

Recent advances in management of genital herpes

Isabelle Tétrault, MD Guy Boivin, MD, MSC, FRCPC

abstract

OBJECTIVE To provide an update on new diagnostic tests and antiviral strategies for managing genital herpes.

QUALITY OF EVIDENCE Treatment guidelines are based on randomized clinical trials and recommendations from the Expert Working Group on Canadian Guidelines for Sexually Transmitted Diseases. Recommendations concerning other aspects of managing genital herpes (eg, indications for using type-specific serologic tests) are mainly based on expert opinion.

MAIN MESSAGE Genital herpes is one of the most common sexually transmitted diseases, affecting about 20% of sexually active people; up to 80% of cases are undiagnosed. Because of frequent atypical presentation and the emotional burden associated with genital herpes, clinical diagnosis should be confirmed by viral culture. Type-specific serologic assays are now available, but their use is often restricted to special situations and requires adequate counseling. New antivirals (valacyclovir and famciclovir) with improved pharmacokinetic profiles have now been approved for episodic treatment of recurrences and suppressive therapy.

CONCLUSION Wise use of new diagnostic assays for herpes simplex coupled with more convenient treatment regimens should provide better management of patients with genital herpes.

résumé

OBJECTIF Présenter une mise à jour sur les nouveaux tests diagnostiques et les stratégies antivirales pour la prise en charge de l'herpès génital.

QUALITÉ DES DONNÉES Les lignes directrices concernant le traitement se fondent sur des essais cliniques aléatoires et les recommandations du groupe d'experts sur les lignes directrices canadiennes pour les maladies transmises sexuellement. Les recommandations portant sur d'autres aspects de la prise en charge de l'herpès génital (c.-à-d. les cas où le recours à des épreuves sérologiques spécifiques de type est indiqué) s'appuient principalement sur l'opinion d'experts.

PRINCIPAL MESSAGE L'herpès génital est l'une des plus courantes maladies transmises sexuellement, touchant environ 20% de la population sexuellement active; jusqu'à 80% des cas ne sont pas diagnostiqués. En raison de sa présentation souvent atypique et du fardeau émotionnel associé à l'herpès génital, le diagnostic clinique devrait être confirmé par une culture virale. Des épreuves sérologiques spécifiques de type sont maintenant disponibles, mais leur usage est souvent restreint à des situations spéciales et exige un counseling approprié. De nouveaux agents antiviraux (le valacyclovir et le famciclovir), dont le profil pharmacocinétique a été amélioré, ont maintenant été approuvés pour le traitement des récurrences et la thérapie de suppression.

CONCLUSION Un recours avisé aux nouvelles épreuves diagnostiques pour l'herpès simplex, combiné à des plans thérapeutiques plus pratiques, devrait permettre une meilleure prise en charge des patients souffrant d'herpès génital.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

Can Fam Physician 2000;46:1622-1629.

Genital herpes is a common sexually transmitted disease; its incidence has been greatly underestimated. A recent seroepidemiologic study revealed that the prevalence of herpes simplex virus type 2 (HSV-2) has increased by 30% in the past 15 years (from 16.0% to 20.8%) in Americans 12 years or older.¹

Most HSV-2 infections do not cause the classic vesicular and ulcerative lesions that are recognized as genital herpes. Indeed, an estimated 80% of people with the disease remain undiagnosed.^{1,2} Two reasons explain this unrecognized infection. First, about 20% of infected people have truly asymptomatic infection. Second, about 60% have atypical herpes symptoms not fitting the characteristic description of genital herpes. Although HSV is transmitted more efficiently in the presence of genital lesions, most cases of transmission occur during periods of asymptomatic shedding.

Such subclinical reactivation of HSV-2 has been shown to occur on about 1% to 2% of days (4 to 8 days yearly) in infected people.^{3,4} Known predictive factors for asymptomatic HSV shedding include time since acquisition of infection (shedding being more frequent during the first year),⁵ type of virus (genital shedding is more frequent with type 2),⁴ and annual number of symptomatic recurrences.⁴ Silent spread is now the rule for HSV-2, and this could help explain the current epidemic proportion of genital herpes.

