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Current Recommendations for the Treatment of Genital Herpes

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Contents

Abstract

The incidence of genital herpes continues to increase in epidemic-like fashion. Aciclovir (acyclovir) has been the original gold standard of therapy. The recent addition of famciclovir and valaciclovir as antiherpes drugs has improved convenience as well as the efficacy of treatment. Although aciclovir remains a widely prescribed and reliable drug, its administration schedule falls short of the ease of

usage that the newer nucleoside analogues offer, for both episodic and suppressive therapy. Suppression of symptomatic disease and asymptomatic shedding from the genitalia have both become popular approaches, if not the primary targets of antiviral therapy. Knowing that asymptomatic disease leads to most cases of transmission strongly suggests that suppression with antiviral agents could reduce transmission risk in discordant couples. Unfortunately, the role for antivirals in reducing transmission remains to be proven in clinical trials. Neonatal herpes is now successfully treated using aciclovir. Current randomised clinical trials are examining aciclovir and valaciclovir administration, as well as safety and efficacy for post-acute suppressive therapy. Prevention of recurrences in pregnancy is also a topic under investigation, with a view to reducing the medical need for Cesarean section, or alternatively (and far less likely to be accomplished) to protect the neonate.

Although resistance is largely limited to the immunocompromised and a change in resistance patterns is not expected, several drugs are available for the treatment of aciclovir-resistant strains of herpes simplex. Foscarnet is the main alternative with proven efficacy in this setting. Unfortunately, administration of foscarnet requires intravenous therapy, although a single anecdote of topical foscarnet efficacy in this setting has been published. Alternatives include cidofovir gel, which is not commercially available but can be formulated locally from the intravenous preparation. Less effective alternatives include trifluridine and interferon. Future possibilities for treatment of genital herpes include a microparticle-based controlled-release formulation of aciclovir and resiquimod (VML-600; R-848). The search for an effective therapeutic vaccine for genital herpes has not been successful to date, although a live virus glycoprotein H-deficient (DISC) vaccine is currently in clinical trials. Recent data suggest that seronegative women are protected (albeit, not fully) by a glycoprotein D recombinant vaccine with adjuvant.

Despite the established safety and convenience of current treatment options, better suppressive options and topical treatment options are much needed. Studies using existing agents as potential tools to avoid Cesarean section, or transmission to neonate or partner are ongoing. Both vaccines and antivirals may eventually play a role in prevention of infection.

Genital herpes is a sexually transmitted disease with persistent latent infection leading to recurrent genital lesions.[1] Most cases (95%)[2] are caused by herpes simplex virus type 2 (HSV-2) infection, though genital herpes due to infection with herpes simplex virus type 1 (HSV-1) is on the rise.[3] According to the National Health and Nutrition Examination Surveys (NHANES) III from 1988 to 1994, the seroprevalance of HSV-2 in people 12 years or older in the US was 21.9%, a 30% increase compared with data from NHANES II, which was collected from 1976 to 1980.[4,5] In this survey, fewer than 10% of seropositive individuals reported a history of genital herpes infection. It is because of this high proportion of unrecognised cases, and the frequency of asymptomatic (absence of symptoms) or subclinical (absence of lesions) shedding, that genital herpes continues to spread worldwide.[6] Antiviral therapy has played an important role in the treatment and suppression of episodes of genital herpes.

1. Existing Therapy

1.1 Drugs Used in Therapy

1.1.1 Aciclovir

Aciclovir (acyclovir), an acyclic guanosine analogue, is a selective inhibitor of the replication of

HSV types 1 and 2 and varicella-zoster virus.[7] In virally-infected cells, it is initially monophosphorylated by HSV-specific viral thymidine kinase (TK),[8] then converted to its di- and triphosphate forms by cellular enzymes. The active form is aciclovir triphosphate, which lacks the 3′-hydroxyl group required to elongate the DNA chain. Aciclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase, thereby terminating viral DNA replication.[9] This results in inactivation of viral DNA polymerase.[10]

Since its discovery 20 years ago,[7,11] aciclovir has become one of the most widely prescribed antiviral drugs in the world. It has proven to be effective and well tolerated for the treatment of genital herpes. As the first generation antiviral, it has had an excellent record of safety and high potency; however, poor oral absorption (bioavailability ≈20%[12]) and compliance issues (5 times daily regimen) have resulted in the developement of newer agents.

1.1.2 Valaciclovir

Valaciclovir, the l-valyl ester and prodrug of aciclovir, is much better absorbed than aciclovir. Valaciclovir is rapidly and almost completely converted to aciclovir in the intestinal wall and liver by valaciclovir hydrolase.[13-15] The absolute bioavailability of aciclovir following oral administration of valaciclovir is 54%,[16] 3 to 4 times higher than oral aciclovir itself. Valaciclovir is virtually completely converted to aciclovir. In a study of four healthy volunteers each receiving [^{14}C]valaciclovir 1000mg, plasma valaciclovir concentrations were undetectable only 3 hours after administration. By 168 hours, more than 99% of the radioactivity recovered in urine and faeces corresponded to aciclovir and its known metabolites. Oral administration of valaciclovir provides a much greater drug exposure with time than a comparable dose of oral aciclovir.[17]

The pharmacokinetics of aciclovir following administration of valaciclovir are similar to those of aciclovir in healthy volunteers, in patients with renal disease, in the elderly, in patients with advanced HIV disease,[18] and in geriatric volunteers with or without concomitant diuretic therapy.[19] Despite the higher drug exposure with valaciclovir, its safety profile is similar to that of aciclovir.[20-22] High doses of valaciclovir have been associated with thrombotic microangiopathy in patients with AIDS[23] and other immunocompromised states; however, thrombotic microangiopathy was not seen in a recent study of renal transplant patients treated similarly high doses of valaciclovir.[24] A direct cause and effect relationship has not been proven, and this high dosage (8 g/day) does not reflect the recommended dosages for genital herpes.

1.1.3 Famciclovir and Penciclovir

Like aciclovir, penciclovir is a nucleoside analogue which inhibits herpesvirus DNA synthesis.[25] Penciclovir also has an antiviral spectrum against human herpesviruses similar to that of aciclovir.[26] Famciclovir is the oral prodrug of penciclovir. Following oral administration of famciclovir, it is absorbed in the upper intestine and rapidly deacetylated to its active compound penciclovir in intestinal wall and liver.[27,28] Little or no unchanged famciclovir is detected in plasma following absorption, meaning that famciclovir undergoes extensive presystemic metabolism. In addition, penciclovir is eliminated unchanged in urine. Famciclovir has a high bioavailability of 77%,[27] which gives it an advantage over the poor bioavailability of oral aciclovir or penciclovir.

