

Contemporary antiviral drug regimens for the prevention and treatment of orolabial and anogenital herpes simplex virus infection in the normal host: Four approved indications and 13 off-label uses

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Herpes simplex virus (HSV) orolabial and anogenital infection causes substantial and recurring disease in healthy individuals due directly to infection of these sites and, indirectly, due to its complications. These complications include eczema herpeticum plus erythema multiforme and neonatal HSV infection, respectively. Four drugs: acyclovir, famciclovir, valacyclovir and penciclovir, are currently licensed by the Therapeutics Products Directorate of Health Canada for the management of HSV infections. Although these drugs are only approved for four orolabial and anogenital infections in healthy persons, their efficacy and safety for 13 other related uses in this population have been demonstrated in controlled clinical trials, so called off-label uses. In this review, the evidence supporting these 17 uses, the drugs and regimens evaluated, and their current costs, are described.

Key Words: *Antiviral therapy; Herpes simplex virus infection; Prophylaxis*

The pharmacological therapy of oral and genital herpes simplex virus (HSV) infection in the immunocompetent host has been dominated by acyclovir (ACV). The introduction of valacyclovir (VCV) oral caplets and famciclovir (FCV) tablets provides clinicians with the option of treating ACV-responsive HSV infection with more convenient dosing regimens. The marketing of penciclovir (PCV) cream will provide patients with an effective treatment for recurrent herpes labialis. Recently reported clinical trials have reinforced our knowledge about appropriate antiviral drug treatments for these infections, while other trials have identified noteworthy off-label uses, which is to say, uses demonstrated in controlled clinical trials for which formal approval has not been sought from or granted by the Therapeutic Products Directorate (TPD) of Health Canada. However, in spite of the numerous controlled trials reported, there is a general paucity of studies directly comparing the relative merits of the available drugs. This has left the physician with little evidence to use to select among the available agents, ACV and PCV, and their respective oral prodrugs, VCV and FCV.

Posologies actuelles de médicaments antiviraux pour la prévention et le traitement d'infections bucco-labiales et ano-génitales au virus de l'herpès simplex chez des hôtes normaux : quatre indications approuvées et treize utilisations non indiquées sur l'étiquette

RÉSUMÉ : Les infections bucco-labiales et ano-génitales au virus de l'herpès simplex (HSV) sont cause directe, par les foyers eux-mêmes, et indirecte, par leurs complications, d'affections sérieuses et récurrentes chez des personnes en bonne santé. Parmi les complications figurent l'eczéma herpétiforme, l'érythème polymorphe et les infections du nouveau-né au HSV. La Direction des produits thérapeutiques de Santé Canada a autorisé l'utilisation de quatre médicaments, soit l'acyclovir, le famciclovir, le valacyclovir et le penciclovir, pour le traitement des infections au HSV. Même si leur emploi n'a été approuvé que pour quatre types d'infection, bucco-labiale et ano-génitale, chez des personnes en bonne santé, leur efficacité et leur innocuité pour 13 autres utilisations connexes dans la même population ont été démontrées dans des essais cliniques comparatifs; c'est ce qu'on appelle les utilisations non indiquées sur l'étiquette. Le présent article de synthèse expose les données à l'appui des 17 utilisations en question, les médicaments évalués et leurs posologies ainsi que les coûts actuels.

Table 1 lists the four indications for which these drugs have been approved by the TPD and the 13 off-label uses, which have been proved in one or more placebo controlled clinical trials.

The data pertaining to these uses follow.

APPLIED CLINICAL PHARMACOKINETICS AND MOLECULAR PHARMACOLOGY

Selected aspects of the clinical and molecular pharmacology of the antiviral drugs have therapeutic implications. First, the enhanced oral bioavailability of PCV and ACV from their respective prodrugs, FCV and VCV, has made it possible to achieve therapeutic results comparable with those obtained with two to five times a day oral ACV using once daily to thrice daily schedules. The absolute bioavailability of ACV from ACV and VCV tablets and PCV from FCV tablets averages 15% to 30% (1), 55% (2) and 77% (3), respectively. Incomplete ACV absorption from the upper intestine is due in part to a saturable process (4). The percentage of drug absorbed

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TABLE 1
Therapeutic Products Directorate (TPD) of Health Canada approved and off-label indications for oral and topical antiherpes drugs in Canada, 2002

Indication	Drugs and formulation
Approved indications	
Cold sores – therapy	Penciclovir cream
Genital herpes – therapy	
First episode	Acyclovir tablets, cream and ointment, injectable
Recurrent	
Episode therapy	Acyclovir, famciclovir and valacyclovir tablets
Suppressive therapy: adults, nonpregnant	Acyclovir, famciclovir and valacyclovir tablets
Off-label indications*	
Orolabial herpes	
Gingivostomatitis	
Therapy	Acyclovir suspension
Prophylaxis in children in daycare	Acyclovir tablets
Recurrent cold sores	
Episode therapy	Acyclovir tablets, cream and ointment
Suppressive therapy	Acyclovir tablets and cream, valacyclovir tablets
Prophylaxis	
After trigeminal nerve surgery	Acyclovir tablets
During sun exposure	Acyclovir cream, tablets
Recurrent erythema multiforme prevention	Acyclovir tablets
Eczema herpeticum – therapy	Acyclovir tablets
Genital herpes – therapy	
First episode	Valacyclovir and famciclovir tablets
Recurrent	
Short course therapy of 2 to 3 days	Acyclovir and valacyclovir, respectively
Suppressive therapy	
Recurrent disease in pregnant women	Acyclovir tablets
Asymptomatic shedding in nonpregnant women	Acyclovir tablets
Herpes proctitis – therapy	Acyclovir tablets

*Off-label use proved in one or more controlled clinical trials

declined from 20% from a 200 mg tablet (1) to 12% from an 800 mg tablet (2). VCV is better absorbed than ACV due to an active stereoselective transporter in the intestinal brush border membrane (5). The extent of absorption averages 55% and is independent of dose. After absorption, VCV undergoes hydrolysis during first-pass through the liver so that only ACV appears in the systemic circulation (6). A mean of 77% of PCV is bioavailable from oral FCV doses ranging from 125 mg to 750 mg. After absorption, FCV is extensively metabolized by oxidation and deacetylation in intestinal epithelial cells and hepatocytes to PCV (7). Food does not affect the oral bioavailability of ACV, VCV or FCV.