Another important concept is the recent increase in the proportion of new cases due to HSV-1. Data from many clinics in North America and Europe show that 20% to 30% of first episodes of genital herpes are now caused by HSV-1.⁶⁻⁸ Obtaining a type-specific diagnosis is important because HSV-1 genital infections are associated with a lower rate of both symptomatic and asymptomatic recurrences.^{9,10}

Finally, genital herpes is associated with devastating psychological consequences for patients. A survey of more than 3000 subjects with the disease by the American Social Health Association in 1993 revealed that most respondents had feelings of depression (82%), fear of rejection (75%), and isolation (69%) during their first episode.¹¹ In this article, we will review new developments in diagnosis and treatment of genital herpes.

.....
Dr Tétrault is a resident in Medical Microbiology and Infectious Diseases at Laval University in Quebec city, Que. **Dr Boivin** is a specialist in Medical Microbiology and Infectious Diseases at CHUQ pavillon CHUL and is an Assistant Professor of Medical Biology (Microbiology) at Laval University.

Quality of evidence

A great deal of literature describes management of genital herpes. We searched MEDLINE using the terms herpes simplex virus, acyclovir, valacyclovir, famciclovir, and resistance. When necessary, recent data presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy and at other selected meetings as well as recommendations from expert panels were reviewed. Evidence about treatment interventions is based predominantly on placebo-controlled randomized clinical trials. Recommendations on nontreatment aspects of herpes management are based primarily on expert opinion and group consensus.

Diagnosis of genital herpes

Although typical vesicular lesions in the genital area are easily diagnosed as genital herpes (**Figure 1**), these lesions are not the most frequent presentation.

Figure 1



CME

.....

Recent advances in management of genital herpes

Lesions can be atypical or absent, or they can appear at a remote site (buttocks, thighs). Thus, a high index of suspicion is required, and any recurrent lesions following S2 or S3 dermatomes should be considered genital herpes unless proven otherwise. **Table 1** shows differential diagnosis. Many laboratory tests diagnose HSV infections (**Table 2**). Whenever possible, a laboratory test (ie, a viral culture or an antigen detection test) should be requested to confirm initial diagnosis. Such confirmation is particularly needed before starting suppressive therapy and for counseling purposes. As previously discussed, the natural history will also vary according to type of virus.

Actually, a conventional viral culture followed by viral typing is still the diagnostic method of choice. In contrast to other viruses, HSV grows rapidly (within 24 to 48 hours) in many cell lines. To improve the recovery rate of HSV in culture, genital swabs should be obtained from fresh vesicles whenever possible and sent on ice in a viral transportation medium for same-day inoculation. Some rapid antigen detection methods are available, but their sensitivity is generally lower than that of viral culture.

Table 1. **Differential diagnosis of genital ulcerative lesions**

NON-INFECTIOUS DISEASES

Dermatologic conditions (eg, psoriasis)

Crohn's disease

Behçet's and Reiter's syndromes

Erosive and allergic conditions

Malignancies

Idiopathic causes

INFECTIOUS DISEASES

Bacterial: *Treponema pallidum* (syphilis),
Haemophilus ducreyi (chancroid),
Calymmatobacterium granulomatis (granuloma inguinale),
Chlamydia trachomatis (lymphogranuloma venereum),
common bacteria ("pyogenic")

Viral: herpes simplex virus, varicella-zoster virus

Fungal: *Candida* species

Parasites: scabies, pediculosis

At present, molecular methods (such as polymerase chain reaction) are reserved for diagnosing HSV encephalitis where small quantities of the virus are undetectable by culture.^{12,13} Polymerase chain reaction technology is based on the ability of the DNA polymerase enzyme to copy a strand of DNA, resulting in exponential amplification of the target. Use of this test is limited, however, by poor availability of commercial kits. Until recently, most available serologic assays could not differentiate between HSV-1 and HSV-2 past infections. Thus, such assays were of little help in diagnosing genital herpes except in some cases of true primary HSV infections. Type-specific serologic tests have recently become available to clinicians. These include Western blot analysis, which is a relatively complex test offered in only a few reference laboratories throughout North America, and enzyme-linked immunosorbent assay (ELISA test), which is becoming available in many virology laboratories throughout Canada.