The intracellular action of penciclovir is very similar to that of aciclovir. Penciclovir is highly selective against herpesviruses because it is phosphorylated in HSV infected cells, with its phosphorylation to the monophosphate highly dependent on HSV TK.[25] Penciclovir monophosphate, like aciclovir monophosphate, utilises cellular enzymes to be further converted to the triphosphate.[26] Penciclovir triphosphate has a significantly longer intracellular half-life than aciclovir triphosphate (20 hours *vs* 1 hour) in HSV-2 infected cells.[29] This allows famciclovir to be administered orally less frequently during active infection. Although penciclovir triphosphate also has a 30-fold higher intracellular concentration than that of aciclovir triphosphate under similar circumstances,[30] the HSV DNA polymerases have a greater affinity for

aciclovir triphosphate compared with penciclovir triphosphate. Thus, to a greater extent, differences in mechanism are quantitative rather than qualitative and tend to balance each other. Like aciclovir triphosphate, penciclovir triphosphate inhibits the viral DNA polymerase through competition with deoxyguanosine triphosphate as a substrate for viral DNA polymerase, thereby terminating viral DNA replication. Plaque reduction assays have shown that the 50% inhibition values of clinical isolates of HSV-2 for penciclovir (1.5 to 2.4 mg/L) are similar to those obtained for aciclovir (0.6 to 1.3 mg/L).[31,26] Unlike aciclovir, penciclovir is not an obligate chain terminator; however, chain termination is rapidly achieved with both drugs. Most aciclovir-resistant clinical isolates of HSV are TK deficient and cross-resistant to penciclovir. However, strains with altered TK or DNA polymerase mutations may be selectively resistant to one or another nucleoside.[32]

Famciclovir has a different effect on latency in a mouse model, compared with valaciclovir. Early therapy with oral famciclovir was superior to valaciclovir in the reduction of reactivation of latent virus in both immunocompetent and immunosuppressed mice.[33-35] Both compounds were effective in preventing disease progression when therapy was commenced up to 5 days after virus inoculation. However, after cessation of therapy, when ganglia of mice from each treatment group were explanted and incubated for 5 days to allow reactivation to occur, there was a significant difference in viral reactivation between the 2 groups.[35] Explanted ganglia from famciclovir-treated mice had marked reductions in viral reactivation compared with explanted ganglia from valaciclovir-treated mice. Clinical trials in first episode disease did not demonstrate a significant difference in post-primary recurrence rates.

Famciclovir has an excellent safety profile. In an analysis of tolerability data from 13 completed clinical studies, famciclovir was found to be well tolerated by patients with genital herpes (n = 791), with an adverse event profile similar to that of placebo.[36] Studies in healthy male volunteers showed no significant pharmacokinetic interactions between famciclovir and allopurinol, digoxin, cimetidine, zidovudine or theophylline.[37] Furthermore, the pharmacokinetics of penciclovir do not appear to be different in the elderly,[38] nor does the intake of food have any influence on the bioavailability of penciclovir in healthy male volunteers.[39,40] In a study of male volunteers treated with famciclovir for 4 months and 12 months, no detrimental effects on semenology parameters were identified (unpublished observations).

1.2 First-Episode Treatment

Oral aciclovir 200mg 5 times daily for 10 days (in the US; 5 days in Europe) effectively treats first episodes of genital herpes, reducing the duration of viral shedding, time to crusting and time to healing.[41,42] Aciclovir may also play a role in modifying the course of neurological complications such as aseptic meningitis and urinary retention.[41] In severe cases with neurological complications, intravenous aciclovir administered 3 times daily should be considered.[43,44] A study of high dose oral aciclovir (4000 mg/day) compared with the standard dose (1000 mg/day) for the treatment of first-episode genital herpes infections did not show any clinical benefit for the higher dosage.[45] There were no significant differences in the duration of symptoms or viral shedding, nor did the median time to first recurrence differ between the 2 groups. Adverse gastrointestinal effects developed in 8% of patients receiving the higher dosage, compared with none for the standard dose group. Unfortunately, despite its efficacy, the requisite administration frequency of oral aciclovir can be both inconvenient and embarrassing.

Valaciclovir has been approved for therapy of first episode genital herpes at a dosage of 1000mg twice daily for 10 days. In an international, multicentre comparative study of valaciclovir 1000mg twice daily versus aciclovir 200mg 5 times daily for the treatment of 643 otherwise healthy adults with first-episode genital herpes, it was shown that the two drugs are equally effective and well tolerated in accelerating the resolution of the episode.

Aciclovir and valaciclovir did not differ significantly in efficacy with respect to duration of viral shedding, time to healing, duration of pain or time to loss of all symptoms. Adverse events were similar in the 2 groups.[46] The reduction in administration frequency is often a clinical advantage, especially because of the embarrassment that often accompanies first clinical episodes. Several countries have chosen to approve a first-episode dose of 500mg twice daily based on pharmacokinetic arguments.

Famciclovir has been studied in the treatment of first-episode genital herpes at a dose of 250mg 3 times daily for 5 to 10 days, and has been shown to be equal in efficacy with aciclovir for the treatment of first-episode genital herpes. A comparative study of famciclovir 750mg 3 times daily for 5 days and oral aciclovir 200mg 5 times daily for 5 days showed no significant differences in the reduction of duration of viral shedding for the treatment of first episodes of genital herpes.[47] In 2 other comparative studies of the treatment of first-episode genital herpes, the effects of famciclovir 125, 250 or 500mg 3 times daily for 10 days were not significantly different from aciclovir 200mg 5 times daily for 10 days.[48] Similarly, famciclovir at 250mg, 500mg and 750mg 3 times daily for 5 days in the treatment of first-episode genital herpes was found to be equal in efficacy to aciclovir 200mg 5 times daily for 5 days. No significant differences in times to cessation of viral shedding, complete healing or loss of all symptoms were observed between the 2 groups in all 3 studies. Again, reduced administration frequency is a practical advantage over aciclovir.

1.3 Episodic Treatment of Recurrent Episodes

Oral aciclovir 200mg 5 times daily for 5 days has been used in the episodic treatment of recurrent episodes of genital herpes. Whereas the duration of viral shedding, time to crusting and time to healing are reduced, there were no improvements in the duration of symptoms nor the length of time to recurrence.[49-51] In a large placebo-controlled randomised trial comparing aciclovir with valaciclovir, both agents were shown to reduce pain.[52] Although oral aciclovir therapy provided a statistically significant benefit over placebo, the degree of clinical improvement perceived by the patient is modest, and 5 times daily administration is inconvenient. The 1998 Genital Herpes Management Guidelines from the Centers for Disease Control (CDC) and Prevention[53] provides treatment options including aciclovir at the standard dose or 400mg 3 times daily or 800mg twice daily for 5 days. Neither alternative dose has been properly studied in clinical trials. Topical 5% aciclovir in polyethylene glycol ointment has been studied in the treatment of recurrent genital herpes. In both patient-[54] and clinic-initiated[55,56] studies, the treatment of recurrent episodes of genital herpes with topically applied aciclovir decreased the duration of viral shedding but had no significant clinical benefits. Topical aciclovir is neither approved nor recommended for the treatment of recurrent genital herpes in the immunocompetent host.

Oral valaciclovir is approved, and is a recommended CDC treatment choice, for the episodic treatment of recurrent genital herpes at a dosage of 500mg twice daily for 5 days. In a placebo-controlled trial of over 900 patients, valaciclovir was found to be effective in the episodic treatment of recurrent genital herpes.[20] Valaciclovir 500mg twice daily or 1000mg twice daily for 5 days, administered within 24 hours of onset of symptoms, accelerated time to episode resolution and lesion healing and time to cessation of viral shedding. Adverse events were similar to placebo. In one study, an additional 10% (valaciclovir 31% *vs* 21% for placebo) of patients failed to progress to full vesiculo-ulcerative lesions as a result of treatment with valaciclovir. A subsequent study suggests that administration for 3 days may be sufficient in keeping with the natural history of viral shedding.[57] In this randomised, double-blind controlled trial of 800 patients, a 5-day regimen of valaciclovir 500mg twice daily was not significantly different from a 3-day regimen in time to healing or duration of pain. In a comparative trial of valaciclovir 500mg twice daily and

aciclovir 200mg 5 times daily in patient-initiated episodic treatment of recurrent genital herpes, valaciclovir was found to have identical efficacy to aciclovir.[58] Similarly, in a large-scale study of 1200 patients, valaciclovir 1000mg twice daily was compared with aciclovir 200mg 5 times daily and placebo for the treatment of recurrences of genital herpes.[52] Both drugs were significantly more effective than placebo in reducing time to resolution of herpetic episodes, lesion healing, duration of viral shedding and duration of pain. Twice daily administration convenience, however, is a significant clinical consideration.

