal symptoms, the features in many patients can be highly variable. The majority of patients will suffer from atypical lesions where signs may be easily confused with other genital dermatoses.<sup>7</sup> In all cases, but in particular for atypical cases, clinical diagnosis alone should be avoided, running the risk of adversely affecting a relationship and adding psychological burden with stigma, without cause.

Herpes is an important cause of proctitis and should be considered in all cases and especially where a sexually transmitted infection is being considered.

### Differential diagnosis

The differential diagnosis of genital ulceration is wide but in the context of young sexually active populations in Europe presenting with painful blistering eruptions an infective cause is usually likely (Table 1. Genital ulcerations—differential diagnosis). Care must be taken to ensure that the possibility of mixed infections is considered. Syphilis is increasing in frequency and can cause painful lesions particularly in the perianal area. Herpes zoster is the cause of the genital blistering in 2% of cases (although mostly at the extremes of age)<sup>8</sup> and is frequently unilateral. Sporadic cases of Mpox are reported in at risk populations despite vaccination.

### Principle changes made to the European guidelines for the management of genital herpes

- The need for and importance of considering a wider range of pathogens when assessing a case of genital ulceration.
- The importance of excluding HSV in proctitis.
- Clearer recommendations around interpretation of type-specific serology.
- Clarification of duration of course of treatment for an initial episode of HSV.
- Recommended regimens for suppressive therapy, including recommendations for second-stage treatment for poorly controlled patients.
- Advice on investigations in those poorly controlled on suppressive therapy.
- Advice on timing the start of antivirals in pregnancy (pre-third trimester disease) based on local epidemiology of preterm delivery and neonatal herpes infection.
- Advice about refraining from sexual intercourse during pregnancy in HSV discordant couples.

Lymphogranuloma venereum can also present as perianal ulceration, with or without proctitis.<sup>9</sup>

### Laboratory diagnosis

#### Virus detection

- Laboratory confirmation is recommended in all patients with suspected genital herpes, using methods that directly demonstrate the virus in genital specimens, typically swabs should be taken from the base of the lesion (vesicles should be unroofed with a needle or scalpel blade) (1, A).<sup>1</sup> Viral detection in early disease (for both first episodes and recurrences) are much more likely to be successful. In suspected recurrent disease, patient taken swabs (at home) can be better at demonstrating virus than those taken in clinical settings. Viral production rapidly peaks during a herpes episode and swabbing for laboratory confirmation should not be delayed.
- HSV typing into HSV-1 and HSV-2 is recommended in all patients with first-episode genital herpes to guide counselling and management (1, C).<sup>4</sup>
- As HSV shedding is intermittent, testing swabs from asymptomatic patients is not recommended for routine diagnosis as it is unlikely to yield confirmation of carrier status (1, A).<sup>4</sup>
- HSV DNA detection is now considered the gold standard for diagnosis. Compared with cell culture it is both more sensitive and specific (1, A)<sup>1,10–14</sup> and increases HSV

detection rates in muco-cutaneous swabs by 11%–71% and is recommended as the preferred diagnostic method (1, A).<sup>1,13,14</sup> Real-time PCR can tolerate less stringent conditions for sample storage and transport than virus culture, and allows the rapid detection and typing of HSV with a lower risk of contamination than traditional PCR assays. Cell culture may occasionally be required to determine anti-viral sensitivity, but it is increasingly unavailable to clinicians.

- Viral antigen detection methods such as direct immunofluorescence assay (IFA), enzyme immunoassay (EIA) and Tzanck and Papanicolaou staining are no longer recommended except in extremely limited resource settings (1, A).<sup>15–17</sup>
- In cases of unexplained culture negative sepsis unresponsive to antibiotic therapy, HSV PCR testing of tissues possibly involved at the possible port of entry are recommended (3, D).<sup>18</sup>

## HSV type-specific serology

Serological testing is not routinely recommended in asymptomatic patients (1, D), but may be useful in the following groups.<sup>2,4,19–23</sup>

- History of recurrent or atypical genital disease when direct virus detection methods have been negative (1, C). HSV-2 antibodies are supportive of a diagnosis of genital herpes; HSV-1 antibodies do not differentiate between genital and oro-pharyngeal infection. Counselling of HSV-2 IgG-negative, HSV-1 IgG-positive patients should take into account that HSV-1 genital infection is showing a substantial increase in incidence among younger populations.<sup>24</sup>
- First-episode genital herpes, where differentiating between primary and established infection guides counselling and management (1, C). At the onset of symptoms, the absence of HSV IgG against the virus type detected in the genital lesion is consistent with a primary infection.<sup>4</sup> Seroconversion should be demonstrated at follow-up, typically at 90 days.
- Sexual partners of patients with genital herpes, where concerns are raised about transmission. Serodiscordant couples can be counselled about strategies to reduce the risk of infection and disease (1, A).<sup>17</sup>
- Asymptomatic pregnant women should be routinely recommended to be tested if there is a history of genital herpes in the partner (1, B).<sup>25–27</sup> HSV-1 and/or HSV-2 seronegative women should be counselled about strategies to prevent a new infection with either virus type during pregnancy.

Care must be taken in interpreting negative results as antibodies to both HSV-1 and 2 may not form or be lost with time.

Limited data suggest an increased risk of perinatal HIV transmission among HSV-2 seropositive HIV-infected women.<sup>28,29</sup> As evidence is not consistent, testing of pregnant

women living with HIV is not routinely recommended (1, D).<sup>30</sup>

HSV serological assays that detect antibodies against the antigenically unique glycoproteins gG1 and gG2 should be used.<sup>17,31</sup> Non type-specific HSV antibody assays are of no value in the management of genital herpes.

Western blot (WB) is the serological diagnostic gold standard. It is >97% sensitive and >98% specific but is labour-intensive and not commercially available.<sup>32,33</sup>

The sensitivities and specificities of commercially available seroassays can vary significantly across populations.<sup>34–43</sup> The positive predictive value (PPV) in low prevalence settings can make results uninterpretable. False-negative results are more likely to occur in early infection and can be resolved by repeat testing.