Western blot analysis, which is considered the criterion standard, can detect antibodies to multiple viral proteins and can accurately distinguish HSV-2 from HSV-1 antibodies. Type-specific assays, based on detection of a distinct viral protein (glycoprotein G) for HSV-2 and HSV-1, are now available in more practical ELISA assays.

Two of these assays have been evaluated extensively. The Gull EIA assay (Gull Laboratories, Salt Lake City, Utah) is an easy and automated test for detecting HSV-1 and HSV-2 antibodies in a micro-well plate format. When compared with Western blot analysis, sensitivity and specificity values of the test for HSV-1 and HSV-2 antibodies were 95%/96% and 98%/97%, respectively.¹⁴ The Pockit test (Diagnology Ltd, Belfast, UK) is a rapid "point of care" kit designed for physicians' offices. With this kit, only antibodies against glycoprotein G-2 are detected with sensitivity and specificity values of 91.3% and 96.4% when compared with Western blot analysis (personal communication from Diagnology Ltd).

Despite great initial enthusiasm for such assays, many limitations preclude widespread use. First, type-specific serologic assays are more difficult to interpret in areas where HSV-1 genital herpes is more prevalent because type 1 antibodies are also present in people with herpes labialis. Second, a "window" period of many weeks after primary infection precedes production of type-specific IgG antibodies.¹⁴ Last, predictive values of these tests vary considerably according to the prevalence of genital herpes in a specific area or setting (eg, an STD clinic).

Table 2. Laboratory tests for diagnosis of herpes simplex virus infections

TESTS	TISSUE CULTURE	ANTIGEN DETECTION	POLYMERASE CHAIN REACTION	TYPE-SPECIFIC SEROLOGY
Samples	Genital swabs	Genital swabs	Genital swabs or cerebrospinal fluid	Serum
Turn-around time (h)	24-72	<5	<24	<24
Advantages	Viral typing	Rapidity	High sensitivity	Type specific
	Isolation of other viruses	Cost	Criterion standard for HSV encephalitis	Does not require lesions
Disadvantages	Cost	Low sensitivity in atypical cases	Cost	Not available in all centres
	Relatively slow		Contamination	Variable sensitivity and specificity
	Requires humid lesions		No commercial kits	Not useful for HSV-1 genital herpes

At present, type-specific HSV serology might be considered in only a few situations (Table 3).^{15,16} Those assays could be particularly useful in evaluating asymptomatic sexual partners of patients and in cases of suspected recurrent genital herpes where serial HSV cultures are repeatedly negative. Until an effective vaccine is available, widespread screening of asymptomatic patients is not recommended. In summary, two "take-home" messages concern type-specific serologic assays: these tests do not replace viral cultures, and pretest and posttest counseling is as important as the test itself. Such counseling should cover the natural history of the disease and should emphasize asymptomatic excretion, preventive measures to decrease sexual transmission, the risk of neonatal infection, and various therapeutic options.

Table 3. Potential indications for type-specific herpes simplex virus serology

Serologic evaluation of an asymptomatic long-term sexual partner
Recurrent undiagnosed genital ulcers*
Screening of pregnant women with infected partners
Diagnosis of primary or initial nonprimary genital HSV-2 infection*

* Type-specific herpes simplex virus serology does not replace viral culture.

Treatment of genital herpes

When considering treatment options for genital herpes, physicians should take into account the unique effects of both disease and treatment on each patient. Thus, treatment should be individualized and patients should be actively involved in managing their disease. There are basically three possible approaches for managing recurrent genital herpes: episodic therapy, suppressive therapy, and no therapy. Because of the physical and emotional burden associated with this disease, most patients should be offered some type of treatment with periodic reassessment.

The choice of suppressive over episodic therapy will depend on several factors including number of episodes per year, the severity of each episode, and the psychological effect of genital herpes. Again, it is important to emphasize that each approach should be discussed with patients. Three drugs (acyclovir, valacyclovir, and famciclovir) are approved for some or all clinical conditions associated with genital herpes, namely primary infections, episodic treatment of recurrences, and suppressive therapy (Table 4).