The second point of clinical relevance concerning the pharmacology of ACV and PCV relates to their intracellular processing as prodrugs. They are nucleoside analogues without antiviral activity until they are converted to nucleotide-triphosphate moieties within HSV-infected cells. The initial and critical step is effected through conversion to the nucleotide-monophosphate form by the virus-encoded enzyme, thymidine kinase (TK) (8,9). This initial phosphorylation step prevents diffusion out of the cell, resulting in the accumulation of nucleotides in HSV-infected cells. This has the dual effect of increasing the drug concentration in cells where it is required and minimizing the drug concentration and, hence, the potential risk of adverse effects in other uninfected cells.

Genomic mutation resulting in the loss of TK activity (TK⁻) is associated with the emergence of ACV-resistance and is the commonest mechanism for the loss of susceptibility (10). Not unexpectedly, such ACV-resistant HSV mutants are cross-resistant to PCV. Fortunately, the emergence of ACV-resistant mutants has been almost completely limited to situations in which ACV is administered for prolonged periods to immunocompromised hosts, such as those with HIV infection (11). Recently, case reports of the development of clinically aggressive ACV-resistant infection due to TK⁻ strains (12) have raised concerns about the possibility that new HSV infections in normal hosts in the future will be caused by ACV- (and PCV-) resistant strains of HSV with attendant treatment failure.

Effective, safe treatments have now been described for initial and recurrent orolabial and anogenital HSV infection in immunocompetent individuals and some of their complications. We review herewith TPD approved indications for treatment of these infections as well as off-label uses that have been demonstrated in controlled clinical trials.

OROLABIAL HSV

Primary gingivostomatitis

Therapy: No antiviral drugs are licensed for the prevention or treatment of primary HSV gingivostomatitis in healthy children. However, gingivostomatitis of mild to moderate severity

that does not preclude oral intake can be effectively and safely treated with oral ACV suspension. In two placebo controlled randomized trials, ACV treatment (15 mg/kg five times per day for seven days [13] or 600 mg/m² four times daily for 10 days [14]) accelerated the resolution of orolabial symptoms and signs by 50% to 80%, fever by 65% (13) and viral shedding from a median duration of five days to one day (13) or 10 days to four days (14). Tolerance measured by the incidence of adverse effects was good in both studies, as was adherence. Safety reflected in an absence of changes in blood chemistry and hematological parameters was not different between ACV and placebo recipients (14), nor was the recurrence rate to one year of follow-up (14). Further studies are required to define the optimal dose and duration of therapy for such children as well as an approach for treating children with severe disease that precludes swallowing. Until such time, clinicians, nevertheless, can prescribe these oral regimens for most paediatric patients; for children with severe disease precluding oral therapy, intravenous ACV would appear to be a logical recommendation, but such a strategy has not been validated in a controlled trial.

Prophylaxis: An outbreak of primary HSV gingivostomatitis in young children in a day-care nursery has been successfully prevented by oral ACV prophylaxis. When the first case was diagnosed, prophylaxis of 53 unaffected children with crushed oral ACV tablets 30 to 60 mg/kg daily in three to five doses for seven days was completely effective in preventing gingivostomatitis. Disease developed in 82% of 22 untreated control children (15). ACV suspension (*vide supra*) could probably replace the crushed tablets used in this study, although the oral bioavailability of ACV from suspension appears to be lower than that from tablets (16).

Recurrent orolabial infection

Recurrent orolabial HSV infection (cold sores) can be managed by treating each recurrence (episode therapy) or by preventing recurrent disease by the continuous ingestion of drugs (suppressive therapy).

Episode therapy: Treatment of recurrent cold sores with topical 5% ACV in a polyethylene glycol ointment base initiated during the prodromal phase (17) or within 8 h of the first symptoms or sign of a recurrence yielded limited and inconsistent therapeutic effects (18). On the other hand, treatment with 5% ACV in a polypropylene glycol cream formulation produced a modest but statistically significant reduction in healing time, albeit without reductions in pain and/or itching (19). The improvement was ascribed to better penetration of ACV from the cream than the ointment formulation into the basal layers of the epidermis where HSV replication is occurring.

Initiating treatment even earlier with oral ACV and, most recently, topical PCV has yielded better results. Initiation of therapy within 1 h of the first symptom or sign of recurrent herpes labialis with oral ACV 400 mg five times per day for five days alleviated some manifestations of the infection (20). In the subgroup of subjects who initiated treatment in the prodromal or erythema stage, median pain duration was reduced by 34% (from 2.9 days to 1.9 days) and median healing time by 26% (from 8.0 days to 5.9 days). No benefit was observed in individuals whose cold sores were in the papular or vesicular stage at the time of initiation of treatment. Mean duration of

HSV shedding in the 31% of volunteers who were virus culture-positive was not different between the groups. Recently, the same therapeutic strategy was used in two large controlled trials (total subjects 3057) comparing the therapeutic efficacy and safety of 1% topical PCV cream (n=1516) and its vehicle (n=1540) as placebo (21). PCV or placebo cream was applied within 1 h of the onset of symptoms or signs of a cold sore and for six times the first day and every 2 h while awake for a further three days (total four days). Uniform and consistent significant subjective and objective therapeutic effects were observed in subjects with both early (prodrome or erythema stage lesions) or later stage lesions (papule or vesicular cold sore). Median time to loss of pain, time to healing and duration of HSV shedding was reduced in the combined studies by 22% to 35% in the PCV recipients. PCV-treated patients in the early lesion subgroup ceased shedding virus faster than the placebo recipients, but no difference was observed between treatment groups who had late stage lesions at the time of treatment initiation. Both oral ACV and topical PCV were well tolerated compared with the corresponding placebo. To achieve these therapeutic effects, it is apparent that patients need to literally carry their medication with them in order to initiate treatment within 1 h of the appearance of symptoms or signs of a cold sore. Delaying the start of oral ACV therapy for 8 h has yielded inconsistent results; the impact of a delay from 2 to 7 h has not been reported. Topical 1% PCV cream has been approved by the TPD for cold sore treatment but is not yet marketed for this use. There have not been any reports of the comparative benefits of topical PCV versus an oral anti-herpes drug.