HSV seroprevalence rates, the presence of risk factors for genital herpes and clinical history influence the PPV of HSV type-specific serology and should guide testing and result interpretation (1, C).<sup>2,29–38</sup> The specificities of ELISA tests can be improved by raising the index value for interpreting positivity and testing all intermediate specimens with an alternate confirmatory test (1, B).<sup>33,34,36–38</sup>

IgM testing is not recommended in routine clinical practice. Studies suggest that 12%–30% of patients lose their HSV type-specific IgG antibodies depending on their HSV types and the test used.<sup>44</sup>

## Other investigations

Zoster PCR tests should be performed to exclude this diagnostic when the genital manifestations are not clearly suggesting HSV infection (e.g. expanding groups of vesicles and unilateral distribution of the lesions).

Tests for other STI: syphilis, chlamydia, *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and *Trichomonas vaginalis* are indicated due to the risk of combined transmission during sexual contact.<sup>45</sup>

## MANAGEMENT OF GENITAL HERPES

### First-episode genital herpes

#### Indications for therapy

First episodes of genital herpes are frequently associated with a prolonged disease course (Figure 1).<sup>46</sup> Untreated, many patients suffer general and local complications. Therapy can be highly effective and should be instigated at the earliest opportunity and on clinical suspicion alone (1,A).<sup>46</sup>

#### Antivirals

Patients presenting within 5 days of the start of the episode, or while new lesions are still forming, should be given oral

**TABLE 1** Genital ulceration—differential diagnosis.

<b>(a) Infectious</b>	<b>(b) Tumoral</b>	<b>(c) Inflammation</b>
Apthous ulcers associated with cytomegalovirus or Epstein-Barr virus	Acanthosis nigricans	Angioedema
Bullous impetigo	<b>Bartholin duct abscess</b>	Atopic dermatitis (eczema)
Candida albicans	Basal cell carcinoma	Behçet's disease
Chancroid	<b>Epidermal cyst</b>	Contact dermatitis (allergic, irritant)
Chlamydia trachomatis L1-L3	Extramammary Paget disease	Crohn disease
Granuloma inguinale (Donovanosis)	Fibroepithelial polyp	Fixed drug eruption
<b>Herpes Simplex Virus</b>	Hidradenoma papilliferum	Fox Fordyce disease
Herpes zoster	Kaposi sarcoma	Hidradenitis suppurativa
<b>Infectious non-STI</b>	Lipoma	Keratosis pilaris
LGV	Melanocytic nevus	Langerhans histiocytosis
Mpox	Melanoma	Lichen planus
Scabies	Miliium	Lichen sclerosus
<b>Syphilis</b>	Neurofibroma	Lichen simplex chronicus
Syphilitic Balanitis of Follmann	Pyogenic granuloma	Lipschutz ulcer
<b>(d) Bullous diseases</b>	Scar	<b>Physiologic hyperpigmentation</b>
Cicatrical pemphigoid	Seborrheic keratosis	Plasma cell vulvitis
Epidermolysis bullosa acquisita	<b>Squamous cell carcinoma</b>	Postinflammatory hypopigmentation
Hailey-Hailey disease	Syringoma	<b>Prurigo nodularis</b>
Linear IgA disease	Verrucous carcinoma	<b>Psoriasis</b>
Non-accidentally trauma in children	Vulvar intraepithelial neoplasia	Pyoderma gangrenosum
<b>Pemphigoid</b>	Vulvar melanosis/lentiginosis	Sarcoidosis
Pemphigoid gestationis	Vulvar papillomatosis	Stevens-Johnson syndrome
<b>Pemphigus</b>	<b>(e) Vascular</b>	Toxic epidermal necrolysis
Subcorneal pustular dermatosis	<b>Angiokeratoma</b>	<b>(f) Trauma</b>
	Cherry angioma	Post-surgical
	Granulomatosis with polyangiitis	Post-irradiation
	Hemangioma	<b>Accidental and self-induced (penile injury, immersion burns, traumatic)</b>
	Lymphangioma	
	Milroy's congenital edema	

First-episode genital herpes	Recurrent genital herpes			
	Episodic antiviral treatment		Suppressive therapy	
	Short course therapies	Alternative longer courses	First stage	Second stage suppressive therapy
Aciclovir 400 mg x3/day, 5-10 days	Aciclovir 800 mg x3/day, 2 days	Aciclovir 400 mg x3/day, 5 days	Aciclovir 400mg x2/day	Aciclovir 400mg x3/day
Aciclovir 200 mg x5/day, 5-10 days		Aciclovir 200 mg x5/day, 5 days		
Valaciclovir 500 mg x2/day, 5-10 days	Valaciclovir 500 mg x2/day, 3 days	Valaciclovir 500 mg x2/day, 5 days	Valaciclovir 500 mg – 1000 mg /day	Valaciclovir 500mg x2/day
Famciclovir 250 mg x3/day, 5-10 days		Famciclovir 125 mg x2/day, 5 days		

**FIGURE 1** Management of genital herpes.

antiviral drugs. Aciclovir, valaciclovir and famciclovir are all effective in reducing the severity and duration of episode (1, A).<sup>46,47</sup> No therapy alters the natural course of genital herpes infection.

Topical agents are not recommended as they are less effective than oral agents and easily generate resistance (1, D).<sup>48</sup>

The only indication for the use of intravenous therapy is when the patient is unable to swallow or tolerate oral

medication because of vomiting. The recommended regimens—all for 5–10 days—are as follows:

- Aciclovir 400 mg three times a day or
- Aciclovir 200 mg five times a day or
- Famciclovir 250 mg three times a day or
- Valaciclovir 500 mg two times a day.

Choice should be made by individual clinicians, taking cost of therapy and likely compliance into account. A number of patients will have extended episodes beyond 5 days. If a decision to provide 5 days of therapy is made, the patient should have early review to ensure they have no further lesion development, systemic symptoms or disease complications—they all will require extended therapy. It will often be expedient to provide at least a 7-day course of treatment to ensure the patient does not run out of therapy at a weekend.

