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**Dermatologic Clinics**

Volume 21 • Number 2 • April 2003

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## Topical cidofovir for the treatment of dermatologic conditions: verruca, condyloma, intraepithelial neoplasia, herpes simplex and its potential use in smallpox

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PII S0733-8635(02)00116-X

**Cidofovir** is a promising new drug that demonstrates pharmacologic activity against a wide variety of DNA viruses. Recent studies have shown that topical **cidofovir** (1% gel or cream) is effective in the treatment of recalcitrant and otherwise unmanageable viral cutaneous lesions induced by herpesviruses, poxviruses, and papillomaviruses. The authors review the pharmacology and uses of **cidofovir** in selected infectious dermatologic conditions.

### Mechanism of action and pharmacology

**Cidofovir** ([S]-1-[3-hydroxy-2-phosphonylmethoxypropyl] cytosine; HPMPC, Vistide) is a nucleotide

<http://home.mdconsult.com/das/article/body/1/jorg=journal&source=MI&sp=12950129&s...> 7/21/2003

analog of deoxycytidine monophosphate. In 1997 the U.S. Food and Drug Administration (FDA) approved an intravenous formulation of **cidofovir** for the treatment of cytomegalovirus retinitis in patients with AIDS <sup>[1]</sup>. **Cidofovir** also has antiviral activity against other DNA viruses, including herpes simplex virus (HSV) <sup>[2]</sup>, human papillomavirus (HPV) <sup>[3]</sup> <sup>[4]</sup>, and molluscum contagiosum virus <sup>[5]</sup> <sup>[6]</sup>. **Cidofovir** diphosphate, cidofovir's active metabolite, acts as a competitive inhibitor of DNA polymerase <sup>[7]</sup> <sup>[8]</sup>. The agent inhibits *viral* DNA polymerase more selectively than *human* DNA polymerase <sup>[9]</sup>, and it is not dependent upon thymidine kinase for activation. Thus, strains of HSV that are resistant to acyclovir, ganciclovir, or foscarnet are usually sensitive to **cidofovir** <sup>[10]</sup>.

The pharmacokinetic properties of **cidofovir** in humans have only been reported for the intravenous preparation <sup>[11]</sup> <sup>[13]</sup>. Approximately 90% of **cidofovir** is recovered in the urine within 24 hours after a single intravenous (IV) bolus dose. Probenecid reduces the renal clearance of **cidofovir**. Therefore, **cidofovir** can be eliminated from the systemic circulation by active tubular secretion in addition to filtration.

The IV formulation of **cidofovir** can be extemporaneously compounded for topical use. It costs approximately \$50 to \$75 per gram when compounded in a cream base containing a 3% concentration. No studies have been performed to investigate the bioavailability of topical or intralesional **cidofovir** in humans; however, several animal studies on topical administration of **cidofovir** are available. Cundy et al <sup>[11]</sup> observed the pharmacokinetic properties of **cidofovir** in African green monkeys by IV, oral, and subcutaneous routes of administration. In the latter investigations, subcutaneous bioavailability of **cidofovir** was noted to be 9.8% to 15.8%. Recently, Cundy et al <sup>[12]</sup> also investigated the availability of topical **cidofovir** on abraded and intact skin of rabbits; the bioavailability of topical **cidofovir** was 0.2% to 2.1% in intact skin and 41% in abraded skin. Furthermore, these investigators found that the bioavailability of **cidofovir** was enhanced in vehicles containing propylene glycol. The authors have used Dermovan (Galderma Laboratory Inc, Forth Worth, TX), a vehicle that contains propylene glycol, to compound topical **cidofovir**. The authors believe that the combination of a vehicle such as Dermovan and the use of occlusion significantly enhances the delivery of **cidofovir**. Most likely, occlusion increases the efficacy and absorption of the drug by increasing the skin surface area, hydration, and temperature, as well as by maintaining a reservoir of the drug within the stratum corneum. Inflammation and erosions produced by this form of delivery might also further increase absorption. The authors did not occlude facial skin or mucous membranes because of the known increased absorption of topical formulations in these areas.