Suppressive therapy: An alternative to early treatment of recurrent herpes labialis is the prevention of the development of cold sores by suppressive oral ACV or oral VCV used off-label. In a double-blind, randomized crossover study, otherwise healthy adults with a history of six or more episodes of cold sores per year were treated with oral ACV 400 mg twice daily or placebo for four months (22). ACV reduced clinically- and virologically-confirmed recurrences by 53% and 71%, respectively, compared with placebo therapy. A comparable result with a 77% reduction in clinically diagnosed recurrences was observed during suppression with oral ACV 200 mg four times daily in a double-blind crossover trial (23). Oral VCV 500 mg once daily for four months increased the time to the first recurrence of cold sores from an average of 10.6 weeks in placebo recipients to 16.7 weeks (P=0.005) (24). VCV tended to reduce the number of recurrences from 70% to 35% (P=0.056). It was well tolerated compared with placebo. The data suggest that VCV 500 mg once daily suppresses recurrent cold sores in healthy adults (24). Collectively, these results suggest that oral ACV and VCV are efficacious for prophylaxis of recurrent herpes labialis.

Prevention of cold sores after trigeminal nerve surgery or during sun exposure: Prophylactic oral ACV is effective for at least two other off-label indications. In otherwise healthy adults undergoing elective surgery for trigeminal neuralgia, recurrent herpes labialis is observed in 38% to 94% of patients postoperatively. Oral ACV 400 mg twice daily started on the evening before surgery and continued for a total of five days reduced the incidence of cold sore from 81% in placebo recipients to 21% (a 74% reduction) (25). In adults with a history

of sun-induced herpes labialis, oral ACV 400 mg twice daily begun 12 h before sun exposure combined with frequent sunscreen use reduced the incidence of cold sore by 74% compared with placebo therapy during seven days of treatment (26). Using a similar short term prophylaxis approach with topical ACV, Raborn et al (27) reported that ACV 5% cream applied 2 h before sun exposure in adult skiers and five times during the day for seven days reduced the frequency of cold sore from 43% in placebo recipients to 23% in ACV recipients, a 47% reduction. In a longer, 16-week, double-blind, crossover trial, adults with herpes labialis recurring six or more times per year were treated with 5% ACV cream or placebo (28). Cream was applied four times daily to any area previously affected by cold sores as well as any area where prodromal symptoms of recurrent herpes labialis developed during the study. Doctor-diagnosed cold sores were significantly reduced from a mean of 1.1 per subject during 16 weeks of placebo treatment to 0.5 during ACV therapy, a 45% reduction. The mean number of days when cold sores were present was significantly reduced by 24%, from 12.4 to 9.5 in the two groups, respectively.

Eczema herpeticum therapy: HSV infection of eczematous skin, often of the facial area, can complicate orolabial herpes infection and cause extensive local disease. Oral ACV was nearly twice as effective as placebo for the treatment of eczema herpeticum (29). In a double-blind, placebo controlled trial, 32 patients were treated with ACV 200 mg tablets or placebo tablets (n=28), both five times per day for five days. A significantly higher percentage of ACV recipients improved, beginning at day four (81%), compared with placebo recipients (43%). No differences in adverse symptoms were reported.

Prevention of recurrent erythema multiforme: Another off-label indication for oral ACV is the prevention of recurrent erythema multiforme (REM). REM is reported to be preceded by recurrent herpes labialis in up to 71% of cases (30). Uncontrolled observations suggested that oral ACV therapy with 200 mg five times per day for five days initiated at the first sign of cold sore or REM was effective in only 11% of cases, which may not be different from a placebo effect (30). However, suppressive oral ACV is effective in preventing REM, whereas early treatment of recurrent cold sore or REM does not appear to be effective (30). Oral ACV 400 mg twice daily during 26 weeks of prophylaxis reduced REM by 86%, from 3.7 to 0.5 in placebo recipients ($P=0.0004$) (31). This paralleled the reduction in recurrent herpes labialis of 71%, from 2.1 to 0.9. When ACV prophylaxis failed, REM was as severe in ACV-treated subjects as in placebo-treated subjects.

GENITAL HERPES

The pharmacological therapy of genital herpes (GH) produces beneficial effects ranging from modest to dramatic.

First-episode genital infection

Severe primary GH infection, whether due to HSV type-1 (HSV-1) or HSV type-2 (HSV-2), is characterized by extensive genital lesions, systemic symptoms, complications and a protracted course that can last for 35 days (32). Nonprimary first GH infections are generally less severe. Both types of initial genital infection are markedly benefited by antiviral therapy.

Topical, intravenous and oral ACV have all been shown to be efficacious and safe compared with the corresponding placebo formulation for treatment of first episodes of GH in the immunocompetent host and all are approved for this indication in Canada. Although no direct comparisons of the three ACV formulations have been conducted, an analysis of results from placebo controlled ACV treatment trials limited to patients with primary GH, by Corey et al (33), strongly suggests that systemic therapy with oral or intravenous ACV produces more marked clinical and antiviral effects than does topical ACV. Practical considerations have resulted in the preference for oral ACV as the treatment of choice for most immunocompetent individuals with first-episode GH. The approved dose is 200 mg five times per day for five to 10 days as demonstrated by Mertz et al (34). A higher dose of oral ACV, 800 mg five times per day, yielded no greater benefit than the recommended dose and tended to cause more adverse gastrointestinal symptoms than the lower dose (35). Treatment is effective when initiated up to seven days after the onset of lesions, in part because of the protracted course of more severe infections. The addition of topical 5% ACV therapy to oral ACV treatment did not yield better results than oral ACV alone (36). For patients unable to take oral ACV, therapy may be started with intravenous treatment of 5 mg/kg infused over 60 min every 8 h and then converted to oral therapy when practicable.