### Supportive measures

Bathing with normal saline and the use of appropriate analgesia are recommended. Frequent application of an anaesthetic cream may also help to prevent the (rare) complication of a labial fusion after a severe first episode. Although the potential for sensitisation exists in the use of topical anaesthetic agents, lidocaine is a rare sensitizer and can be used safely in genital herpes in the form of gel or ointment.<sup>49</sup> Benzocaine, however, is a potent sensitizer and should not be used (1, D). In women with severe dysuria, urination with the genitals submerged in water or physiological saline solution along with spreading the labia can alleviate symptoms.

### Counselling

It is important to provide counselling for the patient with genital herpes covering genital herpes evolution, severity of the lesions and symptoms, recurrences and transmission of the disease. The diagnosis should be communicated in a patient-centred approach (providing patients with information and hope, in a non-dominant, supportive way).<sup>50</sup> Advice on disclosure should be practical and tailored to the patient's personal situation—disclosure to sexual partners would usually be recommended. It is important to be frank about transmission risks including subclinical shedding and the limited impact of condoms and antivirals.<sup>5</sup> The low physical morbidity and high population prevalence should be stressed. Clear information about herpes simplex impact on pregnancy is important to patients and sexual contacts. High distress at diagnosis is common, often persists with recurrences and may be reduced by antivirals (1, A).<sup>51–53</sup> Most patients require one or two sessions but adjustment is difficult to predict and careful follow-up is important with more intensive input for those who do not adjust within 3–6 months. The physician should be prepared for lengthy consultations, for stigma avoidance and improve coping.

Patients may show a fear of rejection and can develop symptoms of depression,<sup>54,55</sup> and believe they have become less sexually attractive.<sup>56</sup> Fear of disclosure may be an important contributor to withdrawal from intimate relationships,<sup>57</sup> and diminished quality of life.<sup>58</sup> Clinicians need to be aware of the poor quality of online information and the patient should only be signposted to trusted information sources or adequate printed materials.

### Management of complications

Hospitalization may be required for urinary retention, meningism, severe constitutional symptoms or adverse social circumstances. If catheterisation is required, consideration should be given as to whether a suprapubic approach offers better symptom control to the individual patient. Super infection of lesions is rare but may occur during the second week. This is characterized by the recrudescence of local symptoms. Candida is most often implicated and is easily diagnosed and treated.

Genital HSV can theoretically be associated with superinfection of atopic dermatitis, relapsing eczema herpeticum, or be associated with recurrent erythema multiformae. Occasional case reports are described and the management is identical to that for these complications when arising from oral HSV-1.

### Information for patients

The following information should be discussed when counselling patients with first-episode genital herpes.

- The course of infection, including subclinical shedding.
- Genital herpes has a high a population prevalence.
- Treatment options.
- The risk of transmission and interventions that may limit or reduce the risk of transmission.
- The risk of transmission to the infant at birth. The patient should be counselled to inform the obstetrician and midwife.
- The utility of partner notification and the possible source of infection.
- That transmissions can occur from an asymptomatic partner some years into a monogamous relationship.
- The value of disclosure to fight stigma, depression or a diminished self-worth.

### Follow-up

Patients are followed up until the episode has resolved and counselling is considered complete. Further follow-up may be required to exclude other causes of genital ulceration that may be co-existent. Patients should be invited to re-attend should recurrences be problematic.

## Recurrent genital herpes

### Indications for therapy

Genital herpes recurrences are self-limiting and generally cause minor symptoms (Figure 1). The level of distress and the disruption caused to individual's sexual and social life is often independent of the frequency of symptoms. Decisions about how best to manage clinical recurrences should be made in partnership with the patient. Management strategies include supportive therapy only, episodic antiviral treatments and suppressive antiviral therapy. The most appropriate strategy for managing an individual patient may vary over time according to recurrence frequency, symptom severity and relationship status. For most patients, management will need to be supportive only, with simple local measures such as saline bathing or topical petroleum jelly being adequate.

### Episodic antiviral treatment

Oral aciclovir, valaciclovir and famciclovir are effective at reducing the duration and severity of recurrent genital herpes. The reduction in duration is a median of 1–2 days (1, A).<sup>59–61</sup> Head-to-head studies of their effects show no advantage of one therapy over another or the advantage of extended 5-day treatment over ultra-short therapy. Prodrugs offer simplified twice-a-day dosing. Patient-initiated treatment started within 24 h is most likely to be effective. Aborted lesions have been documented in up to one-third of patients with early treatment.<sup>62</sup> To ensure prompt treatment, patients should be advised to carry a small quantity of drugs at all times and not rely on sourcing medication after a recurrence starts.

Short course therapies should be tried in the first instance:

- Aciclovir 800 mg three times daily for 2 days or<sup>63</sup>
- Famciclovir 1 g twice daily for 1 day or<sup>64</sup>
- Valaciclovir 500 mg twice daily for 3 days (1, A).<sup>63,65–68</sup>

Alternative longer 5-day courses include the following:

- Aciclovir 400 mg three times daily or
- Aciclovir 200 mg five times daily or
- Valaciclovir 500 mg twice daily or
- Famciclovir 125 mg twice daily.

### Suppressive therapy

The majority of early trials of suppressive therapy were done in patients with a recurrence rate equivalent to  $\geq 6$  recurrences/annum.<sup>69,70</sup> More recently, studies have been completed in patients with much milder disease.<sup>71,72</sup> These indicate that patients across all spectrums of disease will benefit from a reduced rate of recurrence with treatment. The frequency of recurrence at which it is worth starting

suppressive therapy is a subjective issue and needs to balance the frequency of recurrence, the impact of disease on the individual and the need to manage transmission risk against the cost and inconvenience of treatment.

All patients are highly likely to experience a substantial reduction in recurrence frequency on suppressive antiviral therapy. However, the majority of patients on such a regimen will still experience an occasional symptomatic recurrence.