Famciclovir is approved for the episodic treatment of recurrent genital herpes at a dose of 125mg twice daily for 5 days, and is recommended as such by the CDC. In 2 multicentre studies of famciclovir for the treatment of recurrent episodes of genital herpes, famciclovir was significantly more effective than placebo (fig. 1). Famciclovir given 125, 250 or 500mg twice daily, initiated within 6 hours of the onset of symptoms, significantly reduced the time to healing, the time to cessation of viral shedding, and duration of lesion oedema in both patient-[59] and clinic-initiated,[60] placebo-controlled studies. Famciclovir treatment also significantly reduced the symptoms of pain, burning, tenderness and tingling. Famciclovir resulted in abortive episodes of viral shedding (73% of patients treated with 125mg twice daily *vs* 46% of patients in placebo group); however, these studies were not powered to show clinical changes in abortive episode frequencies from early therapy.[61] In both trials, adverse events of famciclovir were similar to those of placebo. Famciclovir is effective for acute episodic treatment of recurrent genital herpes and also provides the convenience of twice daily administration.

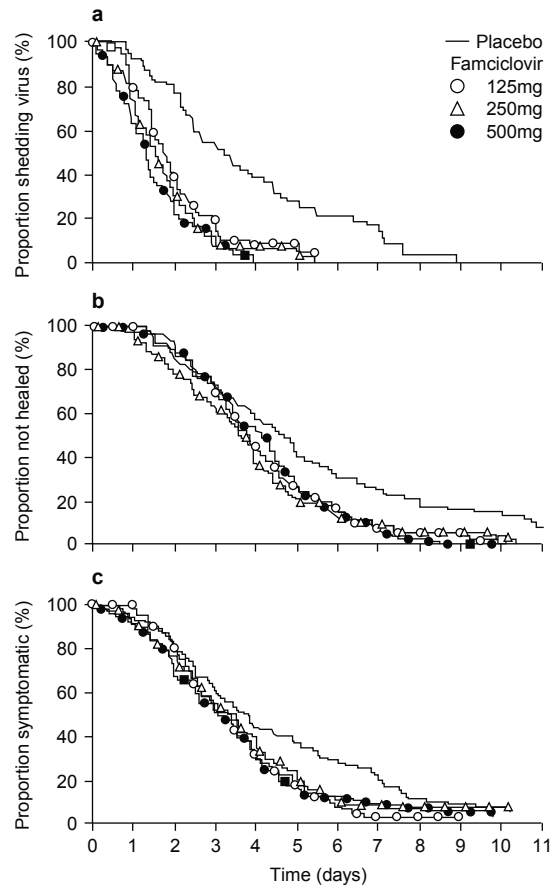

Fig. 1. Kaplan-Meier survival curves for the intent-to-treat population comparing 5 days of oral famciclovir 125, 250 or 500mg twice daily with placebo. The circles and triangles are not placed at specific data points. (**a**) Time to cessation of viral shedding (all lesions); (**b**) time to complete healing (all lesions); (**c**) time to cessation of all uncomfortable lesion symptoms. Reproduced from Sacks et al.,[59] with permission.

1.4 Continuous Suppressive Therapy

Aciclovir 400mg twice daily is effective for continuous suppressive therapy for patients who have frequent recurrences.[62-66] Daily administration reduces the frequency of recurrences by up to 80%, and 25 to 30% of patients had no further recurrences while taking aciclovir.[67,68] Successful suppression can be maintained indefinitely with no evidence of substantial adverse effects.[69] In the past, it has been suggested that treatment be interrupted every 12 months to reassess the need for continued suppression.[70] This is now a contentious issue. Interruption of therapy is not required for all patients and should be tailored to lifestyle and continuing physical and psychosocial needs

for suppression. Reduction of the psychological morbidity of patients is an important benefit of suppressive therapy.[71] Additional benefits on asymptomatic shedding (discussed in section 1.4.1) also need to be considered when interrupting therapy.

Valaciclovir 500mg once daily (for patients with 10 or fewer recurrences/year) and 1000mg once daily (for patients with more than 10 recurrences/year) have recently been approved for the prophylaxis of recurrent genital herpes in the US. In a study comparing valaciclovir 500mg once daily with placebo, 69% of patients receiving valaciclovir 500mg once daily were recurrence free after 16 weeks, compared with only 9.5% of patients receiving placebo.[22] Valaciclovir has been found to be equal in efficacy to aciclovir for the suppression of genital herpes. In a large-scale study of 1479 patients who were immunocompetent, varying doses of once- and twice-daily regimens of valaciclovir were compared with aciclovir 400mg twice daily and placebo for the suppression of genital herpes recurrences.[72] A dose-response relationship for once daily valaciclovir regimens was shown. The estimated proportions of patients recurrence free at the end of one year were 50% for valaciclovir 250mg twice daily, 49% for aciclovir 400mg twice daily, 48% for 1000mg valaciclovir once daily, 40% for valaciclovir 500mg once daily, 22% for valaciclovir 250mg once daily, and 5% for placebo (fig. 2). In patients with a history of <10 recurrences per year, the 500mg once daily regimen was not statistically different from the twice daily regimens. However, valaciclovir 250mg twice daily, 1000mg once daily, or aciclovir 400mg twice daily were more efficacious than 500mg once daily for patients with ≥10 recurrences per year. Accordingly, for patients with relatively low or modest recurrence rates, valaciclovir 500mg once daily is a reasonable suppression option. However, once daily antiviral suppression was studied as, and should be utilised as, a once every 24 hours (q24h) regimen, since, even with the results presented here, there are several hours per day when no antiviral is detectable in the blood. This could explain the increase in breakthroughs seen in patients with higher-frequency recurrences who utilise once daily therapy; however, this remains to be proven.

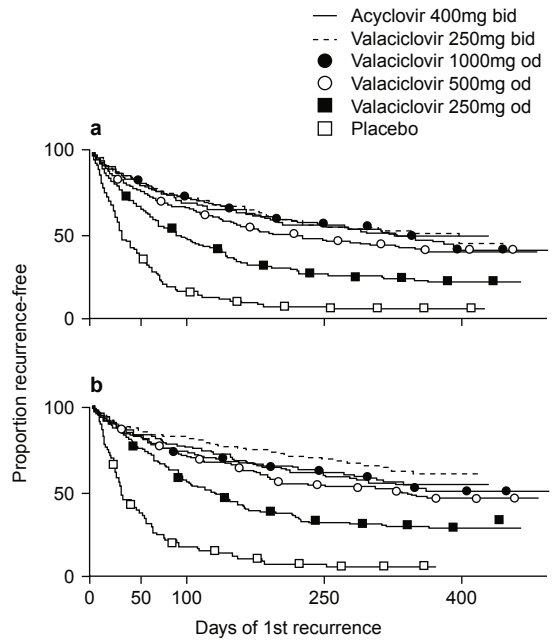

Fig. 2. Proportions of patients recurrence free. (**a**) Results for all patients in the study; (**b**) results for the subpopulation with 9 or fewer annual recurrences prior to the study period. All doses are displayed. Circles and squares are used to clarify the figure and do not represent specific data points. $P < 0.0001$ for all dosages comparing active treatment to placebo. Valaciclovir 1000mg once daily, 250mg twice daily; aciclovir 400mg twice daily are not different for the total population. For the 9 or fewer population, valaciclovir 500mg once daily is also not different among these dosages. Reproduced from Reitano et al.,[72] with permission. **bid** = twice daily; **od** = once daily.