Recently, the efficacy and safety of FCV and VCV compared with oral ACV 200 mg five times per day in immunocompetent adults with first-episode GH has been reported. Results of therapy with FCV 125 mg to 750 mg thrice daily have been described (37,38). In one study, subjects with primary and nonprimary first-episode GH of five days duration or less were randomized to therapy with FCV 750 mg thrice daily (n=38) or oral ACV 200 mg five times per day (n=39) for five days (37). In the other report, data from three trials were combined and overall results described (38). Two of the trials compared FCV 125 mg, 250 mg or 500 mg thrice daily with ACV 200 mg five times per day for 10 days. A total of 951 patients with first-episode GH of less than 72 h duration (40% primary, 60% nonprimary) were enrolled. No differences in symptoms, signs or antiviral effects among treatments or between identical doses of FCV administered for five versus 10 days or in the subgroup with primary infection were demonstrated. Tolerance was good, with no differences among doses or treatments. The large sample sizes reduced the likelihood that a difference in efficacy between FCV and ACV was missed, ie, a type II error. In Europe, FCV 250 mg thrice daily for five days has been approved for the treatment of first episodes of GH in immunocompetent patients.

VCV 1000 mg twice daily was not different in efficacy and safety compared with ACV 200 mg five times per day for 10 days in patients with lesion durations of less than 72 h (39). There were similar proportions of primary and nonprimary infections in both treatment groups. The intent-to-treat analysis revealed identical median times to healing in both groups (nine days). These results combined with data showing that VCV 500 mg twice daily yields a daily area-under-the-plasma concentration versus time curve approximately twofold greater than is achieved with ACV 200 mg five times per day has in part resulted in approval of VCV 500 mg twice daily for 10 days for the treatment of first-episode GH in many European countries. In the United States, the approved dose regimen is

1000 mg twice daily for 10 days. The available data suggest that oral ACV 200 mg five times per day for 10 days, FCV 250 mg thrice daily for five days and VCV 500 mg to 1000 mg twice daily for 10 days are comparable for the treatment of first-episode GH in otherwise healthy patients with disease of less than 72 h (VCV) or up to five days (FCV). Whether oral ACV is the only one of the three agents to be efficacious in patients with first-episode disease from five to seven days duration at treatment initiation is uncertain because only oral ACV has been studied in such individuals. It also remains to be demonstrated that twice daily and thrice daily dosing schedules for VCV and FCV, respectively, are more effective in patients due to the more convenient dose schedule than is recommended for oral ACV.

Recurrent genital infection

Brief courses of therapy for episodes of recurrent GH in immunocompetent adults with topical ACV and oral ACV, FCV and VCV yield modest clinical benefit, whereas chronic suppressive therapy with oral ACV, FCV and VCV produces more dramatic benefits.

Episode therapy: The treatment of episodes of recurrent GH with a brief course of topical or oral ACV yielded modest and inconsistent therapeutic effects of two types. First, the severity and duration of lesion symptoms and signs was reduced, albeit inconsistently, and, second, treatment initiated early in the course of a recurrence aborted some episodes. ACV 5% ointment applied four to six times per day beginning one to two days after the onset of symptoms of recurrent GH in three trials reduced the duration of HSV excretion compared with placebo ointment, although not always in both women and men (40-42). However, the duration of pain was not altered while time to healing was accelerated only in males in one of three studies. When an attempt was made to improve therapy by initiating it within 6 h of the onset of the prodrome of a recurrence and before actual lesion formation had occurred, only limited additional beneficial effects of borderline significance were observed: a reduced interval between lesion formation and crusting in men using ACV was observed in addition to a diminished duration of viral excretion in ACV female recipients only (43). Topical ACV 5% cream initiated by patients during the prodromal stage was more effective than placebo (44). ACV reduced the duration of pain from a median of 4.5 days in placebo recipients to three days in ACV-treated subjects, shortened healing time by 16% from six to five days and reduced new lesion formation by 77% during five days of therapy compared with the placebo cream (44). Neither ACV 5% cream nor ointment is approved for therapy of recurrent GH in Canada. The efficacy of PCV cream, which is approved for the treatment of recurrent herpes labialis, for therapy of recurrent GH, has not been reported.

Early studies with oral ACV 200 mg five times per day for five days demonstrated therapeutic effects that somewhat exceeded those observed with topical 5% ACV ointment or cream, but remained modest in extent and degree (45-47). In the early studies, oral ACV significantly reduced mean healing time by 16% to 25% and also the duration of HSV excretion compared with placebo. The duration of lesion pain was not reduced ($0.05 < P < 0.10$), but the small sample size likely precluded demonstration of a significant effect of ACV (46). In a large study of 688 adult volunteers (48), oral ACV 200 mg five

times per day initiated at less than or equal to 24 h after the appearance of symptoms or signs of a recurrence of GH herpes compared with placebo reduced the median duration of lesion pain by 19%, from 5.9 days to 4.8 days, as well as the severity of pain. Attempts to enhance the therapeutic effect by the earlier initiation of therapy and the use of a larger dose have not been effective: the efficacy of therapy initiated by the patient at the earliest symptom of a recurrence or by the physician as soon as possible in the clinic was formally tested in a double-blind, placebo controlled, crossover trial (49). No significant difference was observed between ACV treatment with 200 mg five times per day initiated at a mean interval of 10 h (patient-initiated therapy) compared with 25 h (clinic-initiated therapy) after the appearance of the first symptom of a recurrence, although ACV efficacy exceeded placebo in both arms. Treatment with 800 mg of ACV twice daily for five days was not more efficacious than the currently recommended dose of 200 mg five times per day for five days (50).

Oral ACV therapy initiated in the prodromal phase of a recurrence may prevent progression to the formation of a lesion. However, this effect has also not been consistently observed: therapy with ACV 200 mg five times per day or 800 mg twice daily or placebo, all for five days, prevented lesion formation in 12%, 11% and 3% of treatment courses, respectively (50). A similar trend was observed in the formal crossover study of patient- and clinic-initiated therapy of Ruhnek-Forsbeck et al (49). Patient-initiated therapy increased the incidence of aborted attacks by 51% ($P=0.067$), from 19% in placebo recipients to 39% in ACV recipients, whereas clinic-initiated therapy increased the incidence by 46% ($P=0.17$), from 14% to 26%. Insufficient sample sizes precluded the demonstration that these differences were statistically significant. Collectively, these data suggest that for oral ACV therapy of recurrent GH, patient-initiated treatment will be required. This will in turn require education and instruction that permits the earliest possible initiation of therapy after the appearance of symptoms of recurrent disease.

