

New Therapies and Prevention Strategies for Genital Herpes

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Genital herpes is among the most prevalent sexually transmitted diseases. Optimal management of genital herpes includes accurate diagnosis, antiviral therapy, and counseling of patients about complications and transmission of herpes simplex virus (HSV). Antiviral therapy offers significant palliation, and the option of episodic or suppressive treatment should be offered to all patients with genital herpes. Valacyclovir and famciclovir are two newer antiviral agents that are effective and safe for the treatment of genital herpes. Prevention strategies for sexual and perinatal transmission of HSV have not been well defined. Availability of type-specific serological tests for HSV antibodies may assist in identifying persons at risk for acquiring or transmitting HSV infection. Further research is needed to define strategies to prevent the spread of this epidemic infection.

Genital herpes is a common chronic sexually transmitted disease (STD) for which there is no cure. Despite the decline in bacterial STDs in the past decade in the United States, the seroprevalence of herpes simplex virus type 2 (HSV-2) in adults has increased 32%, from 16.4% to 21.9% [1, 2]. Both HSV-2 and HSV-1 can cause genital herpes. HSV initially causes epithelial infection but also establishes latency in sacral neuronal ganglia [3]. Once latency is established, neither host immunity nor currently available chemotherapeutic agents can eradicate the latent virus. Reactivation of the virus and infection of the genital skin or mucosa cause the troublesome recurrent disease.

Systemic antiviral therapy results in significant amelioration of clinical disease. Acyclovir has been the standard treatment for genital herpes for the past decade. New antiviral agents with greater bioavailability than acyclovir appear safe and may offer more convenient dosing regimens. Optimal management includes not only antiviral therapy but also counseling of the patient with regard to the natural history of recurrent disease, sexual and perinatal transmission of HSV, and methods to prevent further spread of infection (see table 1). This review focuses on the recent developments in the areas of therapeutics for and prevention of genital HSV infection.

Methods

A MEDLINE search was conducted with use of the term *herpes simplex virus* for articles published since 1992. Additional searches were done for the terms *valacyclovir*, *famciclovir*, *cidofovir*, *trifluridine*, and *neonatal herpes*. Preliminary results of clinical trials published in abstracts of the

Interscience Conference on Antimicrobial Agents and Chemotherapy and meetings of the International Society for STD Research were also included in this review. Experts in the field were contacted to identify completed study reports that are undergoing peer review but have not yet been published.

Diagnostic and Counseling Considerations

Most persons with serologically documented HSV-2 infection do not have a history of clinically recognized genital herpes [4–6]. While many of these persons will never become symptomatic, some will present for medical care with a first-recognized recurrence [7], will seek care for atypical genital complaints [8], or will be evaluated after they transmit the infection to their sex partners [9]. It is clear that manifestations of genital herpes, even at the time of primary acquisition, are extremely variable; as such, clinical diagnosis can be difficult. A classic presentation of genital herpes—a cluster of painful vesicles on an erythematous base—certainly occurs. However, recent studies suggest that these types of lesions are present in only 60%–70% of persons with clinically symptomatic illness. Clinical manifestations include ulcerative lesions, fissures, cervicitis, dysuria, and a wide variety of other clinical signs and symptoms [5, 10]. Therefore, laboratory confirmation of genital herpes is desirable for all persons for whom a definitive clinical diagnosis cannot be made.

Virological typing of the isolate is recommended, as genital HSV-2 recurs much more frequently than genital HSV-1 [11]. For patients, laboratory confirmation helps dispel doubts about the diagnosis and the (understandable) hope that there is an alternative explanation for symptoms. In addition, it is appropriate to confirm the diagnosis for patients given antiviral therapy. Viral isolation and HSV antigen detection are both useful tests. The growth of HSV in tissue culture within 5 days makes viral isolation an especially useful assay, particularly if the isolate can be typed as HSV-1 or HSV-2.

As HSV cannot be reliably recovered even from new lesions, serological diagnoses of persons with HSV-2 would be helpful in management. However, many currently available commer-

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Table 1. Issues in the management of genital herpes.