While topical application of acyclovir can reduce the duration of viral shedding and the length of time before all lesions become crusted, such treatment is less effective than oral therapy and should be discouraged.¹⁷ Oral acyclovir is an effective and safe agent that has been shown to shorten the clinical course of first-episode genital HSV infection and to prevent most recurrences when taken continually at a dosage of 400 mg twice daily.^{18,19} Although viral shedding is significantly reduced, the duration of symptoms during recurrent episodes is only modestly affected when acyclovir is administered within 24 hours of symptom onset.²⁰ The dose of acyclovir approved for treatment of a recurrent episode is 200 mg by mouth five times daily, which is clearly cumbersome.

CME

.....

Recent advances in management of genital herpes

Table 4. **Treatment regimens for genital herpes:** *There is no role for topical antivirals in genital herpes.*

TREATMENT OF PRIMARY INFECTION

Acyclovir 200 mg 5 times daily for 10 days
Valacyclovir 1000 mg twice daily for 10 days*
Famciclovir 250 mg three times daily for 5 to 10 days*

EPISODIC TREATMENT OF RECURRENCES

Acyclovir 200 mg 5 times daily for 5 days
Valacyclovir 500 mg twice daily for 5 days
Famciclovir 125 mg twice daily for 5 days

SUPPRESSIVE TREATMENT

Acyclovir 400 mg twice daily
Valacyclovir 500 mg daily†
Famciclovir 250 mg twice daily

* Not approved for this indication in Canada.

† For subjects with 10 or more recurrences yearly, dosage should be 1000 mg daily or 250 mg twice daily.

New treatments. Two new antiviral agents with improved pharmacokinetics over acyclovir have been recently approved for genital herpes. Valacyclovir is an ester prodrug of acyclovir with an oral bioavailability of 54% (ie, three to five times that of acyclovir). Moreover, the area under the curve of a 1000-mg oral dose of valacyclovir is similar to a 350-mg intravenous dose of acyclovir.²¹ The safety profile of valacyclovir appears comparable to that of acyclovir when administered for up to 1 year. A thrombotic microangiopathy (TMA) syndrome has been reported in up to 3% of immunocompromised patients receiving high doses (8 g/d) of valacyclovir for prevention of cytomegalovirus infection.²² Although the association of valacyclovir and TMA is still unclear, no immunocompetent or immunocompromised patients receiving up to 3 g/d of this drug have developed TMA.

In Canada, valacyclovir is approved for episodic treatment of recurrent episodes and for suppressive therapy (**Table 4**). Compared with placebo, a dose of 500 mg twice daily for 5 days was shown to decrease time to resolution of signs and symptoms by a median of 2 days when treatment was initiated within 24 hours.²³ Valacyclovir also prevented development of vesicular and ulcerative lesions when treatment was initiated early, at the prodromal or papular stage in 31% of patients (vs 21% for the placebo group).

Another study of patients with recurrent genital herpes showed no statistical difference between valacyclovir (500 mg twice daily) and acyclovir (200 mg five times daily) for all efficacy parameters.²⁴ Valacyclovir has also been evaluated for suppression of genital herpes in two clinical trials.^{25,26} Results from these studies showed that a 500-mg, once-daily dose of valacyclovir is equivalent to acyclovir (400 mg twice daily) for subjects with less than 10 recurrences per year. Such a dosage results in a 71% reduction in the recurrence rate of herpetic episodes versus 78% for acyclovir. For subjects with 10 or more episodes per year, valacyclovir at a dose of 1000 mg daily or 250 mg twice daily provides optimal efficacy.²⁶ Although not yet approved for this indication in Canada, valacyclovir (1000 mg twice daily for 10 days) is as effective as acyclovir (200 mg five times daily for 10 days) for treating first-episode genital herpes.²⁷

Famciclovir is the diacetyl-6-deoxy derivative and oral prodrug of penciclovir. Similar to acyclovir, famciclovir is a nucleoside analogue that requires initial phosphorylation by the viral thymidine kinase. The in vitro activity of acyclovir and penciclovir on HSV-1 and HSV-2 strains is comparable. Famciclovir is very well absorbed (bioavailability of 77%) and provides high penciclovir levels.²⁸