VCV 500 mg twice daily and FCV 125 mg twice daily, both for five days, have recently been approved for the treatment of episodes of recurrent GH. VCV 500 mg twice daily initiated at a median of less than 12 h after lesion or symptom onset reduced the median duration of lesion symptoms and signs by 32% (from 5.9 days to 6.0 days to 4.0 days to 4.1 days) compared with placebo (51). Doubling the dose did not yield better results. Median lesion HSV excretion was reduced 50% by both VCV doses, from four days to two days, and both doses increased the proportion of patients with aborted episodes by 33% (VCV 500 mg twice daily) and 48% (VCV 1000 mg twice daily). In another large study, VCV 500 mg twice daily and ACV 200 mg five times per day, both for five days, were equally effective in a patient-initiated study (52). It is difficult to reconcile data demonstrating greater efficacy of VCV than placebo in the study of Spruance et al (51), the lack of substantive difference between ACV and placebo (*vide supra*) and the comparable effects of VCV and ACV (52).

FCV doses of 125 mg, 250 mg and 500 mg twice daily for five days were all more efficacious than placebo for the treatment of recurrent GH with no differences among FCV doses (53). Patients initiated treatment within 6 h of the onset of symptoms or signs of a recurrence. In a novel methodological approach used for the first time in this study, subjects were evaluated twice daily during therapy rather than just once, as was

the usual practice. This permitted more accurate determination of therapeutic endpoints. The duration of lesion symptoms, healing times and HSV shedding from lesions were significantly reduced by all doses of FCV compared with placebo. The study design precluded the evaluation of an effect of FCV therapy on the frequency of aborted lesions. FCV 125 mg twice daily for five days is approved for therapy of recurrent GH.

In two recently reported studies, the benefits of a shorter, two- to three-day course of oral antiviral therapy for the treatment of recurrent GH have been reported. In the first study, three days of treatment of recurrent genital HSV infection with VCV 500 mg twice daily, self-initiated within 24 h of a first symptom or sign of recurrent disease, was as effective and well tolerated as five-day treatment (54). The percentages of patients with aborted lesions were 25% and 26% in the two groups. Large sample sizes were tested: 402 volunteers received three days of VCV plus two days placebo and 398 volunteers received five days of VCV. This element of the study design obviated a Type II error with a power of 80% to detect a difference of 20% or more between treatments. In the second study, Wald et al (55) evaluated the efficacy and tolerance of ACV 800 mg thrice daily compared with placebo for two days of treatment of a recurrent episode of GH. Volunteers self-initiated therapy within 12 h of onset. ACV was more effective than placebo in reducing the duration of all symptoms and lesion duration (both from a median of six days to four days), viral shedding by 57% (from 58.5 h to 25 h) and increasing the proportion of aborted episodes from 11% to 27% (all $P < 0.05$). These effects of two days of oral antiherpes drug therapy are similar to those observed with five days of therapy with ACV, FCV and VCV (*vide supra*). Tolerance was not specifically reported. These studies strongly suggest that a shorter course of treatment than is conventionally recommended for the treatment of recurrent genital HSV infection may be sufficient.

All treatments with topical and oral ACV and VCV and FCV have been well tolerated with no significant differences from placebo. Large study sample sizes, especially with VCV (259 to 368 subjects per group), tended to reduce the likelihood of a Type II error among recorded adverse reactions to therapy.

Suppressive therapy

Nonpregnant adults: The most dramatic clinical benefits of the pharmacological therapy of recurrent GH in the immunocompetent host have been observed during long term suppressive therapy. Initially observed during oral ACV therapy, these observations have now been demonstrated with FCV and VCV as well. Suppressive oral ACV is indicated for individuals with frequently recurring disease, which is usually defined as GH recurring six to eight times or more per year.

Multiple placebo controlled, double-blind trials in which the results of evaluation of a range of ACV doses (56-69) were reported, plus careful longitudinal follow-up of large numbers of subjects for up to five years (70) have provided clinicians with a substantive database that can be used to treat with confidence and to individualize treatment regimens. The dramatic effects will be greater in those with the most frequent recurrences, such as the volunteers in the study of Douglas et al (56), who experienced an average of 13 recurrences in the 12 months before study entry. However, the therapeutic effect is also demonstrable in those with as few as four recurrences per year (61). ACV doses of 200 mg twice daily (56), thrice daily (57,59), four times daily (60-64), five times per day (56) and

400 mg twice daily (65-67,69) and 800 mg once daily (68) were all more effective than placebo in double-blind trials, although none was completely effective in preventing breakthroughs. Both total daily dose and the frequency of tablet taking appear to be determinants of the efficacy of suppression. In the only controlled trial in which placebo and different doses of ACV were compared, ACV 200 mg twice daily was as effective in preventing recurrences as 200 mg five times per day over a 12-week period (56). The efficacy of ACV administered once a day appears to be less than with schedules utilizing the same total daily dose administered in two or more divided doses. This conclusion was suggested by the trial of Mindel et al (71) in which prophylactic efficacy declined as the ACV dose was reduced from 200 mg four times daily to thrice daily to twice daily to once daily, each for 12 weeks. As well, ACV 800 mg in four or two divided doses appeared to be more effective than a once daily dose. All once daily doses (200, 400 or 800 mg) were significantly less effective than ACV 200 four times daily. Only 25% of individuals receiving ACV 200 mg once daily were recurrence-free after 12 weeks. Although no placebo-treated control group was studied concurrently, this 25% level of suppressive efficacy was very low and may approach the lower limit of efficacy. In the only controlled trial utilizing 800 mg once daily, only 28% of recipients were recurrence-free during two years of therapy compared with no placebo recipients (68). In individuals with a reported annual recurrence rate of 12 or more episodes, daily ACV 200 mg thrice daily was more effective than ACV 400 mg thrice daily ingested on Saturday and Sunday only during a 70-day study (58).