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- Accurate diagnosis, with viral typing
 - Information regarding natural history, subclinical shedding, sexual transmission, and neonatal herpes*
 - Antiviral therapy, guided by disease severity and patient preference
 - Counseling about living with a chronic sexually transmitted infection
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* Resources available to persons with genital herpes include organizations, hotlines, publications, Internet sites, and local support groups. The American Social Health Association (1-800-230-6039) provides educational pamphlets; publishes *The Helper*, a quarterly newsletter for people with herpes infections; and sponsors local support groups. The National Herpes Hotline number is (919) 361-8488. The American Medical Association offers a free booklet: "Genital Herpes: A Patient Guide to Treatment." On-line resources include the Herpes Advice Center (www.advicecenter.com), Cafe Herpe (www.cafeherpe.com), and Viridae (www.viridae.com).

cial serological assays do not accurately distinguish between HSV-1 and HSV-2 infection [12]. The availability of accurate type-specific serological methods would allow identification of subclinical HSV infection, confirmation of previous clinical diagnosis, or diagnosis of symptoms that are atypical of HSV infection. Such type-specific assays are expected to be marketed in 1998.

Most HSV appears to be transmitted from persons who have undiagnosed infection, and more active identification of HSV-2-seropositive persons could be initiated in high prevalence settings, such as STD clinics. Recent data suggest that most persons with HSV-2 antibodies but no history of clinical disease shed virus periodically in the genital tract and are potential transmitters of infection [13].

At the initial visit, palliation of symptoms is the most important objective for patients with symptomatic first-episode genital herpes. During the acute illness, the patient is often too concerned with the physical illness and with having an STD to comprehend the chronic nature of the infection. Thus, the long-term issues posed by an incurable STD are often best discussed after the primary illness resolves. The diagnosis of genital herpes is often associated with psychosexual distress. Most patients with diagnosed genital herpes report feelings of depression and isolation and fear of rejection and discovery [14, 15]. These feelings tend to subside with time. The distress associated with HSV infection is exacerbated by the frequent difficulties in obtaining an accurate diagnosis and the perceived lack of interest of the clinician in the emotional and sexual consequences of infection.

Counseling should emphasize the recurrent and highly variable nature of genital herpes, explain the potential for transmission to sex partners and neonates, and the occurrence of subclinical shedding. However, it is also important to reassure the patients that they will be able to continue to have intimate relationships. Women are often concerned about the possibility of transmitting the infection to their children and need reassurance that the risk of transmission during delivery is minimal for women with recurrent genital herpes. Patients also should

be encouraged to tell their potential sex partners of their infection, to abstain from intercourse during recurrences, and to use condoms at other times.

It is useful to reinforce these issues at more than one visit and to see patients at their first recurrence to confirm their ability to recognize recurrences. Many patients are dismayed at their first recurrence because they realize that this infection will recur, while others are relieved that the symptoms are much milder than those during the primary episode. Several publications are available for patients with genital herpes that reinforce the counseling information and offer additional resources. The option of episodic or suppressive antiviral therapy should be offered to all patients (table 1).

New Therapies for Genital Herpes

Acyclovir is an effective antiviral agent that has been shown to shorten the clinical course of the disease when taken acutely and to prevent most recurrences when taken chronically. The clinical effect of acyclovir therapy on first-episode infection is substantial: fever and constitutional symptoms are reduced within 48 hours of initiation of therapy, and local symptoms also diminish. As such, antiviral therapy is recommended for all patients with clinical first-episode genital HSV infection who present with lesions. However, acyclovir does not affect the natural history of the subsequent recurrent disease; that is, patients treated with acyclovir for first-episode genital herpes will still experience recurrent infections.

The dose of acyclovir for episodic therapy currently approved by the U.S. Food and Drug Administration is 200 mg po five times a day. Adherence to this dose is clearly cumbersome. However, acyclovir at a dosage of 400 mg three times a day has been extensively used in clinical practice and appears as effective. It is unlikely that clinical trials comparing the two dosing regimens will ever be done. Higher doses of acyclovir (800 mg five times a day) do not offer additional benefit [16].

The current formulation of topical acyclovir is not as effective as any of the oral medications. Moreover, concomitant use with oral therapy offers no additional benefit [17], and, as such, topical acyclovir is not advised for either first-episode or recurrent infection. Two new therapeutic agents, valacyclovir and famciclovir, have recently become available for treatment of genital herpes. Below is a review of these agents in the treatment of genital herpes (table 2).

Pharmacology of Valacyclovir and Famciclovir

Valacyclovir is an ester of acyclovir that is rapidly and almost completely converted to acyclovir by hepatic and intestinal enzymes [27] and increases the bioavailability of acyclovir from ~15% to 54%. Therefore, a 1,000-mg oral dose of valacyclovir results in an area under the curve similar to that of a 350-mg dose as a 1-hour infusion: 89 and 84 $\mu\text{M} \times \text{h}$, respec-

Table 2. Data from randomized, controlled clinical trials of valacyclovir and famciclovir for immunocompetent persons.