Famciclovir is currently approved in Canada for treating recurrences and for suppressive therapy (**Table 4**). In a multidosage, randomized trial comparing famciclovir with placebo in subjects with recurrent genital herpes, famciclovir recipients had significant reduction in healing time, duration of all symptoms, and duration of viral shedding.²⁹ In addition, the lower dosage of famciclovir (125 mg twice daily for 5 days) was shown to be as effective as higher doses. For suppressive therapy, 250 mg twice daily provided the best results (78% free of recurrences at 4 months) compared with daily regimens (125, 250, and 500 mg) and with placebo (42% free of recurrences at 4 months).³⁰ Although not yet approved for this indication in Canada, the recommended famciclovir dose for treatment of initial episodes is 250 mg three times daily for 5 to 10 days.³¹

The improved pharmacokinetic properties and at least comparable efficacy of valacyclovir and famciclovir when compared with acyclovir means that the former two have now become the drugs of choice for treating genital herpes except perhaps in the context of pregnancy, where more safety data are needed with the new molecules. At present, no randomized trials have compared valacyclovir and famciclovir directly. For a more comprehensive review, consult Health Canada's sexually transmitted diseases guidelines.¹⁶

Additional points. Two additional points concerning antiviral therapy of genital herpes are important. First, the question of preventing sexual transmission by using antiviral suppression remains unanswered. Continued administration of acyclovir has been shown to suppress most viral shedding (94% decrease in culture positivity compared with placebo), but HSV DNA as assessed by polymerase chain reaction was reduced by only 75% to 80%.^{32,33} Whether or not detection of viral DNA by polymerase chain reaction means that infectious virus is transmissible to sexual partners is unknown. The ability of most recent drugs (ie, valacyclovir and famciclovir) to suppress the risk of viral transmission is being evaluated. Another point to consider when using antivirals for prolonged periods (suppressive therapy or repetitive courses of episodic treatment) is the potential for emergence of drug-resistant viral mutants. In immunocompetent subjects, the rate of acyclovir resistance in HSV isolates recovered after years of suppressive therapy compares favourably with the rate in pretherapy strains (prevalence of resistance of 0.5% and 0.3%, respectively).^{34,35} Further, with the exception of two cases,^{36,37} the occasional detection of acyclovir-resistant HSV isolates has not been associated with clinical failure in this setting. Acyclovir resistance in HSV strains recovered from treated immunocompromised subjects is high and has been roughly estimated to be 5% to 10%.³⁸⁻⁴⁰ In this setting, in vitro resistance correlates well with development of chronic HSV lesions.⁴¹⁻⁴³

In conclusion, new diagnostic tools (ie, type-specific HSV serology and polymerase chain reaction) are now available at many centres, but their place in managing genital herpes still requires careful evaluation. In addition, new antivirals with more convenient dosages have now replaced acyclovir as the drug of choice for treatment and suppression of genital herpes. Despite these advances, counseling remains key to optimal management. ❖

Correspondence to: Dr Guy Boivin, CHUQ, pavillon CHUL, RC-709, 2705 blvd Laurier, Sainte-Foy, QC G1V 4G2; telephone (418) 654-2705; fax (418) 654-2715; e-mail Guy.Boivin@crchul.ulaval.ca

References

1. Fleming DT, McQuillan GM, Johnson RE, Nahmias AJ, Aral SO, Lee FK, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* 1997;337:1105-11.
2. Corey L. The current trend in genital herpes. Progress in prevention. *Sex Transm Dis* 1994;21(Suppl):38-44.

Key points

- Genital herpes is a common sexually transmitted disease, affecting about 20% of sexually active people; up to 80% of cases are undiagnosed.
- Given atypical presentation and the emotional burden associated with genital herpes, clinical diagnosis should be confirmed by viral culture.
- Type-specific tests are available in some centres but are useful only in specific situations. Pretest and posttest counseling is as important as the test itself.
- Two new antivirals, valacyclovir and famciclovir, are available with improved pharmacokinetics and simpler dosing schedules.

Points de repère

- L'herpès génital est une maladie transmise sexuellement plutôt courante, touchant environ 20% de la population sexuellement active; 80% des cas ne sont pas diagnostiqués.
- Compte tenu de sa présentation atypique et du fardeau émotionnel associé à l'herpès génital, le diagnostic clinique devrait être confirmé par une culture virale.
- Des épreuves spécifiques de type sont disponibles dans certains centres, mais ne sont utiles que dans des situations précises. Le counseling préalable et ultérieur à l'épreuve revêt autant d'importance que le test lui-même.
- Deux nouveaux agents antiviraux, le valacyclovir et le famciclovir, sont disponibles et comportent un profil pharmacocinétique amélioré et une posologie plus simple.