In Canada, ACV doses of 200 mg thrice daily to five times per day or 400 mg twice daily are all approved for the suppression of frequently recurring GH in healthy adults. The data suggest that the dose-response curve of ACV from 400 to 1000 mg/day in divided doses is relatively flat and that increasing the dose over this range is unlikely to enhance the suppressive effect. Whether ACV doses substantially greater than 1000 mg/day, such as 4000 mg/day, used to treat patients with herpes zoster will be more efficacious for the suppression of recurrent GH is unknown.

The safety of ACV for the suppression of frequently recurring GH in immunocompetent adults has been repeatedly demonstrated in multiple placebo controlled trials of nine weeks (57), 12 weeks (60-64,67), 17 to 18 weeks (56,57), 26 weeks (59) and one year (65,66,68,69). This favourable safety profile compared with concurrent placebo treatment has been paralleled by a report of ACV safety during open-label use for one year (71) and up to five years (70). In these immunocompetent adults, resistance has not been demonstrated by *in vitro* testing of HSV isolates obtained before, during or after ACV suppressive therapy (56,60,65-67,72).

Not surprisingly, FCV (73,74) and VCV (69,75) are also efficacious and safe for the suppression of frequently recurring GH. Two studies have demonstrated the efficacy and safety of FCV for the suppression of frequently recurring GH. Three hundred seventy-five women with six or more episodes of GH in the previous 12 months were randomly assigned to four months of treatment with one of six different treatments: placebo, FCV 125 mg or 250 mg once or twice daily, or 500 mg once daily (73). The most effective regimen for suppressing recurrent genital lesions was 250 mg twice daily. Once daily doses of 125 mg or 500 mg were ineffective compared with placebo, while 125 mg twice daily and 250 mg once daily were interme-

diate in efficacy. All doses were well tolerated compared with placebo. No resistance to PCV was demonstrable in HSV isolates recovered during or after FCV suppressive therapy. In another study, 223 healthy men and 232 healthy women with six or more episodes of GH per year were randomly allocated to FCV 125 mg or 250 mg thrice daily, 250 mg twice daily or placebo for 52 weeks (74). At one year, 71% to 80% of volunteers receiving FCV were recurrence-free compared with 22% of placebo recipients. There was no difference in efficacy between men and women and all doses were as well tolerated as placebo. Based on the greater convenience of FCV 250 mg twice daily, this regimen has been selected for marketing and is approved by the TPD for the suppression of frequently recurring GH.

VCV suppressive efficacy and safety have been evaluated in two large trials (69,75). Reitano et al (69) undertook a formal dose-response evaluation of the suppressive efficacy of VCV administered once daily for a period of one year. In a randomized trial of 1479 adults (709 men), VCV once daily doses of 250 mg, 500 mg and 1000 mg, 250 mg twice daily, ACV 400 mg twice daily and placebo were compared. After one year, the percentages of patients who were recurrence-free were 22%, 40%, 48%, 50%, 49% and 5%, respectively. All active treatments were more effective than placebo and were as well tolerated. The once daily dose-response evaluation demonstrated that VCV 500 mg and 1000 mg were more effective than 250 mg. There was no statistically significant difference between VCV 250 mg twice daily or 1000 mg once daily or ACV 400 mg twice daily; VCV 250 mg twice daily tended to be more effective than 500 mg once daily. In those with 10 or more recurrences of GH per year, VCV 1000 mg appeared to be more effective than 500 mg once daily and was similar to VCV 250 mg twice daily and ACV 400 mg twice daily. In another randomized study of 382 volunteers, VCV 500 mg once daily for four months was efficacious and safe compared with placebo (75). Approximately equal proportions of male and female volunteers with a history of eight or more recurrences per year were studied. After four months, 69% of VCV recipients were still recurrence-free compared with 9.5% of

placebo recipients. VCV is licensed in Canada for suppressive therapy: 500 mg once daily is recommended for those with nine or fewer recurrences per year and 1000 mg once daily for those with more recurrences.

The durability of the suppressive effects of ACV has been demonstrated in 1146 subjects with 12 or more recurrences per year who received placebo or ACV 400 mg twice daily for the first year with ACV 200 mg five times per day for five days to treat recurrences, followed by the treatment of all subjects thereafter with ACV 200 mg twice daily for four more years (70). Fifty-three per cent to 70% of patients were recurrence-free in any given year and 20% were recurrence-free for the entire five years; 3.3% of subjects required an increased dose of 800 mg twice daily for 12 or more recurrences per year. The durability of the suppressive effects of FCV beyond four months remains to be demonstrated; VCV is effective for at least one year (69).

The relative costs of ACV, FCV and VCV in Manitoba for the treatment of GH outbreaks using drugs and regimens approved by the TPD are shown in Table 2.

Pregnant women: ACV suppressive therapy given to pregnant women with GH prevented recurrent GH disease and obviated caesarean section for the prevention of neonatal herpes in two reports (76,77). In one study, 46 women with a history of recurrent GH received ACV 200 mg four times daily beginning one week before the expected date of confinement, while 46 controls received no treatment (76). In a placebo controlled, double-blind clinical trial, 46 women who had a first clinical episode of GH in pregnancy were randomly allocated to receive 400 mg ACV thrice daily (21 women) or placebo (n=25) beginning at 36 weeks of gestation (77). ACV recipients did not develop recurrent disease in either study and, therefore, did not require caesarean section to prevent neonatal herpes, whereas 12 of 46 and nine of 25 recipients in the control group in the two trials, respectively, had recurrent disease at delivery; nine of 12 and nine of 25 in the two studies with recurrent disease, respectively, had caesarean sections to

TABLE 2
Therapeutic Products Directorate (TPD) of Health Canada approved indications for the treatment of mucocutaneous herpes simplex virus infections in the normal host