Famciclovir has also been shown to be effective in the suppression of genital herpes recurrences, and has been recently approved at a dose of 250mg twice daily. In two studies of suppressive treatment of recurrent genital herpes with famciclovir, oral famciclovir administered continuously was significantly better than placebo in the prevention of genital herpes recurrences, effectively prolonging the time to the next episode of genital herpes. In a multicentre dose-finding study of 375 women with a history of ≥6 recurrent episodes of genital herpes, multiple-dose (125mg once daily, 125mg twice

daily, 250mg once daily, 250mg twice daily, 500mg once daily) famciclovir was given for a period of 4 months (fig. 3).[73] The median time to recurrence of a symptomatic episode of genital herpes was significantly ($p < 0.001$) longer for recipients of famciclovir 250mg twice daily (>120 days) than for recipients of placebo (82 days). Furthermore, famciclovir 250mg twice daily, which was found to be the optimal dose, suppressed recurrences in 90% of its patient group, compared with 48% recurrence suppression in the placebo group. In another study, famciclovir suppressive therapy was given for 1 year at 125mg 3 times daily, 250mg twice daily or 250mg 3 times daily or placebo (fig. 4).[74] All 3 dosages of famciclovir significantly delayed the appearance of clinically confirmed recurrences (median time to first recurrence was 336 days for the 250mg twice daily group) compared with placebo (median time to first recurrence was 47 days), with the twice daily as effective as the 3 times daily regimens.

Aciclovir, valaciclovir and famciclovir are all effective for long term suppression of recurrent genital herpes. Comparative studies involving all three agents are needed to make any clinical decisions

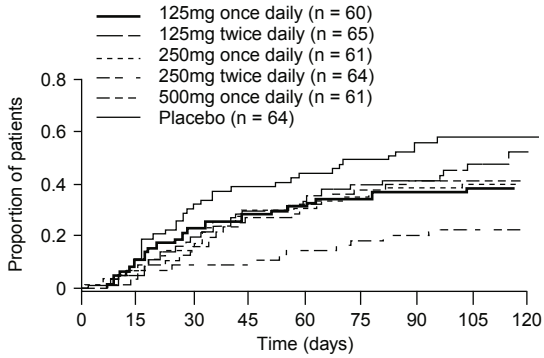

Fig. 3. Time to first clinically confirmed genital herpes episode (in the intention-to-treat population) among patients treated with oral famciclovir once or twice daily or with placebo for 120 days. The time to first clinically confirmed genital herpes episode was significantly prolonged by treatment with famciclovir 250mg twice daily ($p < 0.001$) and 125mg twice daily ($p = 0.03$), but not with 500mg once daily ($p = 0.06$), 250mg once daily ($p = 0.07$) or 125mg once daily ($p = 0.22$) when compared with placebo treatment. Reproduced from Mertz et al.,[73] with permission.

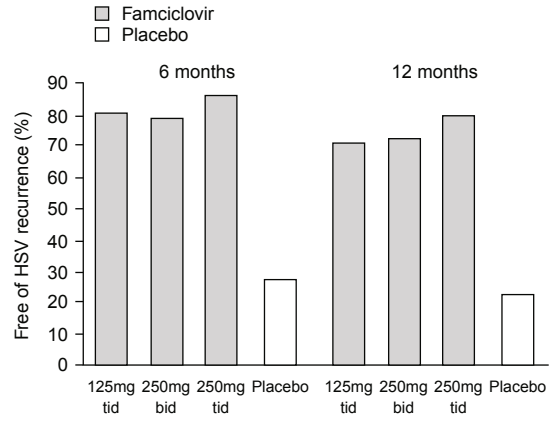

Fig. 4. Proportion of patients who remained free of herpes simplex virus recurrence. All comparisons are statistically significant ($p < 0.001$). Reproduced from Diaz-Mitoma et al.,[74] with permission. **bid** = twice daily; **tid** = 3 times daily.

favouring one drug over another. Suppression studies of the individual agents are notoriously difficult to compare because of differences in antiviral experience and recurrence rate between entry patients as well as differences in disease and efficacy definitions. Comparative studies between valaciclovir and aciclovir show equivalence.[73] Famciclovir and valaciclovir have been compared, but data have not yet been presented. Factors such as yearly costs, administration regimen and anticipated clinical efficacy have to be considered before commencing long term suppressive therapy.

1.4.1 Asymptomatic Shedding

Asymptomatic shedding of HSV is thought to play a major role in transmission.[75] Antivirals have been shown to significantly reduce asymptomatic and subclinical (includes shedding on days of prodrome) viral shedding when used as continuous suppressive therapy. In a crossover clinical trial of 34 women with a history of genital herpes for less than 2 years, aciclovir 400mg twice daily for 70 days was found to suppress subclinical shedding (fig. 5).[76] Patients using aciclovir had significantly less ($p < 0.001$) subclinical shedding, detected by viral

isolation (0.3% of days), than patients in the placebo group (6.9% of days).

Famciclovir has also been shown to reduce asymptomatic shedding of herpes virus, measured by both virus isolation and polymerase chain reaction.[77] In a study comparing famciclovir with placebo in the suppression of viral shedding in women, famciclovir significantly reduced the percentage of days of asymptomatic shedding.[78] The asymptomatic shedding rates were 0.52, 0.41 and 3.1% of days, for famciclovir 125mg 3 times daily, famciclovir 250mg 3 times daily and placebo, respectively. Another study found famciclovir 250mg twice daily was significantly more effective than placebo in the suppression of asymptomatic shedding in men.[79] Famciclovir reduced asymptomatic shedding rates to 0.08% of days, compared with 1.09% of days for placebo ($p < 0.05$). This confirms that famciclovir is effective for the suppression of asymptomatic shedding for both sexes. In a study of patients with HIV infection, famciclovir 500mg twice daily was found to be significantly better than placebo in reducing both symptomatic and asymptomatic shedding.[80] Asymptomatic shedding was reduced from 5.1% of days for placebo to 1.2% of days for patients who received famciclovir. Similarly, symptomatic shedding was reduced from 4.6% of days for placebo to 0.1% of days for famciclovir.

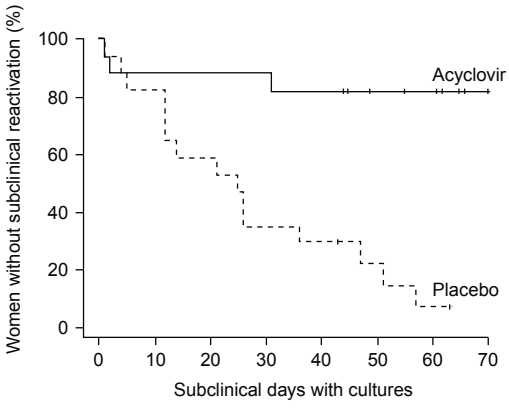

Fig. 5. Time to first subclinical shedding of herpes simplex virus among 34 women. Reproduced from Wald et al.,[76] with permission.