Experience with suppressive antiviral therapy is most extensive with aciclovir (1, A).<sup>73</sup> Safety and resistance data on patients on long-term therapy now extends to over 18 years of continuous surveillance. There is no accumulative toxicity or organ damage in long-term use. Dose adjustments are only required in severe renal disease. Regular blood monitoring in otherwise well patients is not recommended. Although not essential, it may be prudent to regularly assess the need for continuing therapy since patient circumstances may alter significantly. However, even after prolonged periods of suppression, many patients do not find a significant alteration in disease frequency or severity upon discontinuation and reassessment.

A few patients continue to experience frequent virologically confirmed symptomatic recurrences despite full dose antiviral therapy. Outside the immunocompromised population this is very unlikely to be due to resistant HSV. Investigations hoping to find a treatable immunological cause in these patients are not useful and, other than excluding HIV, no further investigations are warranted. Therapy involving interferon to improve control cannot be recommended, as these have not been widely assessed and are only available in parts of Eastern Europe.<sup>74</sup>

### Recommended regimens

The optimal total daily dose of suppressive aciclovir therapy is 800 mg. The only published clinical dose-ranging study concluded that 200 mg four times a day was marginally superior to 400 mg twice daily ( $p < 0.02$ ) (1, B).<sup>75</sup> However, ability to adhere with a four times a day dosing regimen should determine prescribing decisions for individual patients. Twice-daily valaciclovir (250 mg twice daily) has been shown to be as effective as twice-daily aciclovir (400 mg twice daily). Once-daily aciclovir does not suppress genital herpes recurrences. There is some debate as to whether once-daily therapy is as effective as twice-daily therapy with valaciclovir. For those patients experiencing  $< 10$  recurrences per annum, a dose of 500 mg once-daily valaciclovir will be adequate; for those patients experiencing  $> 10$  recurrences per annum, 250 mg twice a day or 1 g once a day is required.<sup>76</sup>

No major clinically significant differences between suppressive therapy with valaciclovir (500 mg daily) and famciclovir (250 mg twice daily) have been documented (1, D).<sup>14</sup> In patients with an insufficient clinical response with daily suppressive treatment, therapy may need to be doubled or

its frequency increased (1, D). Routine blood monitoring (e.g. serum creatinine, complete blood count and AST) of standard dose therapy is not required.<sup>77</sup> Occasionally a mild headache or nausea may occur with valaciclovir.

The decision to continue suppressive therapy should be reviewed at least annually. Discontinuation of therapy at this time, if the patient is willing, will allow a reassessment of recurrence frequency. A small number of patients will experience a reduction in recurrence frequency compared with pre-suppression symptomatic levels. The minimum period of assessment should include two recurrences to allow a view to be taken both on the frequency and severity. It is safe and reasonable to restart treatment in patients who continue to have significant disease (1, D).<sup>78</sup>

Short courses of suppressive therapy to prevent clinical symptoms may be helpful for some patients (for holidays, exams, etc.). Clinicians need to note that full suppressive effect is usually only obtained 5 days into treatment.

Recommended doses:

- Aciclovir 400 mg twice daily (for all frequencies of disease recurrence).
- Valaciclovir 500 mg daily (if fewer than 10 recurrences per annum).
- Valaciclovir 1 g daily (if more than 10 recurrences per annum).

Second stage therapy for poorly controlled patients:

- Aciclovir 400 mg three times a day.
- Valaciclovir 500 mg twice a day.

### Viral shedding and transmission on suppressive therapy

Subclinical shedding of infectious virus occurs in most individuals with genital HSV-1 and/or HSV-2. This virus is viable and is transmissible. Viral shedding is more likely to occur in patients with genital HSV-2, in the first year after

infection or in individuals with frequent symptomatic recurrences. Aciclovir, valaciclovir and famciclovir all suppress symptomatic and asymptomatic viral shedding.

Even if it seems biologically plausible, partial suppression of viral shedding does not necessarily equate to reduced transmission. However, suppressive therapy with valaciclovir 500 mg once a day (in those with 10 or fewer recurrent episodes per year) significantly reduced transmission—by nearly 50%—in serodiscordant couples (1, A).<sup>22</sup> Twice-daily aciclovir 400 mg achieves similar levels of reduction in asymptomatic shedding to once-daily valaciclovir. Suppressive antiviral therapy may be considered in addition to the use of condoms and selective sexual abstinence when transmission concerns are present.


## SPECIAL SITUATIONS

### Management of HSV in people with immunocompromise and in those living with HIV

For those patients that have a CD4 count in the normal range and an undetectable viral load, any management of HSV disease can follow the same protocol as those who are HIV negative (Figure 2). There is epidemiological synergy between HSV and HIV infections.<sup>79,80</sup> Herpes simplex infections activate HIV replication and may facilitate onward HIV transmission to sexual partners.<sup>81–88</sup> Suppressive treatment of HSV-2 infection with valaciclovir has been shown to reduce genital HIV shedding in women (not on ARVs).<sup>89</sup> In addition, both prevalent and incident HSV-2 infections are associated with an increased risk of HIV acquisition.<sup>90,91</sup>

The natural history of genital herpes in untreated people living with HIV is significantly different from that in HIV-negative individuals. The most important risk factor for herpes reactivation is the degree of HIV associated immunosuppression.<sup>92–94</sup>

Standard systemic antiviral drugs, as used to treat genital herpes in HIV-negative patients, have been shown to

Management of initial episode HSV in people living with HIV	Management of recurrent disease in people living with HIV	
	Episodic therapy for HSV in people living with HIV	Suppressive therapy for HSV in people living with HIV
Aciclovir 400mg x5/day, 7-10 days	Standard doses of antivirals short course or 5 days	Aciclovir 400mg x2-3/day
Valaciclovir 500-1g x2/day, for 10 days		Valaciclovir 500mg x 2/day
Famciclovir 250-500mg x3/day, 10 days		<i>If disease not adequately controlled: double the dose</i>
<i>If fulminant herpetic disease:</i> Aciclovir iv 5-10mg/kg body weight every 8 hours, for 2-7 days or until clinical improvement, and followed by oral antiviral therapy to complete 10 days total treatment	<i>In people living with advanced HIV: double the dose and &gt;5days therapy</i>	
<i>In patients living with advanced HIV: double the standard dose (or higher dose if needed)</i>		