Indication	Drugs and formulation	Dose regimen	Treatment cost
Cold sores	Penciclovir 1% cream	Apply 6 times in day 1, then every 2 h while awake for 3 days	Not available
Genital herpes			
First-episode	Acyclovir 200 mg tablets	200 mg 5 times per day for 10 days	\$49.00
	Acyclovir 5% cream or ointment	Apply 4 to 6 times per day for a maximum of 10 days	\$45.00 per 15 g tube
	Acyclovir injectable	Intravenous 5 mg/kg over 60 min every 8 h for 7 days	\$4.35 per 500 mg vial
Recurrent			
Episode therapy	Acyclovir 200 mg tablets	200 mg 5 times per day for 5 days	\$25.00
	Famciclovir 125 mg tablets	125 mg twice during waking hours for 5 days	\$28.00
	Valacyclovir 500 mg tablets	500 mg twice during waking hours for 5 days	\$33.00
Suppressive therapy	Acyclovir 200 mg tablets	200 mg thrice during waking hours to 5 times per day or 400 mg twice during waking hours for 1 month	\$90.00, \$150.00 or \$120.00
	Famciclovir 250 mg tablets	250 mg twice during waking hours for 1 month	\$228.00
	Valacyclovir 500 mg tablets	500 mg or 1000 mg once daily for 1 month	\$102.00 or \$204.00

TABLE 3
Thirteen off-label indications for drug therapy of mucocutaneous herpes simplex virus infections in the normal host

Indication	Drugs and formulation	Dose regimen	Treatment cost
Orolabial herpes			
Gingivostomatitis			
Therapy	Acyclovir suspension	15 mg/kg 5 times per day for 7 days or 600 mg/m ² 4 times during waking hours for 10 days	\$29.00 for 125 mL of 40 mg/mL
Prophylaxis	Acyclovir 200 mg tablets	30 to 60 mg/kg in 3 to 5 doses per day for 7 days	\$1.00 per tablet
Recurrent cold sores			
Episode therapy	Acyclovir 200 mg tablets	400 mg 5 times per day for 5 days	\$48.50
Suppressive therapy	Acyclovir 200 mg tablets	400 mg twice during waking hours or 200 mg 4 times during waking hours	\$4.00 per day \$4.00 per day
Prophylaxis after trigeminal nerve surgery	Acyclovir 200 mg tablets	400 mg twice during waking hours started at bedtime before surgery and for 5 days	\$19.40
During sun exposure	Acyclovir 200 mg tablets	400 mg twice during waking hours for 7 days before sun exposure	\$27.00
	Acyclovir 5% cream	Apply 2 hours before sun exposure and then 6 times per day for 7 days skiing	\$45.00 per 15 g tube
	Valacyclovir 500 mg tablets	Apply 4 times during waking hours to sites of recurrent disease 500 mg once daily	\$3.40 per day
Recurrent erythema multiforme prevention	Acyclovir 200 mg tablets	400 mg twice during waking hours or 200 mg 4 times during waking hours	\$4.00 per day both
Eczema herpeticum – therapy	Acyclovir 200 mg tablets	200 mg 5 times per day for 5 days	\$25.00
Genital herpes – therapy			
First-episode	Valacyclovir 500 mg tablets	500 mg twice during waking hours for 10 days or 1000 mg twice during waking hours for 10 days	\$68.00 \$135.20
		Famciclovir 250 mg tablets	250 mg thrice during waking hours for 5 days
Recurrent			
Short course therapy of 2 to 3 days	Valacyclovir 500 mg tablets	500 mg twice during waking hours for 3 days	\$20.40
	Acyclovir 200 mg tablets	800 mg 3 times during waking hours for 2 days	\$23.30
Suppressive therapy in pregnant women	Acyclovir 200 mg tablets	200 mg 4 times during waking hours beginning 1 week before expected date of confinement	\$27.20 per week
		400 mg thrice during waking hours beginning at 36 weeks' gestation	\$163.00 for 4 weeks
Asymptomatic shedding in nonpregnant women	Acyclovir 200 mg tablets	400 mg twice during waking hours	\$4.00 per day
Herpes proctitis	Acyclovir 200 mg tablets	400 mg 5 times per day for 5 days	\$97.00

prevent neonatal herpes. Asymptomatic shedding from the exocervix or vulva at parturition was only observed in one of the 71 control women. ACV was well tolerated by the mothers and seemingly so by the neonates. No neonate developed herpes, but neither study was powered to demonstrate a protective effect of ACV. These data are consistent with the suppressive effect of ACV in nonpregnant women, but this use of ACV remains an off-label one whose efficacy and safety remain to be rigorously tested before it is recommended as a standard in contemporary obstetrical practice.

Asymptomatic HSV shedding in women

The favorable effect of suppressive ACV on lesion recurrence has been paralleled by a reduction in subclinical shedding in women (78). In a double-blind, placebo controlled crossover trial of 34 women with recurrent GH, ACV 400 mg twice dai-

ly for 70 days reduced the number of days when HSV was detected in exocervix, vulvar or perineal swabs, in the absence of genital lesions, by 94% from a mean of 6.9 days to 0.3 days. Shedding was reduced similarly in all sites but was completely prevented by ACV in 78% (20 of 26) of women who completed both arms of the study and by placebo in 23% (six of 26), demonstrating that this pharmacological effect is not absolute. It is likely, but has not been demonstrated, that a similar effect would be observed on asymptomatic genital HSV shedding in men. Whether ACV-induced suppression of asymptomatic HSV genital shedding can reduce the risk of transmission is not known.

In addition to preventing recurrent genital HSV lesions, suppressive ACV has been demonstrated to ameliorate the psychological morbidity of the disease (79). In 102 unselected patients (mean age 31 years; 54% male; 62% single), psycho-

logical tests demonstrated pathological levels of "illness concern" and anxiety in approximately 60% of subjects. ACV therapy for a year was associated with a 42% to 60% reduction in the number of subjects with these types of morbidity by three months, a therapeutic effect that was sustained thereafter. It is likely that FCV and VCV will produce similar beneficial effects on the mental health of patients with GH, although this has not yet been demonstrated.

Thus, at this time, approved doses for the suppression of frequently recurring GH include ACV 200 mg twice daily to five times per day or 400 mg twice daily, FCV 250 mg twice daily and VCV 500 mg or 1000 mg once daily. Whether once daily VCV therapy will result in better compliance than multiple dose schedules has not yet been studied, but the convenience of taking a minimum of daily doses has an intuitive appeal for the prescribing doctor recommending a long term suppressive pharmacological regimen. Notwithstanding the substantial effects of suppressive therapy, two caveats must be kept in mind. First, neither the effects of drug therapy on lesion recurrence, nor their effects on shedding of virus during lesions-free periods, is absolute. Second, it cannot be assumed that transmission will be prevented, although the risk of this would intuitively be expected to be reduced during chronic therapy.