Valaciclovir 500mg twice daily was compared with aciclovir 400mg twice daily and placebo for its effectiveness in the suppression of subclinical viral shedding in both men and women in a crossover study which utilised both viral culture and polymerase chain reaction (PCR) techniques to identify viral shedding.[81] Measured by culture, subclinical shedding occurred on 15.3% of days for placebo, 0.7% of days for valaciclovir and 0.9% of days for aciclovir. Measurement by PCR produced subclinical shedding rates of 40.0, 7.5 and 8.4% of days, respectively. Asymptomatic shedding has not yet been assessed with once daily valaciclovir, although studies are underway. Despite clear benefits of all suppressive antivirals on asymptomatic shedding, it remains to be proven that suppressive therapy can result in a reduction of transmission risk. Clearly, transmission can occur while a source partner is taking suppressive therapy.[82] Studies of discordant partners are ongoing to determine the importance of suppressive treatment on transmission.

2. Recent Issues in the Treatment of Recurrent Genital Herpes

2.1 Suppression of Viral Shedding in Pregnant Women

The main cause of neonatal herpes infection is through contact with the herpes simplex virus at the time of delivery from the mother's birth canal.[83] Infection could theoretically result from transplacental infection, although this is very rare.[84] In the neonate, presentations have been characterised as disseminated, central nervous system, or skin and mucous membrane disease, with treated mortality rates of 50, 15 and 0% respectively. Significant morbidity may result with long term neurological damage for up to half of the survivors.[85,86] Because of the large numbers of patients who have herpes but no history,[87] the risk of asymptomatic shedding during labour is high. Identifying those at risk is difficult. Clinical tools, such as a detailed history

of genital symptoms, may also not be helpful.[88] Neonatal transmission occurs in 20 to 50% of infants born to mothers delivered vaginally with first episode infections at term.[89,90] Transmission rates are substantially lower (≈4%) for mothers with recurrent episodes.[85,91]

In a recent survey, among the infants born to 9 women who acquired genital HSV infection shortly before labour, neonatal HSV infection occurred in 4 infants, one of whom died.[90] Neonatal risk from mothers with established recurrent infection (positive HSV-2 Western blot in this study) is far lower. However, because recurrences account for the vast majority of active episodes, recurrent episodes still account for some of the overall risk. To reduce transmission rates to the neonate it has been recommended that Caesarean sections be performed on mothers with genital herpes lesions.[92,93] However, this imposes risks to the mother and fails to properly address the differences in risk between first and recurrent episodes. Caesarean sections for suspected active recurrences are often unnecessary in mothers with established recurrent disease, given the low incidence of neonatal herpes infection in this population.[94]

In order to reduce the rates of Caesarean section, several groups have considered the use of suppressive therapy late in pregnancy. A study of 5 women undergoing suppressive aciclovir therapy did not show any clinical benefit, and 1 out of the 5 neonates was infected with HSV.[95] However, a study of 46 pregnant women with first episodes of genital herpes showed a significant reduction in clinical recurrence and Caesarean section when given aciclovir 400mg 3 times daily compared with placebo.[96] No woman treated with aciclovir had a Caesarean delivery as a result of herpes, compared with 9 of the 25 placebo recipients. In a group of pregnant women receiving aciclovir, there was evidence of a predictable marked reduction in the number of women experiencing symptomatic recurrences, after trial entry.[97] In addition, 150 women with a history of genital herpes were given either aciclovir 200mg 3 times daily or placebo, beginning at 38 weeks.[98] While 33 patients in the placebo group had recurrences, with 21 of them recurring in delivery, there were no recurrences in the treatment group. No infants showed a clinically-evident adverse reaction to aciclovir in any of the above studies. Unfortunately, no studies in late pregnancy suppression have been conclusive because of small sample size and/or failure to stratify by serological status, asymptomatic shedding or recurrence frequency rates. Intuitively, it would be expected that aciclovir suppression would reduce frequency rates of both symptomatic and asymptomatic recurrences. Nevertheless, more definitive details are needed.

Although there have been no reports of adverse effects attributable to its use in this setting,[99] aciclovir is not licensed for use for any indication during pregnancy. In a study of oral aciclovir suppressive therapy in neonates,[100] 12 of 26 infants developed neutropaenia while receiving aciclovir, with 10 of the 12 having spontaneous recovery without interruption of treatment. Further studies of the effects of aciclovir on the newborn are also warranted. Routine use of aciclovir in late pregnancy has become the standard of care in some communities. Although it appears to be both desirable and cost effective, this remains an unproven approach, with adverse effects unlikely but safety is not fully proven.

While there have not been any studies on famciclovir use in pregnancy, the pharmacokinetics of oral valaciclovir in late pregnancy have been evaluated.[101] Oral valaciclovir 500mg twice daily suppressive therapy was compared with oral aciclovir 400mg 3 times daily in 20 women with a history of recurrent genital herpes at 36 weeks' gestation. Valaciclovir therapy resulted in higher plasma aciclovir concentrations than aciclovir therapy, and further studies are underway to evaluate the efficacy and safety of valaciclovir in pregnancy.

2.2 Resistance and Alternative Therapies

First reported in 1982,[102] aciclovir-resistant strains of HSV have primarily been found in immunocompromised individuals, and have been associated with clinical disease progression.[103-107] In that setting, studies have shown that the preva-

lence of aciclovir-resistant isolates of HSV from immunocompromised patients is approximately 5%.[107-109] Aciclovir resistance in a bone marrow transplant population[110,111] has also been reported. Although reports of emergence of resistance in immunocompetent patients[112-114] are rare (0.1 to 0.6% prevalence in one study[108]), no correlation between *in vitro* resistance and clinical progression has been established. In the majority of cases, the mechanism for viral resistance to aciclovir involves mutant HSV strains unable to produce TK.[115-118] In most cases, latent infection is not influenced by treatment. Therefore, upon withdrawal of drug pressure, reactivations most often revert to wild type. However, reactivations of resistant virus have been observed and may be explained by *in vivo* complementation with viral heterogeneity[119] or alterations in the quantity of TK production. Such cases demonstrate that latent infection can be affected by resistant mutations. However, these can appear to revert to wild type eventually, if drug therapy is withdrawn. Presumably, this reflects the persistence of sensitive virus in latency as well as the strong virulence advantage associated with expression of viral TK. Although much less common than TK depletion, isolates have also been found to have a mutation altering TK function[116] or the DNA polymerase.[120,121] Such modifications would leave virulence factors unaltered. These findings reveal the need for alternative mechanistic approaches with antivirals against herpes.

Despite concerns over resistance, there is very little cause for concern regarding a change in resistance patterns overall. TK deficiency was observed at the same levels prior to the introduction of aciclovir and the prevalence of resistant isolates has been stable since the introduction of this drug. Vast increases have been experienced in antiviral drug use over the past 15 years with no alterations in resistance patterns. Blower et al.[122] have suggested, based on mathematical models, that any change in resistance patterns, were they to occur, would take decades to develop. This probably reflects the established, largely unalterable pool of wild type latent infection in the population, as well as the natural episodic nature of the infection.

3. Drugs for the Treatment of Aciclovir-Resistant Herpes Simplex Virus

3.1 Foscarnet

Foscarnet is a pyrophosphate antagonist that exhibits broad activity against DNA and RNA viruses.[123,124] It noncompetitively inhibits viral DNA polymerase by binding to pyrophosphate binding sites of viral DNA, thereby preventing pyrophosphate exchange.[125] Since it does not require phosphorylation, it is active against aciclovir-resistant TK-deficient HSV strains.[126] However, foscarnet can be toxic in some situations. Potential adverse effects of renal dysfunction, gastrointestinal symptoms, metabolic abnormalities (such as with magnesium and calcium), genital ulcers and seizures have been reported.[127] Serious events can usually be avoided through hydration, careful monitoring and avoidance of concomitant use of pentamidine.