**FIGURE 2** Special situations: management of genital herpes in people with immunocompromise and in those living with HIV.

successfully treat genital herpes in people living with HIV.<sup>95–100</sup> Resistance to anti-herpes drugs is more common in those with HIV co-infection and is associated with treatment failure of genital herpes.<sup>101</sup> Suppressing antiviral therapy with currently available agents has been shown in multiple studies to have no impact on HIV acquisition or transmission risk. HSV treatment used only to manage or reduce HIV transmission or acquisition risk cannot be recommended (1, A).<sup>102,103</sup>

Much of the evidence on herpes management in people living with HIV comes from studies performed before the era of combination antiretroviral therapy; prospective studies performed early in the epidemic showed that clinical lesions might be persistent and progressive in those living with HIV. Genital herpes, including chronic erosive lesions may occur as a manifestation of the immune reconstitution inflammatory syndrome (IRIS) following antiretroviral therapy.<sup>104–108</sup> Patients with a low CD4 count typically have a higher susceptibility to HSV-2 shedding, with a high risk of lesion manifestation within the first 6 months after ART initiation, particularly in the first 2 months. High levels of HSV viral shedding are associated with a high HIV load before ART commences.<sup>109,110</sup> HSV associated IRIS may be unresponsive to previously effective anti-herpes viral therapy in the absence of increased antiviral resistance. Management is difficult but the judicious use of prednisolone as in other situations with IRIS may be useful.

### Management of initial episode HSV in people living with HIV

There is no trial data for any antiviral in initial episode genital HSV in people living with HIV. The vast majority of adults living with HIV have serological evidence of established HSV-1 and -2 infections making acquisition trials extremely difficult to perform.

Case studies report that acquisition of genital HSV may be associated with a prolonged and uncertain clinical course. Systemic symptoms may predominate, and chronic lesions may become established if immunological clearance of the skin does not occur. In the absence of HIV therapy, primary genital herpes may be severe and prolonged with risk of progressive, multifocal, and coalescing mucocutaneous anogenital lesions. Moreover, serious complications such as meningitis, and potentially life-threatening systemic complications such as fulminant hepatitis, pneumonia, neurological disease and disseminated infection, have been reported.

In the absence of data, most authorities advise that multiples of the standard levels of treatment for first-episode HSV be used in the immunocompromised. Some clinicians advocate a 10-day course of treatment at twice the standard dose of any of the usual agents (1, D).<sup>111</sup>

However, for those living with HIV these may not always be required particularly for those with normal CD4 counts.

In patients living with advanced HIV, double the standard dose of antiviral should be considered and if new lesions continue to form at Days 3–5, a higher dose should be considered. Prompt initiation of therapy is recommended. If new lesions

are still forming after 3–5 days, a repeat viral isolation should be attempted, and susceptibility testing arranged (if possible). The dose of HSV therapy should also be increased.

Recommended initial doses in all people living with HIV<sup>45,78</sup>:

- Aciclovir 400 mg five times daily, for 7–10 days (1, D)
- Valaciclovir 500 mg–1 g twice daily, for 10 days (1, D)
- Famciclovir 250–500 mg three times daily, for 10 days (1, D)

Treatment should be given for at least 10 days or until all lesions have re-epithelialized—this will often exceed the usual 10-day duration of treatment that is given to HIV-negative patients.

If fulminant disease ensues, then intravenous aciclovir be substituted at 5–10 mg/kg body weight every 8 h, for 2–7 days or until clinical improvement and followed by oral antiviral therapy to complete a minimum of 10 days total treatment (1, D).<sup>45</sup>

### Management of recurrent disease in people living with HIV

Both clinical and subclinical reactivations of genital herpes are more frequent in people living with HIV and may lead to persistent and progressive anogenital mucocutaneous lesions, especially with CD4 cell counts <50 per mm<sup>3</sup>. Features can be atypical in nature and larger, deeper and hypertrophic lesions can occur. Optimizing the control of HIV replication with antiretroviral therapy is of fundamental importance for the management of recurrent genital herpes. Antiretroviral therapy will reduce the frequency of clinical recurrences but has less effect upon asymptomatic viral shedding. Thereafter, specific antiviral drugs can be used for either episodic or suppressive treatment. A number of trials of antiviral therapy in the immunocompromised have been reported.<sup>112,113</sup>

### Episodic therapy for HSV in people living with HIV

It is likely that 5 days of therapy will be adequate for most patients. It should be noted that with advanced HIV 13%–17% of patients have been reported to have new lesions developing at the end of a 7-day course of treatment. Shorter courses of therapy may be adequate in those with good CD4 counts (>500 cell/mm<sup>3</sup>); although only one trial with famciclovir has reported this effect (1, A).<sup>64</sup>

Standard doses of antivirals should suffice in those with no evidence of immune failure (1, A). In those living with advanced HIV, it may be necessary to double the standard doses and to continue therapy beyond 5 days (1, A).<sup>45,78</sup> Caution should be exercised in using ultra-short courses of episodic therapy as these have not been evaluated fully in the immunocompromised.



## Suppressive therapy for HSV in people living with HIV

Suppressive antiviral therapy for HSV appears to be less effective in people living with HIV than in HIV-negative people but remains well tolerated. All three agents have been trialled. Standard suppressive doses of aciclovir are effective. Valaciclovir is more effective when given twice daily (500 mg bid) compared to once-daily dosing (1000 mg). The valaciclovir 500 mg once-daily dose has not been evaluated in those living with HIV. Trial data for the efficacy of high-dose famciclovir is only available over much shorter durations.