The duration of suppressive therapy to prevent recurrent genital lesions can be tailored to the need of the individual patient, having regard for the limited data on duration for suppression with FCV. ACV ingested continuously for up to five years, FCV for 16 weeks and VCV for 52 weeks have been demonstrated to be efficacious and safe. However, if one wishes to minimize drug exposure and its attendant cost, one can interrupt treatment periodically and expect that a few individuals will have experienced regression of their GH to a latent state. During 12 weeks of placebo therapy in ACV trials, a median of 7% (range 0% to 10%) (60-64,67) were recurrence-free; during 17 to 26 weeks, a median of 0% (range 0% to 6%) (56,57,59) were recurrence-free and during one year of suppressive placebo therapy, a median of 4% (range 0% to 5%) (65,66,68,69) were recurrence-free. Spontaneous remission was also observed during trials of placebo controlled FCV and VCV suppressive therapy. In individuals with six or more recurrences in twelve months treated with placebo, 10% (75) and 42% (73) were recurrence-free at four months, 27% (74) were recurrence-free at six months and 5% (69) to 22% (74) were recurrence-free after one year of placebo therapy. Factors contributing to this relatively high prevalence of recurrence-free placebo recipients in FCV and VCV trials compared with ACV suppressive therapy trials may have included a high (55%) withdrawal rate due to lack of efficacy (74) or enrolment of subjects with a lower median frequency rate in the year before the study, 7 (73), compared with median yearly frequency rates of 11 (63) to 13 (65) in almost all studies of ACV for the suppression of frequently recurring GH (56-69,71). In conclusion, one strategy to minimize the use of ACV, FCV and VCV for suppressive therapy is to stop treatment every 12 to 24 weeks and only to reinstate it if the next two consecutive recurrences occur in a one- to two-month period, consistent with greater than or equal to six recurrences per year.

HERPES PROCTITIS

Oral ACV was more effective than placebo for the treatment of a first episode of culture-proved HSV proctitis in 29 HIV-negative homosexual men (80). Of 15 men treated with

ACV, seven had primary infection as did 10 of 14 treated with placebo. ACV 400 mg five times per day initiated within 12 days of the onset of symptoms and continued for 10 days reduced the median healing time from 14 to five days in the placebo recipients ($P < 0.01$) and the median duration of virus shedding from 11 to zero days ($P < 0.05$), respectively. Durations of local symptoms and signs of proctitis were reduced in ACV recipients, but the small sample sizes precluded the demonstration of a statistically significant effect of ACV therapy on these parameters. ACV 2 g per day was as well tolerated as placebo. Treatment of first-episode herpes proctitis up to 12 days after the onset of symptoms in HIV-negative men would appear to be an appropriate off-label use for ACV.

CONCLUSIONS

ACV has been the prototype agent and mainstay of contemporary pharmacological therapy of orolabial and anogenital HSV infection in the immunocompetent host as demonstrated by data supporting TPD-approved indications and off-label uses. For most off-label indications, the evidence base is limited to studies conducted using ACV as the antiherpes drug (Table 3). The absence of comparative trials precludes definitive conclusions about the relative advantages of ACV, FCV, PCV and VCV for these infections. However, VCV and FCV for the treatment of first-episode GH will be more convenient than five times per day oral ACV. Topical PCV and oral FCV and VCV for therapy of episodes of recurrent orolabial and genital infection, respectively, may be more efficacious and convenient than ACV formulations for these infections. Recently reported studies strongly suggest that alternative regimens of VCV for three days and ACV at an increased dose for two days yield therapeutic effects comparable with traditional five-day treatments for episode therapy. Once daily VCV is more convenient than multiple dose regimens for suppression of frequently recurring GH, but a larger total daily dose appears to be necessary. For the suppression of HSV infection in pregnant women, ACV is the antiherpes agent of choice, based on substantial cumulative evidence. Drug resistance has not been a limiting factor in the treatment of HSV infections in the immunocompetent host.

Until robust comparative trials identify the best agent and optimal dose regimen, infectious disease clinicians will need to judiciously select among the available agents, formulations and dose regimens based on clinical trials data, as well as cost, to provide the most appropriate therapy for their patients.

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ERRATA

In the Original Article "Guidance on patient identification and administration of recombinant human activated protein C for the treatment of severe sepsis" published in the November/December issue of *The Canadian Journal of Infectious Diseases* on pages 361 to 372 Figure 2 on page 365 was printed as an incomplete figure. Please see the next page for the complete figure.

In the Original Article "Distribution of serogroups of *Neisseria meningitidis* and antigenic characterization of serogroup Y meningococci in Canada, January 1, 1999 to June 30, 2001" published in the November/December issue of *The Canadian Journal of Infectious Diseases* on pages 391 to 396 a mistake appeared in the Results section on page 392. The mistake relates to the sentence (column 2, paragraph 1, line 10) "This molecular method identified two isolates as serogroup B, two as serogroup Y and one each as serogroups C and W135". The sentence should read "This molecular method identified four isolates as serogroup B, one as serogroup C and two each as serogroups Y and W135".

The authors for the CIDS Position Paper "Contemporary antiviral drug regimens for the prevention and treatment of orolabial and anogenital herpes simplex virus infection in the normal host: Four approved indications and 13 off-label uses" published in the January/February issue of *The Canadian Journal of Infectious Diseases* on pages 17 to 27 should have been printed as: Fred Y Aoki MD, for the CIDS Antimicrobial Agents Committee. The paper originated from the Committee. The Committee members involved were:

Gerald A Evans, Kingston, Ontario (Chair)
Susan King, Toronto, Ontario
Michel Laverdiere, Montreal, Quebec
Lindsay Nicolle, Winnipeg, Manitoba
Peter Phillips, Vancouver, British Columbia
Corinna Quan, Windsor, Ontario
Coleman Rotsteiin, Hamilton, Ontario