Topical foscarnet had been studied, but has not proven to be effective in the management of genital herpes. In a study of 86 patients, therapy with 0.3% foscarnet cream was patient initiated within 24 hours of a recurrent episode, then treatment continued with application every 2 hours for the first day then 6 times daily for the next 4 days. Topical foscarnet was found to be statistically significant in reducing the time to healing of lesions.[128] However, a larger study of 230 patients demonstrated no statistically significant efficacy.[129] Treatment with 0.3% foscarnet cream for men and 1% foscarnet cream in women was clinically initiated within 6 hours of a recurrence. There has been a single case report of successfully utilised topical foscarnet for herpes resistant to treatment with both aciclovir and valaciclovir.[130] Studies of this approach in immunocompromised patients are ongoing.

Use of intravenous foscarnet for aciclovir-resistant herpes simplex infections was first described by Sacks et al.[131] and its utility confirmed

in subsequent studies.[106,132-135] In an uncontrolled study, clinical response occurred in 81% of aciclovir-resistant infections in patients with AIDS treated with foscarnet.[136] In another study, intravenous foscarnet was found to be more effective than vidarabine in time to healing and time to cessation of viral shedding in the treatment of aciclovir-resistant mucocutaneous HSV infection in patients with AIDS.[137]

Foscarnet has been approved for intravenous use in aciclovir-resistant herpesvirus infections in immunocompromised patients. Due to the nature of intravenous administration, there are limitations to this application. However, there are no oral formulations of foscarnet because of its poor oral bioavailability. Foscarnet-resistance strains of HSV have been reported,[138,139] and strains resistant to both foscarnet and aciclovir have also appeared.[140] Resistance to foscarnet occurs as a result of mutations in viral DNA polymerase.[141]

3.2 Cidofovir

Cidofovir (HPMPC, GS-504), an acyclic nucleoside phosphonate analogue of deoxycytosine monophosphate, is active against a broad spectrum of viruses. Cidofovir is phosphorylated by cellular enzymes into its active diphosphate metabolite.[142,143] Since cidofovir is a nucleotide, it bypasses the first HSV-dependent phosphorylation step required for nucleosides such as aciclovir. Therefore, cidofovir's conversion to its active metabolite is independent of virally-encoded enzymes such as TK.[144] Since cidofovir's metabolism is not affected by HSV infection,[142] it is active against both aciclovir-sensitive and aciclovir-resistant HSV. This has been demonstrated *in vitro*,[145] in animal models,[146] and clinically.[147,148] Indeed, cidofovir showed enhanced *in vitro* potency against strains of HSV resistant to aciclovir.[149] Cidofovir has also been successful in the treatment of an aciclovir- and foscarnet-resistant HSV-1 strain in a bone marrow transplant patient.[140]

The antiviral effect of cidofovir is the result of its interaction with viral DNA polymerase. The diphosphate metabolite of cidofovir acts during the DNA polymerase reaction either as a competitive inhibitor to terminate chain elongation or as an alternative substrate to allow chain growth.[142,150] Inhibition constants against HSV-1 and HSV-2 viral DNA are 50- to 600-fold lower than the constants for human DNA polymerase.[142,150,151] Cidofovir was found to completely inhibit cytomegalovirus (CMV) DNA synthesis at concentrations at least 100-fold lower than the concentrations required for cellular DNA synthesis.[152] It is a broad spectrum antiviral, with activity against HSV-1, TK-negative HSV-1, HSV-2, varicella zoster virus, Epstein-Barr virus, CMV, human herpesvirus type 6, human herpesvirus type 8, human adenoviruses, poxviruses, hepadnaviruses and papovaviruses.[153] In animal models of genital herpes infection, successful outcomes have been observed in single-dose therapy for guinea pigs that have been inoculated with HSV-2.[146,154] In another genital herpes model, a single topical application of 0.3, 1 or 3% cidofovir topical gel 24 hours after HSV-2 inoculation significantly prevented viral replication and lesion development.[155]

Cidofovir has a very long intracellular half-life. After removal of cidofovir from the cell culture medium, the intracellular concentrations of cidofovir monophosphate and cidofovir diphosphate are 24 and 65 hours, respectively.[142,156] In the intravenous treatment of CMV retinitis in patients with AIDS, this long intracellular half-life permits systemic administration at intervals of every 1 to 2 weeks. However, cidofovir has a poor oral bioavailability of <5%, with a plasma half-life of 2.6 hours.[157,158]

There have been several studies using cidofovir as a gel formulation for the topical treatment of genital herpes. In a study of cidofovir gel compared with placebo applied once daily for 5 days in the treatment of aciclovir-unresponsive HSV infection in 30 patients with AIDS, cidofovir was found to have significant antiviral and clinical efficacy.[159] Complete healing occurred in 27% of patients receiving 0.3% cidofovir, 33% for the 1% cidofovir group, and 0% for patients treated with placebo. Median lesion areas were decreased by 58% for

those treated with cidofovir versus 0% for placebo-treated patients. However, the US Food and Drug Administration (FDA) did not approve cidofovir gel for this indication because studies were not large enough to provide statistical power for proof of efficacy. Given the low incidence of this problem, such FDA requirements could obviate the approval of any drug for this indication. Furthermore, a multicentre dose-escalation study of single-dose cidofovir gel compared with placebo in the treatment of lesions of recurrent genital herpes in immunocompetent patients showed that cidofovir gel had a significant antiviral effect.[160] Placebo or cidofovir gel 1, 3 or 5% was given to patients within 12 hours of lesion appearance. Cidofovir gel at all doses significantly decreased the median time to negative virus culture compared with placebo. The size of this pilot was not sufficient to show significant differences in the median time to complete healing, in part because of local toxicities, which prolonged healing times in some recipients. Local toxicity was dose-dependent and seen in three of the 23 patients treated with 5% cidofovir gel and one of the 21 patients treated with 3% cidofovir gel. While the efficacy of cidofovir in the treatment of genital herpes has been demonstrated, the maximum strength that could be tolerated still has to be determined by further studies.

3.3 Trifluridine

Trifluridine is a pyrimidine nucleoside analogue that, like cidofovir, acts independently of viral TK, but toxicity prevents systemic administration; however, an ophthalmic preparation has been successfully employed in herpes keratitis.[161] Using gauge pads, this ophthalmic product has been topically applied in some cases of aciclovir-resistant genital herpes. It has been reported to be beneficial for the treatment of infection of aciclovir-resistant HSV-2 in a patient with AIDS.[162] In patients with HSV isolates that were either aciclovir- or aciclovir/foscarnet-resistant, 3 episodes of recurrent anogenital HSV lesions were improved with topical trifluridine 3 times daily.[163] In another report, trifluridine showed potential synergy with interferon (IFN)-α for isolates of aciclovir- or aciclovir/foscarnet-resistant HSV.[164] Larger, controlled studies would be required to establish the clinical efficacy of trifluridine in the treatment of genital herpes.

3.4 Interferon-α, -β

In the humoral immune system, INF production is induced by viral infection. INF inhibits viral protein translation and creates an antiviral state in the cell, causing resistance to infection, and playing an important role in the host defence mechanism.