Topic of study, reference	Study population (n)	Treatment	Outcome measures	Findings and comments
First-episode genital herpes				
[18]	Healthy adults (643) with first-episode HSV infection	VAL (1,000 mg b.i.d.) vs. ACV (200 mg 5 times a day), for 10 d	Lesion healing time, viral shedding, loss of pain	No significant differences in the two arms
[19]*	Adults (951) with first-episode HSV infection	FCV (125 mg, 250 mg, or 500 mg t.i.d.) vs. ACV (200 mg 5 times a day), for 10 d <i>and</i> FCV (250 mg, 500 mg, or 750 mg t.i.d.) vs. ACV (200 mg 5 times a day), for 10 d	Lesion healing time, loss of symptoms, viral shedding	No significant differences between any arms
Episodic therapy for recurrent genital herpes				
[20]	Healthy adults (987) with recurrent genital HSV infection (≥ 4 recurrences in past year)	VAL (500 mg b.i.d. vs. 1,000 mg b.i.d.) vs. PLC, for 5 d (patient-initiated)	Median duration of episode, pain, viral shedding; fraction with aborted recurrences	VAL decreased lesion duration from 6 to 4 d, decreased viral shedding from 4 to 2 d; rate of aborted recurrences increased from 21% to 31%
[21]	Healthy adults (739) with recurrent genital HSV infection (≥ 4 recurrences in past year)	VAL (500 mg b.i.d.) vs. ACV (200 mg 5 times a day), for 5 d (patient-initiated)	Duration of all signs, symptoms, viral shedding	No differences between the two treatment arms; sufficient power to detect equivalence
[22]	Healthy adults (467) with recurrent HSV infection (≥ 3 recurrences/y)	FCV (125 mg, 250 mg, or 500 mg b.i.d.) vs. PLC, for 5 d (patient-initiated)	Duration of episode, signs, and symptoms; viral shedding	FCV decreased episode duration from median of 4.8 d to 3.8 d, decreased viral shedding from 3.3 d to 1.7 d; no differences between FCV doses
Suppressive therapy for recurrent genital herpes				
[23]	Healthy adults (382) with recurrent genital HSV infection (≥ 8 recurrences/y)	VAL (500 mg once a day) vs. PLC, for 16 w (ratio, 3:1)	Time to first clinical recurrence	Hazards rate for VAL vs. PLC = 0.16 (95% CI, 0.11–0.21); 69% of VAL recipients, vs. 9.5% of PLC recipients, were recurrence-free
[24]	Healthy women (375) with recurrent genital HSV infection (≥ 6 recurrences/y)	FCV (125 mg q.d. or b.i.d., 250 mg q.d. or b.i.d., or 500 mg q.d.) vs. PLC, for 4 mo	Time to first clinical recurrence	42% of placebo and 78% of FCV (250 mg b.i.d.) recipients were free of recurrences
[25]	Healthy adults (455) with frequently recurring genital herpes	FCV (125 mg t.i.d., 250 mg b.i.d., or 250 mg t.i.d.) vs. PLC, for 1 y	Time to first clinical recurrence	Median time to recurrence: PLC, 1.5 mo; FCV 250 mg b.i.d., 11 mo; FCV 125 mg t.i.d., 8 mo; FCV 250 mg t.i.d., 10 mo
[26]	Healthy adults (1,479) with frequently recurring genital HSV infection	VAL (250 mg q.d. or b.i.d., 500 mg q.d., or 1,000 mg q.d.) and ACV 400 mg b.i.d. vs. PLC, for 1 y	Time to first clinical recurrence	48%–50% of VAL (250 mg b.i.d. or 1,000 mg q.d.) and ACV (400 mg, b.i.d.) recipients were recurrence-free; 40% of VAL 500 mg q.d., 22% of VAL 250 mg q.d., and 5% of placebo recipients were recurrence-free

NOTE. ACV = acyclovir; FCV = famciclovir; HSV = herpes simplex virus; PLC = placebo; VAL = valacyclovir.

* Three randomized, controlled clinical trials.

tively [28]. The safety profile of valacyclovir appears comparable to that of acyclovir when administered for up to 1 year.