It is recommended that intermittent cessation of suppressive antiviral therapy for genital herpes should occur, especially in those in whom there is also adequate inhibition of HIV replication and rising CD4 cell counts. In some people living with HIV with less frequent outbreaks of genital herpes, episodic treatment may be substituted. In others, where the pre-treatment pattern of recurrences resumes, suppressive treatment may need to restart (1, D).<sup>45,78</sup>

There is a considerable body of data on the safety of oral antivirals in those living with HIV who are immunocompromised. Two studies in the pre-HAART era looked at high-dose aciclovir (400 mg four times a day) and more recently at standard dose regimens. For valaciclovir, a number of studies looked at the value of valaciclovir for the suppression of recurrent genital herpes. High-dose valaciclovir (2 g four times a day) has been studied and reported in people living with HIV and those immunosuppressed and recovering from bone marrow transplants. Most recently a large number of studies looking at the efficacy of aciclovir and valaciclovir suppression and its impact on HIV transmission from co-infected patients have been reported. These trials indicate that use of oral aciclovir at standard dose and valaciclovir at 1 g once daily and 500 mg twice a day is associated with little or no adverse effect or toxicity as compared with HIV-negative people. High-dose valaciclovir (8 g daily) has been associated with microangiopathic haemolytic uraemic syndrome.

Recommended drug regimens for daily HSV suppressive treatment in people living with HIV<sup>45,114–116</sup>:

- Aciclovir 400 mg orally twice to three times a day;
- Valaciclovir 500 mg orally twice a day.

If these options do not adequately control disease, then the first option should be to double the dose. If control is still not achieved then famciclovir 500 mg orally twice a day can be tried (1, B).

## HSV suppression to limit HIV progression

Suppressive antiviral therapy with aciclovir or valaciclovir has been shown to decrease the levels of HIV viraemia in those patients with detectable HIV viral loads through a mechanism not yet fully elucidated.<sup>117</sup> Such a strategy will impact on HIV progression, particularly for those individuals

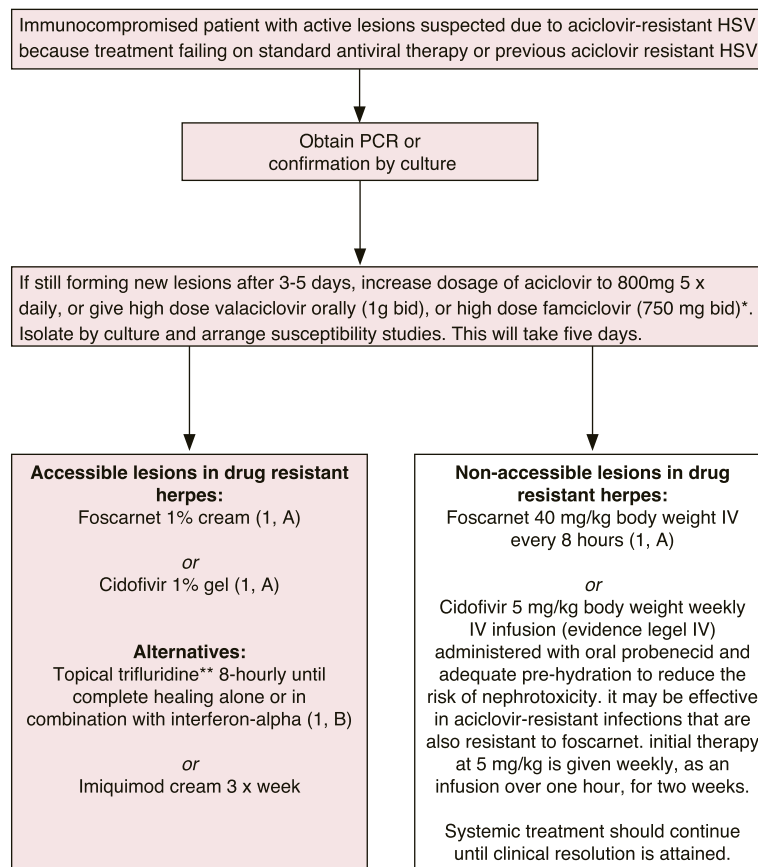
not on antiretroviral therapy. A large RCT in people with early HIV (those individuals not on antiretroviral therapy and with CD4 counts above 250 cells/mm<sup>3</sup>) has shown that standard doses of suppressive antiviral therapy (aciclovir 400 mg twice a day) will sustain CD4 counts above 250 cell/mm<sup>3</sup> and this effect reduced the need for antiretroviral at 2 years by 16% in the treatment group. However, benefits of suppressive antivirals have not been demonstrated in the presence of effective antiretroviral therapy.<sup>103,104</sup> Effective antiretroviral therapy remains the priority for people living with HIV for their own health outcomes and to prevent transmission and therefore HSV antiviral suppression to control HIV is unlikely to be clinically relevant.

## Management of recalcitrant herpes in immunocompromised individuals

Although rare in immunocompetent individuals, clinically refractory lesions due to genital HSV are a major problem in patients with severe immunodeficiency, including late-stage HIV. Algorithms for treatment in such situations are shown in Figure 3. Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug-resistant herpes in those living with HIV.<sup>118</sup> There is evidence for alternating courses of treatment with aciclovir and cidofovir for subsequent recurrences as a strategy that may reduce the development of cidofovir-resistant strains. The efficacy, safety and durability of the therapeutic response of these agents have yet to be determined in prospective controlled trials.

In prospective studies, aciclovir-resistant strains have been found in around 5%–7% isolates from genital herpes lesions in people living with HIV.<sup>48,119,120</sup> Aciclovir resistance is confirmed if isolates require aciclovir concentrations >1–3 mg/L for inhibition. Aciclovir resistance is most commonly related to a mutation in the gene encoding HSV thymidine kinase (TK), which is responsible for initial phosphorylation of aciclovir to its active form, resulting in TK that either has reduced affinity for aciclovir or is not synthesized. TK-deficient strains are of reduced pathogenicity in immunocompetent individuals but may cause serious local and systemic disease in severely immunocompromised individuals.<sup>121,122</sup> They appear less likely to be associated with the development of latency; hence, subsequent clinical reactivations of genital herpes are often caused by aciclovir sensitive isolates. Partially resistant strains may sometimes be successfully treated with high-dose intravenous aciclovir and other nucleoside analogues but fully aciclovir-resistant strains are resistant to valaciclovir and ganciclovir, and the majority are resistant to famciclovir.<sup>121–123</sup> TK-deficient strains are susceptible to foscarnet and cidofovir which do not depend upon TK but which inhibit viral DNA polymerase.