INF inhibits the proliferation of HSV types 1 and 2 *in vitro*.[165,166] Several studies have investigated the efficacy of INF gel for the treatment of genital herpes.[167-170] A clinic-initiated study found that topical INFα-2a administered 6 times daily in an aqueous solution to unroofed vesicles after lesion onset was not effective in the treatment of genital herpes lesions.[171] Another study failed to show significant benefit with an INFα formulated with nonoxinol-9, though a significant delay in re-epithelialisation was observed with the application of a high dose.[172] In a patient-initiated study of 188 patients with recurrent genital herpes,[173] high- or low-dose INFα, formulated in a methylcellulose gel containing nonoxinol-9, or placebo was topically applied 3 times daily for 5 days after onset of lesions. Recipients of the high dose had reductions in time to negative virus culture, duration of symptoms and times to healing. Similarly, a placebo-controlled trial of 387 patients receiving either INFα-2a gel or placebo 4 times daily for 4 days upon onset of lesions found that INF treatment was effective in the treatment of recurrences of genital herpes.[174] INF decreased the duration of viral shedding for all patients, and there was a significant reduction of pain, itching and time to crusting for males. More recent studies have demonstrated better efficacy in the use of INF. In a study of 25 patients, INFβ was found to have beneficial effects.[175] Topical INFs are not approved for the treatment of recurrent genital herpes.

4. New Drugs Under Development

4.1 Lobucavir

Lobucavir is a deoxyguanosine nucleoside analogue. Like aciclovir, it is phosphorylated to the monophosphate form by viral TK, then further phosphorylated by cellular kinases into the active triphosphate form.[176-178] It is a nonobligate DNA chain terminator,[176,179-181] acting as an alternative substrate for deoxyguanine triphosphate. Chain termination results from the incorporation of lobucavir triphosphate, a poor primer, into the DNA by DNA polymerase. The intracellular half-life of lobucavir triphosphate was found to be 10 hours.[182] Lobucavir's inhibition constants against HSV-1 and HSV-2 DNA polymerase (K_i = 0.017181 and 1.0183 μmol/L, respectively) were comparable with that of aciclovir. Against HSV-1 and HSV-2 *in vitro*, the concentration effective against 50% (EC_{50}) was 0.04 to 0.007 and 0.04 to 0.01 mmol/L, respectively, with lower values than aciclovir in both cases.[182,183] However, the EC_{50} of lobucavir against a TK deficient variant of HSV-1 was only increased by about 30-fold (2 mmol/L), compared with >700-fold for aciclovir.[183] This evidence suggests that phosphorylation by viral TK is important, but not essential, for the antiviral activity of lobucavir. Furthermore, a study of lobucavir in human CMV-infected and mock-infected cells show that phosphorylation of this drug can occur in the absence of viral factors.[184] Phosphorylated metabolite levels were only 2- to 3- times higher in infected than mock-infected cells, with total lobucavir metabolites being 2.3 and 0.8 pmol/10^6 cells, respectively.

In mouse models, oral lobucavir was effective in a variety of HSV-1, HSV-2 and murine CMV infections, with a bioavailability of 80% based on urinary excretion.[183,185] Topically applied lobucavir has been evaluated for the treatment of herpes lesions in guinea pigs.[186] Starting at 3 hours after inoculation, 5% lobucavir or 5% aciclovir cream was applied twice daily to randomly assigned areas for 5 days. Lobucavir was found to be significantly better at reducing the duration and severity of lesions than aciclovir cream at all concentrations tested.

Several early safety and pharmacokinetic studies in humans have investigated the effects of lobucavir on HIV- and CMV-seropositive individuals. In a single-dose, placebo-controlled study in 40 patients, the absolute oral bioavailability was found to be about 40%.[187] In a subsequent multiple-dose study in 32 patients, twice daily administration for 28 days produced linear increases in the area under the plasma concentration/time curve (AUC) at 20, 70 and 200mg, but not for the 400mg dose.[188] In another placebo-controlled multiple-dose (70mg or 200mg twice daily, 200mg or 400mg 4 times daily) study of lobucavir, there was a linear relationship between exposure and dose up to 200mg.[189] Lobucavir was well tolerated in the above trials, and the pharmacokinetics of lobucavir is not influenced by the intake of food. Unfortunately, the development of lobucavir for the treatment of genital herpes has been discontinued.

4.2 Crofelemer (SP-303)

Crofelemer (SP-303) is a natural bioflavonoid plant extract, isolated from *Croton lechleris*, which inhibits viral penetration into cells. It is a proanthocyanidin oligomer and is active against both HSV-1 and HSV-2. In one study, 15% crofelemer ointment 3 times daily for between 14 and 42 days was given to immunocompromised patients who had undergone a period (median 1.5 months) of ineffective aciclovir therapy.[190] There was no complete healing in any patients, and adverse events included local burning and pain. In a subsequent trial, the drug was tested as a topical formulation in a phase II study for safety and effectiveness against recurrent genital herpes in patients with AIDS.[191] Given 3 times daily for 3 weeks, 41% of the patients given crofelemer versus 14% of the placebo group had complete healing. Unfortunately, subsequent clinical trials of crofelemer for the treatment of genital herpes have not shown efficacy, and further investigations have been discontinued.

4.3 Edoxudine

Edoxudine (EDU) is a deoxythymidine analogue that demonstrates significant *in vitro* and *in vivo* antiherpesviral activity,[192-195] and has been approved for the treatment of recurrent genital herpes in Germany and for recurrent genital herpes episodes in women in Canada. Like other nucleoside analogues, edoxudine needs to be phosphorylated by viral TK into its active form, which inhibits DNA polymerase. Edoxudine is better absorbed from its aqueous cream base than aciclovir from its polyethylene glycol base; however, it is degraded to its component base and sugar by pyrimidine nucleoside phosphorylases virtually instantaneously. The rate of absorption of edoxudine increases with longer time allowed after application. In a multicentre study of topical 3% edoxudine cream for 5 days for the treatment of recurrent genital herpes compared with placebo, edoxudine significantly reduced viral shedding in both sexes.[196] Viral shedding was reduced from 3.4 for the placebo group to 2.7 days for edoxudine-treated men. Similarly, shedding was reduced from 3.5 to 2.0 days in women. Edoxudine also reduced several signs of active, recurrent herpes in women, such as lesion and groin tenderness and groin adenopathy.

4.4 Controlled-Release Aciclovir

A microparticle-based controlled release formulation of aciclovir has been developed.[197] It is reported to result in prolongation of the short plasma half-life (2.5 hours) of aciclovir and resulting burdensome regimen. Treatment trials from Europe suggest equivalence with oral aciclovir. It is possible that breakthrough recurrences often seen on suppressive therapy regimens could be further reduced through any approach which prolongs the plasma half-life of an effective antiviral. Further studies are required, however, to determine whether the prolonged half-life of this formulation can be translated into a therapeutic advantage.

4.5 Resiquimod (VML-600)

Resiquimod (VML-600, R-848, S-28463), is a synthetic immune response modifier, a member of the imidazoquinolines. An analogue of imiquimod, resiquimod has been shown to induce the release of a number of cytokines *in vivo*, including INFα, tumour necrosis factor-α and several interleukins, through modulation of monocyte/macrophage activity.[198] Resiquimod was found to reduce the number of genital herpes recurrences in a guinea pig model, even after discontinuation of the drug.[199] It has also shown significant immunomodulating effects when applied topically to humans in gel form.[200] A recent clinical trial showed that topical resiquimod treatment delayed recurrences of genital herpes when applied to lesion ≤24 hours from onset. In 52 immunocompetent adults with a history of ≥6 recurrences a year, median time to first recurrence was 169 days for the resiquimod-treated group and 57 days for those treated with placebo.[201] This novel antiviral is currently in phase III clinical trials.

5. Vaccines

Although vaccines for HSV have been studied for decades, there have not been any effective ones found for the prevention of infection.[202] The nature of HSV infection, which includes regional infection leading to latency, and which does not include systemic viremia, implies that even successful induction of serum antibodies would still be ineffective against mucosal infection. Recent studies of genital mucosal and sensory ganglia immunity has established the importance of T cell protection, even in the presence of HSV-specific antibodies.[203,204] These findings indicate that future vaccine strategies must take into account the importance of the T cell response.