3. Brock BV, Selke S, Benedetti J, Douglas JM Jr, Corey L. Frequency of asymptomatic shedding of herpes simplex virus in women with genital herpes. *JAMA* 1990;263:418-20.
4. Wald A, Zeh J, Selke S, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infection. *N Engl J Med* 1995;333:770-5.
5. Koelle DM, Benedetti J, Langenberg A, Corey L. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992;116:433-7.
6. Nahmias AJ, Lee FK, Beckman-Nahmias S. Sero-epidemiological patterns of herpes simplex virus infection in the world. *Scand J Infect Dis Suppl* 1990;69(Suppl):19-36.
7. Woolley PD, Kudesia G. Incidence of herpes simplex virus type-1 and type-2 from patients with primary (first attack) genital herpes in Sheffield. *Int J STD AIDS* 1990;1:184-6.
8. Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* 2000;181:1454-7.

CME

.....

Recent advances in management of genital herpes

9. Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. *N Engl J Med* 1987;316:1444-9.
10. Reeves WC, Corey L, Adams HG, Vontver LA, Holmes KK. Risk of recurrence after first episodes of genital herpes. Relation to HSV type and antibody response. *N Engl J Med* 1981;305:315-9.
11. Catotti DN, Clarke P, Catoe KE. Herpes revisited. Still a cause of concern. *Sex Transm Dis* 1993;20:77-80.
12. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. *J Infect Dis* 1995;171:857-63.
13. Rowley AH, Whitley RJ, Lakeman FD, Wolinsky SM. Rapid detection of herpes simplex virus DNA in cerebrospinal fluid of patients with herpes simplex encephalitis. *Lancet* 1990;335:440-1.
14. Ashley RL, Wu L, Pickering JW, Tu MC, Schnorenberg L. Premarket evaluation of a commercial glycoprotein G-based enzyme immunoassay for herpes simplex virus type-specific antibodies. *J Clin Microbiol* 1998;36:294-5.
15. Munday PE, Vuddamalay J, Slomka MJ, Brown DWG. Role of type specific herpes simplex virus serology in the diagnosis and management of genital herpes. *Sex Transm Inf* 1998;74:175-8.
16. Health Canada. *Canadian STD guidelines*. Ottawa, Ont: Laboratory Centre for Disease Control (Canada); 1998. p. 160-6.
17. Corey L, Nahmias AJ, Guinan ME, Benedetti JK, Critchlow CW, Holmes KK. A trial of topical acyclovir in genital herpes simplex virus infections. *N Engl J Med* 1982;306:1313-9.
18. Mertz GJ, Critchlow CW, Benedetti J, Reichman RC, Dolin R, Connor J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA* 1984;252:1147-51.
19. Straus SE, Takiff HE, Seidlin M, Bachrach S, Lininger L, DiGiovanna JJ, et al. Suppression of frequently recurring genital herpes. A placebo-controlled double-blind trial of oral acyclovir. *N Engl J Med* 1984;310:1545-50.
20. Reichman RC, Badger GJ, Mertz GJ, Corey L, Richman DD, Connor JD, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir. A controlled trial. *JAMA* 1984;251:2103-7.
21. Soul-Lawton J, Seaber E, On N, Wootton R, Rolan P, Posner J. Absolute bioavailability and metabolic disposition of valaciclovir, the L-valyl ester of acyclovir, following oral administration to humans. *Antimicrob Agents Chemother* 1995;39:2759-64.
22. Feinberg JE, Hurwitz S, Cooper D, Sattler FR, MacGregor RR, Powderly W, et al. A randomized, double-blind trial of valaciclovir prophylaxis for cytomegalovirus disease in patients with advanced human immunodeficiency virus infection. *J Infect Dis* 1998;177:48-56.
23. Spruance SL, Tyring SK, DeGregorio B, Miller C, Beutner K. A large-scale, placebo-controlled, dose-ranging trial of peroral valaciclovir for episodic treatment of recurrent herpes genitalis. *Arch Intern Med* 1996;156:1729-35.
24. Bodsworth NJ, Crooks RJ, Borelli S, Vejlsgaard G, Paavonen J, Worm AM, et al. Valaciclovir versus acyclovir in patient-initiated treatment of recurrent genital herpes: a randomised, double-blind clinical trial. *Genitourin Med* 1997;73:110-6.
25. Patel R, Bodsworth NJ, Woolley P, Peters B, Vejlsgaard G, Saari S, et al. Valaciclovir for the suppression of recurrent genital HSV infection: a placebo controlled study of once daily therapy. *Genitourin Med* 1997;73:105-9.
26. Reitano M, Tyring S, Lang W, Thoming C, Worm AM, Borelli S, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. *J Infect Dis* 1998;178:603-10.
27. Fife KH, Barbarash RA, Rudolph T, Degregorio B, Roth R. Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection. Results of an international, multicenter, double-blind, randomized clinical trial. *Sex Transm Dis* 1997;24:481-6.
28. Perry CM, Wagstaff AJ. Famciclovir: a review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs* 1996;50:396-415.
29. Sacks SL, Aoki FY, Diaz-Mitoma F, Sellors J, Shafran SD. Patient-initiated, twice-daily oral famciclovir for early recurrent genital herpes. A randomized, double-blind multicenter trial. *JAMA* 1996;276:44-9.
30. Mertz GJ, Loveless MO, Levin MJ, Kraus SJ, Fowler SL, Goade D, et al. Oral famciclovir for suppression of recurrent genital herpes simplex virus infection in women. A multicenter, double-blind, placebo-controlled trial. *Arch Intern Med* 1997;157:343-9.
31. Loveless M, Harris W, Sacks S. Treatment of first episode genital herpes with famciclovir. In: *Program and abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy*; 1995 Sept 17-20; San Francisco, Calif. Washington, DC: American Society for Microbiology; 1995. Abstract no. 12.
32. Wald A, Zeh J, Barnum G, Davis LG, Corey L. Suppression of subclinical shedding of herpes simplex virus type 2 with acyclovir. *Ann Intern Med* 1996;124:8-15.
33. Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. Frequent genital HSV-2 shedding in immunocompetent women. *J Clin Invest* 1997;99:1092-7.
34. Collins P, Ellis MN. Sensitivity monitoring of clinical isolates of herpes simplex virus to acyclovir. *J Med Virol* 1993;41(Suppl 1):58-66.
35. Fife KH, Crumpacker CS, Mertz GJ, Hill EL, Boone GS. Recurrence and resistance patterns of herpes simplex virus following cessation of > or = 6 years of chronic suppression with acyclovir. *J Infect Dis* 1994;169:1338-41.
36. Kost RG, Hill EL, Tigges M, Straus SE. Brief report: recurrent acyclovir-resistant genital herpes in an immunocompetent patient. *N Engl J Med* 1993;329:1777-82.