Hypertrophic herpes simplex is an unusual condition often presenting with painful and exophytic tumoral nodules with or without an ulcerated surface located predominantly in the anogenital region. It is often refractory to first-line systemic antiviral agents such as aciclovir (administered orally or intravenously), valaciclovir and



**FIGURE 3** Algorithm for the treatment of herpes in immunocompromised individuals.

famciclovir; a higher frequency of drug-resistant HSV strains has been described. Immunomodulators, such as topical imiquimod, or thalidomide, can be useful in treating this condition.<sup>124-126</sup>

Reports of outcomes in the open access pritelivir programme for immunocompromised people living with refractory lesions has shown great promise for this novel helicase primase inhibitor.<sup>127</sup> Amenamevir (a helicase-primase inhibitor, currently licensed for the treatment of herpes zoster) has also been used for this indication.<sup>128</sup>

Antiviral susceptibility testing for HSV has limited availability and therefore the clinical response to antiviral therapy is often used to guide decisions. Advice from a clinical virologist about appropriate drug dosages and duration may be sought when clinical resistance is suspected.

## Management of pregnant women with genital herpes

### Management of pregnant women with first-episode genital herpes

#### First- and second-trimester acquisitions

Management of the woman should be in line with her clinical condition and will often involve the use of either oral or intravenous aciclovir in standard doses (Figure 4).

Providing that delivery does not ensue, the pregnancy should be managed expectantly, and vaginal delivery anticipated (1, D).

Daily suppressive aciclovir 400 mg three times a day from 36 weeks gestation may prevent HSV lesions at term and hence the need for delivery by caesarean section (1, A).<sup>129-134</sup> In countries where the risk transmission in premature neonates is particularly high, suppressive therapy should be started at an earlier time such as from 32 weeks gestation and from 22 weeks in those identified as being at particularly high risk of premature delivery.

#### Third trimester acquisition (1, D)

Late pregnancy acquisitions are associated with high risks of transmission and morbidity in the neonate. Caesarean section should be considered for all women, particularly those developing symptoms within 6 weeks of delivery, as the risk of viral shedding in labour is very high (1, A).

Daily suppressive aciclovir 400 mg three times a day to delivery should be considered to be continued to term.

If vaginal delivery is unavoidable, prolonged rupture of membranes and invasive procedures, including the use of scalp electrodes, should be avoided. Intrapartum IV aciclovir given to the mother and subsequently to the baby may be considered and the paediatrician should be informed.<sup>135</sup>

Management of pregnant women with first episode genital herpes		Management of pregnant women with recurrent genital herpes	
First and second trimester acquisition	Third trimester acquisition	Management of recurrent HSV in early pregnancy	Management of recurrent HSV in late pregnancy
Standard doses in line with the clinical condition of the pregnant woman	<i>Suppressive</i> Aciclovir 400mg x 3 /day to delivery	<i>Continuous or episodic therapy</i> is not licensed for use in early pregnancy but has not been associated with adverse effects; a decision on its use should be made on a case-by-case basis.	<i>Suppressive</i> Aciclovir 400mg x 3/ day from 36 weeks gestation (earlier if there is any risk of prematurity) in all women with a history of genital herpes
<i>Suppressive:</i> Aciclovir 400mg x 3/day daily from 36 weeks gestation (earlier if risk of premature delivery) to prevent HSV lesions at term (and the need for Caesarean section)	Caesarean section		<i>If pregnant women living with HIV with recurrent HSV infection:</i> Aciclovir 400mg x 3/day from 36 weeks gestation (earlier if there is any risk of prematurity)
			<i>If genital lesions at onset of labour:</i> Caesarean section may be considered

**FIGURE 4** Special situations: management of genital herpes in pregnant women.

## Management of pregnant women with recurrent genital herpes (1, C)

Women with recurrent genital herpes should be informed that the risk of neonatal herpes is low.

### *Management of recurrent HSV in early pregnancy*

Continuous or episodic therapy is not licensed for use in early pregnancy but has not been associated with adverse effects in a large pregnancy registry. A decision on its use should be made on a case-by-case basis. Famciclovir should not be used and the dose of aciclovir titrated down to the minimum effective level.

### *Management of recurrent HSV in late pregnancy*

Symptomatic recurrences of genital herpes during the third trimester will be brief; vaginal delivery is appropriate if no lesions are present at delivery.

For women with a history of recurrent genital herpes, the use of antiviral suppression has been demonstrated to reduce asymptomatic HSV shedding and lesions at term, and may also reduce premature delivery, but have not been studied sufficiently to definitively demonstrate prevention of neonatal HSV disease.<sup>130-139</sup> Daily suppressive aciclovir 400 mg three times a day from 36 weeks gestation should therefore be offered to all women with a history of genital herpes (1, A).<sup>140</sup> This may be started earlier if there is any risk of prematurity such as from 32 weeks gestation and from 22 weeks in those identified as being at particularly high risk of premature delivery; and should be guided by national neonatal HSV epidemiology.

If there are no genital lesions at delivery, there is no indication for a caesarean section to prevent neonatal herpes.

Sequential PCR during late gestation to predict viral shedding at term is not indicated.<sup>141</sup>

The utility of taking PCR at delivery, in order to identify women who are asymptotically shedding HSV, is unproven.