Famciclovir, a prodrug of penciclovir, is a nucleoside analogue that effectively inhibits HSV-1 and HSV-2 [29]. Similar to acyclovir, penciclovir requires viral thymidine kinase (TK) for phosphorylation to the monophosphate [30]. Penciclovir triphosphate inhibits viral DNA synthesis with in vitro activity similar to that of acyclovir [31]. Oral famciclovir is 77% bioavailable. The safety and efficacy of famciclovir have been evaluated in several clinical trials, and the drug appears to be

well tolerated [32]. The most common reported adverse effects were nausea, headache, and diarrhea, occurring in similar proportions of famciclovir and placebo recipients.

First-Episode Genital Herpes

Valacyclovir (1,000 mg b.i.d. for 10 days) was compared to acyclovir (200 mg five times a day for 10 days) for treatment of first-episode genital herpes [18]. No significant differences in clinical or virological outcomes were noted between

acyclovir and valacyclovir recipients, and both drugs were well tolerated. In clinical studies comparing famciclovir with acyclovir (200 mg five times daily) for the treatment of first-episode genital herpes, the two drugs appeared comparable in their ability to effect viral shedding, lesion healing, and resolution of symptoms [19]. The dosage of famciclovir (250 mg po t.i.d.) was effective and well tolerated.

Recurrent Genital Herpes

Valacyclovir has been evaluated for the treatment of genital herpes in two studies [20, 21]. In a double-blind, placebo-controlled trial of 987 patients with recurrent genital herpes whose therapy was initiated at the first sign or symptom of a recurrence, valacyclovir provided significant reduction in the duration of the lesion and accompanying discomfort [20]. Time to complete resolution of signs and symptoms was decreased by a median of 2 days among valacyclovir recipients. Healing of lesions was faster in valacyclovir (4.1 days) than placebo recipients (6.0 days), as was resolution of viral shedding. No differences in outcomes were noted between the two groups, which received valacyclovir (500 mg b.i.d. vs. 1,000 mg b.i.d.) for 5 days. Therefore, the lower dose is recommended. Adverse effects were rare and did not occur at a different rate among placebo or valacyclovir recipients. As expected from experience with acyclovir, headache and nausea were the most frequent complaints. Another study of 739 patients with recurrent genital herpes, which compared valacyclovir (500 mg b.i.d.) to acyclovir (200 mg five times a day) given for 5 days, showed that the two regimens were equivalent [21].

The efficacy of oral famciclovir for the treatment of recurrent genital herpes has been evaluated in a randomized, placebo-controlled study. In a patient-initiated trial of 467 subjects with recurrent genital herpes, famciclovir recipients (compared to placebo recipients) had significant reductions in healing time (median, 3.8 days for famciclovir recipients vs. 4.8 days for placebo recipients), duration of viral shedding (1.7 days vs. 3.3 days), and duration of all symptoms (3.2 days vs. 3.7 days) [22]. Famciclovir (125 mg twice daily) was effective, and higher doses did not confer additional benefit.

Suppressive Therapy for Genital Herpes

Valacyclovir has been evaluated for suppression of genital herpes recurrences [23]. Valacyclovir (500 mg once daily) was compared to placebo for 382 patients with a history of at least 8 recurrences per year. The drug was taken until the first recurrence or for 16 weeks. At that time, 69% of valacyclovir recipients were recurrence-free, vs. 9.5% of placebo recipients. Results of a year-long study of suppressive valacyclovir suggest that the benefit of valacyclovir at a dosage of 500 mg once a day is greater in patients with ≤ 9 recurrences per year. In patients with ≥ 10 recurrences per year, valacyclovir at a dosage of 250 mg po b.i.d. or 1,000 mg po q.d. provides substan-

tially better relief from recurrences [26]. In both groups of patients, the proportion of patients without recurrences was similar among those receiving valacyclovir and standard acyclovir suppressive therapy.

Studies indicate that famciclovir is also effective and well tolerated when taken daily. Several dosing regimens have been investigated, and it appears that a dosage of 250 mg b.i.d. results in the most reliable suppression of genital herpes recurrences [24]. In a study of 375 women with frequently recurring genital herpes who were treated with daily famciclovir for 4 months, 78% of those receiving 250 mg po b.i.d., vs. 42% of placebo recipients, had no recurrences. This dosage was clearly superior to lower dosages and to 500 po q.d. regimens of famciclovir. Another study, of 455 patients with recurrent genital herpes, confirmed the benefit of 250 mg po b.i.d. as the most effective dosage of famciclovir [25]. It is of interest that the effective dosage of famciclovir is lower for episodic treatment (125 mg b.i.d.) than for suppressive treatment (250 mg b.i.d.).