CME

.....

37. Swetter SM, Hill EL, Kern ER, Koelle DM, Posavard CM, Lawrence W, et al. Chronic vulvar ulceration in an immunocompetent woman due to acyclovir-resistant, thymidine kinase-deficient herpes simplex virus. *J Infect Dis* 1998;177:543-50.
38. Englund JA, Zimmerman ME, Swierkosz EM, Goodman JL, Scholl DR, Balfour HH. Herpes simplex virus resistant to acyclovir: a study in a tertiary care center. *Ann Intern Med* 1990;112:416-22.
39. Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, Meyers JD. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med* 1982;96:265-9.
40. Christophers J, Clayton J, Craske J, Ward R, Collins P, Trowbridge M, et al. Survey of resistance of herpes simplex virus to acyclovir in northwest England. *Antimicrob Agents Chemother* 1998;42:868-72.
41. Safrin S, Elbeik T, Phan L, Robinson D, Rush J, Elbaggari A, et al. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 1994;38:1246-50.
42. Erlich KE, Mills J, Chatis P, Mertz GJ, Busch DF, Follansbee SE, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989;320:293-6.
43. Gaudreau A, Hill E, Balfour HH, Erice A, Boivin G. Phenotypic and genotypic characterization of acyclovir-resistant herpes simplex viruses from immunocompromised patients. *J Infect Dis* 1998;178:297-303.

...