## Management of pregnant women living with HIV with recurrent HSV infection (1, D)

There is some evidence that women living with HIV with genital HSV ulceration in pregnancy are more likely to transmit HIV infection independent of other factors.<sup>28,30</sup> However, this is not a consistent finding across all studies.<sup>30</sup>

Women who are HIV antibody positive and have a history of genital herpes should be offered daily suppressive aciclovir 400 mg three times a day from 32 weeks gestation to reduce the risk of transmission of HIV-1 infection especially in women where a vaginal delivery is planned. Starting therapy at an earlier gestation than usual should be considered in view of the increased possibility of preterm labour and consideration may be given to starting at 22 weeks of gestation in those at particularly high risk of premature delivery (1, D).

There is currently insufficient evidence to recommend daily suppressive treatment for HIV-1 antibody-positive women who are HSV-1 or -2 seropositive but have no history of genital herpes.<sup>139,142</sup>

## Management of women with genital lesions at onset of labour

Caesarean section may be considered for women with recurrent genital herpes lesions at the onset of labour but the risk of neonatal herpes following vaginal delivery is small and must be set against risks to the mother of caesarean section. Evidence from the Netherlands shows that a conservative approach, allowing vaginal delivery in the presence of a recurrent anogenital lesion, was not initially associated with a rise in numbers of neonatal HSV cases (1, C).<sup>143,144</sup> However, this approach can only be adopted if fully supported by obstetricians and neonatologists, and if consistent with the local medico-legal advice.

Clinical diagnosis of genital herpes at the time of labour correlates relatively poorly with HSV detection from genital

sites by PCR and fails to identify women with asymptomatic HSV shedding.

Note: None of the antiviral drugs is licensed for use in pregnancy but the use of aciclovir in pregnancy has not been associated with any consistent pregnancy or foetal/neonatal adverse effects other than transient neutropenia.<sup>143–145</sup> Safety data for aciclovir may be extrapolated to valaciclovir in late pregnancy, as it is the valine ester, but there is less experience with use of valaciclovir.<sup>137</sup> Famciclovir should currently be avoided.<sup>146,147</sup>

## Prevention of acquisition of infection (1, D)

Maternal risk of HSV acquisition in pregnancy varies geographically and local epidemiological surveillance should guide strategy for prevention (Table 2). Any strategy for prevention of neonatal herpes needs to involve both parents.

All women should be asked at their first antenatal visit if they or their partner have had genital or oral herpes.

Female partners of men with genital herpes, but without a personal history of genital herpes should be advised about reducing their risk of acquiring herpes in pregnancy and of subsequent transmission to their baby. Strategies include selective and complete abstinence (especially in the third trimester) and conscientious condom use.

Daily suppressive treatment has been shown to significantly reduce the risk of transmission of HSV to a seronegative partner; however, the effectiveness of suppressive treatment of the male partner to reduce transmission to a pregnant woman has not been evaluated so can currently only be recommended with caveats.

Pregnant women should be advised of the risk of acquiring HSV-1 as a result of receptive orogenital contact especially in the last trimester of pregnancy.

Identifying susceptible women by means of type-specific antibody testing has not been shown to be cost effective and is not indicated in Europe unless the history suggests they may be in a discordant relationship.

All women, not just those with a history of genital herpes, should undergo careful vulval inspection at the onset of labour to look for clinical signs of herpes infection.

Mothers, staff and other relatives/friends with active oral HSV lesions or herpetic whitlow should be advised to avoid direct contact between lesions and the neonate.

**TABLE 2** Strategies to prevent neonatal herpes in the sero-discordant couple.

1	Complete abstinence from 26/40 of the pregnancy
2	Use of condoms for all sex acts irrespective of the absence of symptoms
3	Avoid sex when any symptoms or signs suggestive of genital herpes are present
4	Anti-viral medication for suppression of HSV in the affected non pregnant partner

## Management of the neonate

*Babies born to mothers with first-episode genital herpes at the onset of labour*

The paediatrician should be informed.

HSV PCR from the oropharynx, nose, conjunctiva, rectum and any visible lesions, should be taken to allow early identification of infected babies. HSV PCR should be performed on a blood sample (it may take over 24 h for sufficient HSV replication to occur for a positive result to occur and so a negative test does not exclude infection, may need to be repeated) and a lumbar puncture for CSF should be considered.

The potential benefits and risks of starting intravenous aciclovir without waiting for the results of these tests should be discussed.

If aciclovir is not started immediately the neonate should be closely monitored for signs of lethargy, fever, poor feeding or lesions.

*Babies born to mothers with recurrent genital herpes at the onset of labour*

Although some clinicians feel that taking a set of specimens for viral PCR collected 24–48 h after delivery may help with early identification of infection there is no evidence to support this practice. However, healthcare workers and parents should be advised to consider HSV in the differential diagnosis if the baby shows any signs of infection or develops skin, eye or mucous membrane lesions, particularly in the first 2 weeks of life or features of sepsis in the neonatal period.

## Management of partners

There is no evidence on which to base recommendations for partner notification. On an individual basis, it may be appropriate to offer to see partners to help with the counselling process. Partner notification in relation to pregnancy is discussed below. It is worth considering the following points when counselling partners:

- The use of condoms is advisable especially when transmission concerns are present—even when the index case is on suppressive antiviral treatment.<sup>22</sup>
- Asymptomatic shedding plays a major role in the transmission of HSV infection and selective abstinence (abstinence during the presence of symptoms or signs) is therefore not an effective strategy for managing transmission risk.
- Partner notification is an effective way of detecting uninfected or asymptomatic individuals especially when combined with type-specific antibody testing.
- Up to 50% of asymptomatic HSV-2 seropositive women can be taught to recognize some of their genital herpes recurrences after counselling.<sup>148</sup>
- Virus transmission can be reduced either with suppressive antiviral treatment or by using condoms.

## Aciclovir intolerance

Aciclovir intolerance is rare but is described. Minor allergic reactions to aciclovir or the excipients within tablets are difficult to distinguish but changing between the many generic brands often manages the problem. Urticarial reactions should be investigated and managed as per well-established, dermatological protocols. Neurotoxic reactions are rare and changing between aciclovir and valaciclovir will not be helpful.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.


## ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details. No other ethical approval was required for this study.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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