About 3% of isolates obtained from healthy patients demonstrate *in vitro* resistance to acyclovir. The frequency of *in vitro* resistance has not changed from that prior to availability of acyclovir and does not appear to increase among patients who have received several years of daily suppressive therapy with acyclovir [33]. The demonstration of *in vitro* acyclovir resistance in HSV strains from immunocompetent persons has not been associated with clinical failure of acyclovir therapy. An immunocompetent person with genital herpes caused by an HSV-2 strain with an altered TK level has been reported [34]. All isolates recovered from this person during multiple recurrences had an altered TK level, and acyclovir did not offer clinical benefit. Another report documents TK-deficient persistent genital herpes in an otherwise immunologically normal woman that resolved after topical foscarnet therapy [35].

Treatment of Patients with HIV Infection and Genital Herpes

Anecdotal observations suggest that patients with HIV infection have more frequent and prolonged episodes, with slower response to acyclovir, even in the absence of overt acyclovir resistance. However, few studies have examined the impact of HIV on the natural history of HSV infection. Natural history studies suggest that persons with HIV infection may have a modest increase in the rate and duration of recurrences but a substantial increase in the rate of subclinical shedding [36, 37].

Most HSV infections in persons with HIV infection will respond to acyclovir, although often slower than those in immunocompetent persons. Many patients with HIV infection benefit from chronic suppressive therapy. Famciclovir at a dosage of 500 mg b.i.d. has been studied as suppressive therapy for genital herpes in HIV-infected persons [38] (table 3). In a crossover, placebo-controlled study of 48 patients in which culture specimens from the genital area were obtained daily, the relative

Table 3. Data from clinical trials of therapy for genital herpes in persons with HIV infection.

Reference	Study design	Study population (n)	Treatment	Outcome measure(s)	Findings and comments
[39]	Case series	AIDS patients (36) with HSV unresponsive to ACV	Topical 1% ophthalmic trifluridine solution	Lesion healing	29% had complete lesion healing (median time, 7.1 w)
[38]	Randomized, controlled, crossover	HIV+/HSV+ patients (48) with median CD4 cell count of 384/mm ³ (range, 0–921/mm ³)	FCV (500 mg b.i.d.) vs. PLC, for 8 w each; viral culture specimens obtained daily	Viral shedding (clinical and subclinical); days with lesions	Intent-to-treat analysis; decrease in viral shedding, from 11% to 1% of days, and in days with lesions, from 11% to 4% of days; most reactivation was subclinical
[40]	Randomized, controlled	AIDS patients (30) with HSV unresponsive to ACV	CDV gel (0.3% or 1%) or PLC topically b.i.d. for 5 d	Lesion healing; viral shedding	50% of CDV recipients vs. no PLC recipients had complete or good response; 87% and none, respectively, became culture-negative
[41]	Randomized, controlled	HIV+/HSV+ patients (1,062) with median CD4 cell count of 320/mm ³	VAL (500 mg b.i.d.) vs. VAL (1,000 mg q.d.) vs. ACV (400 mg b.i.d.) for 1 y	Time to first clinical recurrence	Hazard ratio for VAL 500 mg b.i.d. vs. ACV, 0.7 (95% CI, 0.5–1.0); for VAL 1,000 mg q.d. vs. ACV, 1.3 (95%CI, 0.9–1.8)

NOTE. CDV = cidofovir; FCV = famciclovir; HSV = herpes simplex virus; PLC = placebo; VAL = valacyclovir.

risk of viral shedding was 0.15 (95% CI, 0.06–0.42) during administration of famciclovir vs. placebo. Among 26 persons who completed both arms of the study, HSV-2 was isolated on 9.7% of the days of placebo administration, compared to 1.3% of the days of famciclovir administration, an 87% reduction. The proportion of days for which lesions were evident was also reduced, from 13.7% of days with placebo to 4.4% of days with famciclovir. Thus, daily oral therapy with famciclovir effectively reduced the frequency of recurrences as well as the frequency of clinical and subclinical viral shedding in HIV-infected patients.

The efficacy of valacyclovir for suppression of genital herpes for 1 year in HIV-seropositive persons with a history of recurrent genital herpes was analyzed in a randomized, placebo-controlled study [41]. Patients who received 500 mg b.i.d. of valacyclovir had a significantly longer interval before the first recurrence than did patients who received 1,000 mg q.d. There were no significant differences in the time to first recurrence between patients who received valacyclovir (either dosage) and those who received a standard dose of acyclovir (400 mg b.i.d.). The occurrence of adverse events was comparably low in acyclovir and valacyclovir recipients.