5.1 Recombinant Glycoprotein-Subunit Vaccine

Recent investigations have focused on recombinant HSV-2 envelope glycoproteins D (gD) and B (gB), 2 of the 8 glycoproteins embedded in the viral

envelope. Both of these subunits have a high degree of homology (86% of DNA and amino acid sequences are identical) between HSV-1 and HSV-2, and they are highly conserved (99%) among different strains for the same viral type.[205] Both proteins are highly immunogenic in humans, eliciting strong antibody responses.[206] Mice that are immunised with the glycoproteins purified from virus-infected cells are protected from viral challenge.[207] Immunisation in guinea pigs with recombinant virus expressing HSV-2 gD reduced the severity of genital herpes.[208]

In a clinical trial of an inactivated HSV-2 glycoprotein vaccine administered to HSV-2 seronegative sexual partners of individuals with genital herpes,[209] both humoral and cell-mediated immune responses were elicited, but the vaccine was not significantly better than placebo in preventing the acquisition of infection. In a study of patients with a history of recurrent genital herpes, a recombinant gD vaccine increased HSV-2 and gD2-specific antibody levels;[210] however, there was no significant effect on the frequency of symptomatic outbreaks. In a study of 137 HSV-2 seronegative individuals, a recombinant subunit vaccine containing gB2 and gD2 combined with a MF59 adjuvant produced an increase in both humoral and cellular responses to HSV-2.[211] However, 2 large, multicentre, randomised trials of this vaccine showed that the high titres of specific neutralising antibodies do not confer increased protection against HSV-2 infection.[212] In over 2000 HSV-2 seronegative patients, the HSV-2 acquisition rates did not significantly differ between the placebo and vaccine recipients.

A study of recombinant HSV-2 gB2 and gD2 in an intramuscular subunit vaccine administered to HSV-seronegative and HSV-1 seropositive women showed that the vaccine elicited immunoglobulin (Ig)G and IgA antibody levels comparable with those of HSV-2 gB2 and gD2 responses to recurrent HSV-2 genital infection.[213] Furthermore, in a placebo-controlled trial of recombinant gD2 and gB2 in MF59, a novel adjuvant, either both glycoproteins in MF59 or of MF59 alone were administered at 0, 2, 12 and 14 months.[214] The glycoprotein group had significantly reduced time to healing in the first genital herpes outbreak after the vaccination in both men and women. Furthermore, glycoprotein-specific and neutralising antibodies were boosted by the vaccination. However, significant reduction in the severity of the episode was only shown in women, and the monthly rate of recurrences was not significantly reduced in either group. Therefore, this vaccine is not being currently pursued for genital herpes.

A multicentre study compared the effects of a killed vaccine with episodic treatment of aciclovir in the suppression of recurrent HSV infection.[215] Compared with the aciclovir group, the vaccinated group had significant reductions of recurrences, disease-free days, recurrence duration and active disease days per year. However, several technical aspects of this study are insufficient to support the use of this vaccine as a preventative. Further studies are warranted. A recent clinical trial of a recombinant gD2 vaccine with the adjuvant SBAS4 showed significant efficacy in preventing genital herpes disease in HSV-1 and HSV-2 seronegative females.[216] Vaccine efficacy was not observed in either males or HSV-1-positive females. Although full protection was not achieved, this finding warants further studies into the immunopathogenesis of this disease.

5.2 DNA-Based Vaccine

DNA-based vaccines have also been under investigation for their possible role in immunisation, first demonstrated in an experimental influenza virus infection model in mice.[217] Subsequent studies have examined this immunisation strategy in other species,[218-221] and in other viral infections[222-225] including the herpes virus,[226] and have shown effectiveness. In a study targeting the herpes virus, a plasmid expressing the gene for HSV-2 gD2 and under the control of the CMV immediate-early gene promotor was used to immunise guinea pigs before intravaginal infection with HSV-2, while control animals were given gG2 and gD2 with Freund's adjuvant.[227] The DNA vaccine elicited humoral

immune responses similar to those seen after HSV-2 infection, and protected the animals from primary genital HSV-2 infection. HSV-2 replication in the genital tract was significantly reduced and there were fewer recurrences after the primary infection, with significantly reduced latent infection in the sacral root ganglia. Phase I studies in human are underway.

5.3 Replication Incompetent Vaccines

A disabled infectious single cycle (DISC) vaccine, which has an altered gH, has shown immunogenicity in phase I clinical trials.[228] Several issues could impede development of this vaccine. First, there is no established serological assay that will distinguish the gH-negative versus wild-type immune response. Second, although this virus is reactivation-impaired, the possibility that superinfection with wild type could provide an exogenous source of gH sufficient to allow for reactivation will be difficult to rule out. Assuming these issues are possible to address, the potential for a live vaccine against genital herpes is very good.

6. Conclusion

Significant advances have been made in the management of genital herpes over the past few years. Two new agents, valaciclovir and famciclovir, have been added to the treatment armamentarium. At the same time, aciclovir has become available through several generic sources, reducing its cost substantially. All three drugs appear to be equipotent in the treatment of first episodes. Since these are often complicated and prolonged, all patients should be treated. Administration advantages with both famciclovir and valaciclovir offer compelling reasons for use of either prodrug. Five times daily administration of aciclovir is impractical and may be especially problematical during this emotionally-intense phase of infection. All three drugs are also effective in early treatment of individual episodes. Again, the administration advantages of the prodrugs are valuable. Famciclovir appears to have a broad effect against multiple symptoms, while valaciclovir has shown a 10% improvement over placebo in preventing classical lesions. Such differences may have more to do with study designs than inherent differences in the nucleosides themselves. Direct comparisons have not been presented. It is valid to try each drug in patients (not simultaneously) to determine which they prefer. However, episodic therapy is not the option of choice for many patients. Suppressive therapy is becoming more universally recommended because of good safety and efficacy. Benefits against asymptomatic shedding provide hope that these agents may also be shown in the future to modify transmission. However, this has yet to be demonstrated. Aciclovir is conveniently administered for suppression. It is just as effective as valaciclovir, but has not been studied against famciclovir. For patients with low frequency disease, there is a potential administration convenience advantage to once-daily valaciclovir. However, it is generally thought that breakthroughs in immunocompetent patients occur because of the short plasma half-lives of each of these compounds, leading to trough periods without antiviral activity. Accordingly, it is our suggestion to reinforce with the patient that once daily dosing means every 24 hours, twice daily means every 12 hours, 3 times daily means every 8 hours, and so forth. We often commence therapy with a twice daily approach, moving selected patients down to once daily valaciclovir. Other clinics may start patients with modest frequency disease on a single daily dose and increase frequency of administration in the case of treatment failure.

We continue to face an epidemic of genital herpes, which increases despite our best safer sex messages. While small strides have been made in prevention with vaccination, much more work needs to be done and significant advances in our understanding of immunopathogenesis are required. Topical agents for recurrences and systemic agents with prolonged plasma half-lives which might reduce the potential for breakthroughs during suppressive therapy are lacking. Advances in preventing or reducing asymptomatic shedding provide hope that transmission may be influenced through

this approach; however, no transmission data are yet available. It is worth considering the fact that, if long term suppressive therapy may reduce the risk of transmission, withdrawal of the same might increase the risk. Accordingly, these issues should be carefully followed in the design of future studies and patients coming off suppressive therapy should be so advised. Pending data from current trials, suppressive therapy should be withdrawn carefully, and only where necessary and appropriate, and with counselling and reinforcement of safer sex practices.

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