Valacyclovir (8 g/d) has been evaluated in clinical trials for the prevention of cytomegalovirus disease in immunocompromised patients. A syndrome of thrombotic microangiopathy has been described in up to 3% of patients with HIV infection or bone marrow transplants who received this high dose of valacyclovir for a prolonged period. Among HIV-infected patients, administration of several concomitant medications was

also associated with development of thrombotic microangiopathy [42]. No immunocompetent patients or patients receiving up to 3 g of valacyclovir daily have developed thrombotic microangiopathy [43]. The syndrome most likely results from use of very high doses rather than underlying immunosuppression. Therefore, valacyclovir can be used for treatment of genital herpes in patients with HIV infection or other immunocompromising conditions.

The frequency of acyclovir resistance in HIV-infected patients appears low, and the risk factors for the development of resistance have not been well defined. At present, routine in vitro testing of HSV isolates for susceptibility to acyclovir is not recommended. However, isolates from patients with persistent HSV infections unresponsive to acyclovir, especially those with advanced HIV disease, should be tested for resistance to acyclovir. In this setting, in vitro resistance correlates well with acyclovir failure [44]. Most acyclovir-resistant HSV infections require therapy with alternative agents. The most common mechanism for acyclovir resistance is TK deficiency. Because famciclovir is also dependent on TK for initial phosphorylation, most acyclovir-resistant strains are also famciclovir-resistant.

Foscarnet

Foscarnet is a phosphonate viral DNA polymerase inhibitor. Systemic toxicity during intravenous administration limits the use of foscarnet to patients whose acyclovir therapy fails because of development of resistance. In this population, however, foscarnet has become the preferred agent. Foscarnet infu-

sion healed 81% of 26 patients with acyclovir-resistant HSV infection [45]. A comparative study of foscarnet (40 mg/kg q8h) and vidarabine (15 mg/kg q.d.) showed that foscarnet therapy led to the healing of all eight patients, while therapy failed for all patients assigned to vidarabine [46]. The most common toxic effects are renal insufficiency and metabolic disturbances, especially hypophosphatemia. HSV infections that recur after foscarnet therapy can be either acyclovir-susceptible or acyclovir-resistant. HSV resistance to foscarnet has also been reported, usually in the setting of prolonged foscarnet therapy [47]. In that setting, the addition of acyclovir to the treatment regimen may be beneficial.

Cidofovir

Cidofovir is an acyclic nucleoside phosphonate that, unlike acyclovir, is phosphorylated only by cellular enzymes. Therefore, cidofovir is active against HSV strains with a deficient or altered TK level [48]. Topical and intravenous cidofovir has been used successfully to heal acyclovir-resistant lesions in patients with AIDS and after marrow transplantation [49]. A recently completed randomized, double-blind, placebo-controlled trial of topical cidofovir gel (0.3% or 1.0%) in 30 patients with AIDS who did not respond to acyclovir therapy showed that lesions of 10 of 20 cidofovir recipients healed by at least 50%, compared with none of the placebo recipients [40]. Twenty-three percent of cidofovir recipients had mild or moderate local cutaneous adverse effects. Because of the potential for renal toxicity with intravenous administration, topical cidofovir may be preferred for treatment of genital herpes. Topical cidofovir is currently available on a compassionate basis for treatment of acyclovir-resistant herpes infection and may be an alternative for patients who are poor candidates for foscarnet therapy.

Trifluridine

Topical trifluridine is frequently used for treatment of ophthalmic herpes infections. In a series of 26 patients with AIDS and mucocutaneous herpes infections unresponsive to acyclovir, there was complete healing in 7 patients and partial healing in 14 patients [39]. Anecdotal reports also suggest that the use of IFN- α may potentiate the antiviral effects of trifluridine [50]. These agents may be useful in some cases.

Antivirals in Pregnancy

While routine use of acyclovir during pregnancy is not recommended, some experts recommend the use of acyclovir for amelioration of signs and symptoms in women with symptomatic primary genital herpes. Because the goal of such therapy is palliation and not prevention of an adverse pregnancy outcome, the decision to treat should involve the collaboration of the pregnant patient. A pharmacokinetic evaluation of acyclovir

in the third trimester of pregnancy showed that the disposition of acyclovir in pregnant women and in other adults appears similar [51]. A potential concern is the development of obstructive uropathy in the newborns, secondary to acyclovir crystals, yet no such abnormalities were observed in that study or among a much larger number of infants with neonatal herpes treated with prolonged, and often high-dose, intravenous acyclovir [52]. However, the effects of postnatal exposure may not mirror exposure in utero.

Glaxo-Wellcome, in collaboration with the Centers for Disease Control and Prevention, maintains a voluntary registry of women who have received acyclovir and valacyclovir during pregnancy. Such patients can be reported to this registry by telephone (1-800-722-9292, extension 38465). The data are evaluated at 6-month intervals. As of June 1996, 636 women who received acyclovir in the first trimester and whose birth outcomes are known had been prospectively reported. Fifteen (2.3%) of their children had birth defects, compared to a background rate of 3%. No consistent pattern of abnormalities has been noted. Although the number of women evaluated is insufficient to exclude a small increase in the rate of congenital abnormalities, the lack of a statistically significant increase in the incidence of defects or a pattern of abnormalities is reassuring. The safety and pharmacokinetics of valacyclovir and famciclovir in pregnancy have not been established.

Strategies for Prevention of Sexual Transmission and Neonatal Herpes

Prevention of Sexual Transmission

Strategies for the control of genital herpes have not been well defined, and a combination of methods may be needed to contain the current epidemic of genital herpes (table 4). For persons with recognized HSV infection, behavioral change is probably the most important tool for protection of sex partners. Abstinence is advised during lesional episodes and condom use at all other times. Despite the advice to use condoms for prevention of HSV, their effectiveness has not been evaluated for viral STDs. Given the wide anatomic distribution of HSV during reactivation, the protection offered by a condom is most likely incomplete.

While nonoxynol-9 has been shown to be protective in models of HSV vaginitis in mice [56], human data are lacking, and the compound is ineffective as therapy for established HSV infection. Acyclovir (400 mg po b.i.d.) has been shown to effectively suppress subclinical shedding [53]. Therefore, chronic antiviral therapy may result in a decrease of HSV transmission to sex partners. However, HSV DNA remains detectable on 8% of days of suppressive acyclovir therapy [57]. Clinical trials to evaluate the ability of the antiviral drugs to interrupt transmission are in progress. Chronic suppression of viral reactivation may become one of the strategies for HSV control in selected settings. However, given that most people

Table 4. Data regarding prevention of sexual and perinatal transmission of HSV and maternal morbidity associated with abdominal deliveries.

Topic of study, reference	Study design	Study population (n)	Treatment	Outcome measures	Findings and comments
Prevention of sexual transmission [53]	Randomized, controlled, crossover	Healthy women (34) with genital HSV-2 infection for <2 y	ACV (400 mg b.i.d.) vs. PLC, for 10 w each	Subclinical viral (positive culture, no lesion) evident by daily viral cultures	Intent-to-treat analysis; subclinical shedding decreased from 6.9% to 0.3% of days
Prevention of neonatal herpes [54]	Prospective cohort	Pregnant women (7,046) at risk for HSV seroconversion		Acquisition of HSV during pregnancy, as defined by seroconversion; neonatal HSV infection; premature delivery; decreased birth weight, head circumference, length	No difference among 94 infants whose mothers seroconverted (vs. not); 9 additional women acquired HSV at term, and 4 of 9 had an infant with neonatal HSV infection. Upper 95% confidence limit for neonatal HSV for women who seroconverted before delivery, $\leq 3.2\%$
Avoidance of abdominal deliveries [55]	Randomized, double-blind, controlled	Consecutive women (60) with first diagnosed episode of HSV infection during pregnancy	ACV (400 mg t.i.d.) vs. PLC, at 36th week until labor	Cesarean-section rate; lesions at delivery	Zero of 21 women receiving ACV vs. nine of 25 women receiving PLC had a cesarean section because of HSV infection ($P = .002$); no serologic or virological classification of HSV infections; difference not statistically significant if any cesarean section included

NOTE. ACV = acyclovir; HSV = herpes simplex virus; PLC = placebo.

with HSV-2 infection have unrecognized disease or mild symptoms, the public health impact of suppressive therapy for discordant couples is likely to be limited.

Since most persons with HSV-2 infection do not have a history of genital herpes, serological testing with type-specific antibody assays to identify those who are infected may also be an important component of the prevention strategy. Behavioral change and, possibly, suppressive therapy can then be used for prevention of transmission to sex partners. The settings in

which serological screening may be particularly useful have not been identified.

Prevention of Neonatal Herpes and HSV Acquisition in Pregnancy

The risk of transmitting neonatal HSV is low (<2%) among women who are HSV-seropositive at the time of labor. Acquisition of HSV in the first or second trimester is not associated

with increased risk of adverse neonatal outcome [54]. Patients with a clinical history of recurrent genital herpes should be carefully examined at the time of labor. Women who have no clinical evidence of lesions in the genital area or prodrome should give birth vaginally. The presence of active genital lesions of the cervix or external genitalia is an indication for abdominal delivery [58]. Obstetric management of genital herpes acquired in late pregnancy is controversial and should be done in consultation with an expert. While abdominal delivery is thought to decrease the risk of neonatal herpes, it does not eliminate it completely.

The key to prevention of neonatal HSV is the prevention of acquisition of genital HSV-1 or HSV-2 infection late in pregnancy, as women who acquire genital herpes in late pregnancy are at high risk (30%–50%) for transmitting HSV to their infants. Such risk exists for HSV-seronegative women who acquire HSV-1 or HSV-2 infection and for HSV-1-seropositive women who acquire HSV-2 infection. Counseling to avoid sexual contact, including oral-genital contact, in late pregnancy is recommended. A greater appreciation of the potential to acquire HSV-1 via oral-genital sex in late pregnancy is needed, as nearly 30% of neonatal HSV infection is due to HSV-1. Accurate serological tests to identify women at risk of acquiring HSV infection may guide prevention strategies in the future.

Avoidance of Abdominal Deliveries for Women with Genital Herpes

While neonatal herpes is a rare event, many women with genital herpes have abdominal deliveries to avoid exposure of an infant to potentially infectious secretions. Antiviral therapy may also be potentially useful in this setting to limit the morbidity associated with cesarean section. A small randomized, double-blind clinical trial of women with clinically diagnosed first-episode genital herpes during pregnancy showed a reduction in the number of abdominal deliveries among women who received daily acyclovir treatment initiated in week 36 of gestation [55]. These data are promising, and further such research is needed.

Conclusions

Oral acyclovir, famciclovir, and valacyclovir have all been shown to reduce the duration of first and recurrent attacks of genital herpes. In recurrent disease, patient-initiated therapy tends to offer greater benefit because it starts earlier than physician-initiated therapy [59]. The recent studies of episodic therapy for genital herpes show that the clinical benefit of treatment of recurrences may be greater than previously appreciated and should receive more attention in the treatment of genital herpes. This increased benefit may reflect both marginally better performance of the newer antiviral agents in comparison with that

of acyclovir and a more carefully designed evaluation schedule during the clinical trials.

Regardless of the agent chosen, therapy should be initiated by the patient at the first sign or symptom of a recurrence. Such management requires education of patients regarding the manifestations of genital herpes and provision of an appropriate supply of the antiviral drug for use at home. Not all episodes or patients with recurrent HSV require antiviral therapy, but for persons with infrequent severe symptomatic episodes, episodic antiviral therapy is useful. Patients with frequent recurrences should be considered for suppressive rather than episodic therapy.

Suppressive therapy with acyclovir, valacyclovir, and famciclovir is also effective in preventing most episodes of genital herpes. Comparative studies between these newer agents have not been done, but the convenience of the dosing regimens, their costs, and clinicians' experiences are likely to guide their usage. Long-term safety of acyclovir has been demonstrated [33, 60, 61], and famciclovir and valacyclovir appear safe when used daily for 1 year.

Clear gaps exist in our knowledge of the relative effectiveness of the three available oral agents for treatment of genital herpes. In addition, only acyclovir has been demonstrated to reduce subclinical viral shedding, although such data should be forthcoming for the newer agents and are already available with regard to famciclovir administered to HIV-infected persons. The main reason to demonstrate a reduction in subclinical viral shedding is to evaluate the usefulness of antiviral agents for interruption of sexual and possibly perinatal transmission of HSV. However, such studies have not yet been done, and the degree of protection offered by such therapy is unknown.

Given that (1) genital HSV affects a substantial proportion of the population, (2) most infections are subclinical, and (3) behavioral measures are difficult to institute, the development of an effective vaccine against HSV-2 would provide a powerful tool for control of the epidemic. Unfortunately, the recently completed clinical trials of recombinant HSV-2 glycoprotein D/glycoprotein B vaccine showed that it did not offer protection against acquisition of HSV-2 infection, despite the induction of high neutralizing titers [62]. Other vaccines are currently undergoing clinical testing.

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