Topical application of **cidofovir** on intact rabbit skin leads to negligible systemic exposure to the drug. In humans, a systemic adverse reaction has been reported in a single patient treated with intralesional **cidofovir** (2.5 mg/mL) for recurrent laryngeal papillomatosis <sup>[14]</sup>. This individual developed "precardial complaints," but no cardiac abnormalities were found. The pharmacokinetics of 0.3% and 1% **cidofovir** gel in HSV subjects has been described briefly <sup>[2]</sup>. Nephrotoxicity, neutropenia, and metabolic acidosis are potential serious systemic adverse effects of IV **cidofovir** therapy. In a bone marrow transplant patient with chronic renal failure and treatment-resistant condyloma, Bienvenu et al <sup>[15]</sup> recently reported topical-induced acute renal failure. After topical **cidofovir** application (1% once daily for 5 days, then 4% for 12 days), the lesions improved, whereas local erosions appeared. Acute renal failure with features of tubular acidosis occurred at day 19, but spontaneous recovery was observed after **cidofovir** was withdrawn.

**Cidofovir** has been reported to be embryotoxic in animals, including rats and rabbits. Furthermore, fetal soft tissue and skeletal anomalies have been reported in rabbits treated with 1.0 mg/kg IV daily. The use of **cidofovir**, even in topical form, should therefore be avoided in infants and pregnant women.

Andrei et al <sup>[16]</sup> reported that in vitro treatment of HPV-positive cells (compared with normal primary

human keratinocytes) with **cidofovir** results in a concentration- and time-dependent inhibition of cell proliferation. These authors also measured different parameters of apoptosis in HPV-positive cell lines, including induction of caspase-3 protease activity, translocation of phosphatidylserine from the inner part of the plasma membrane to the outer layer, disintegration of the nuclear matrix protein, DNA fragmentation, and the number of cells in apoptotic phase following cell cycle analysis. These studies showed that **cidofovir** induced apoptosis in HPV-positive cells. They also found that treatment of HPV-positive cells with **cidofovir** was associated with the accumulation of the tumor suppressor proteins p53 and Rb, as well as the cyclin-dependent kinase inhibitor p21/WAF-1. These findings suggest that the regression of papillomatous tumors observed in patients treated with **cidofovir** might be caused by (at least in part) the induction of apoptosis.

## Clinical effects

### *Anogenital squamous cell carcinoma in situ*

HIV-infected individuals are at increased risk for persistent HPV infection and HPV-associated anogenital intrasquamous epithelial neoplasms, including squamous cell carcinoma (SCC). Anogenital SCC is emerging as a major problem in HIV-infected individuals [17]. Homosexual and bisexual men with HIV are also at increased risk for persistent HPV infection and anogenital squamous intraepithelial lesions (ASIL), with prevalence rates of 20% to 45% [18] [19] [20]. Risk factors for ASIL include low CD4+ T cell counts and HPV infection [21] [22]. Studies on the natural history of anal disease have shown that ASIL can progress to high-grade disease in a relatively short time and that spontaneous regression of high-grade ASIL is rare [19] [20]. Like cervical cancer, anogenital SCC is associated with particular oncogenic HPV subtypes, specifically types 16, 18, 31, 33, and 51 [23] [24]. Perianal Bowen's disease (SCC in situ) is also most likely associated with HPV infection [25].

Recently, the authors treated three AIDS patients with recurrent anogenital Bowen's disease that was resistant to cryotherapy and electrocautery with topical **cidofovir**. Clinically, the patients exhibited multiple inguinal, perineal, and perianal pigmented papules in a mosaic pattern. Some areas exhibited multiple solitary lesions, whereas other areas showed confluence of papules to form plaques. The surfaces of the lesions were velvety with a dark brown, pink, or white discoloration. Anoscopic exam did not reveal anal lesions. Microscopic examination of lesional skin revealed SCC in situ. Sections revealed full-thickness atypia of the epidermis with cell crowding and an irregular "windblown" arrangement of the nuclei and scattered atypical mitotic. Patients were treated with 3% **cidofovir** in Dermovan once daily, 5 days a week, for 3 weeks. Topical 3% **cidofovir** was compounded as follows: 15 mL of **cidofovir** (75 mg/mL) was mixed with 22.5 g of Dermovan. The most common adverse effects were irritation and painful erosions during the first 2 weeks of treatment. All patients developed erythema and painful erosions at sites of previous lesions 5 to 13 days following application of the drug. Upon development of erosions, therapy was withheld for 3 to 5 days because erosions healed within 4 to 5 days. Treatment was then continued for a total of 3 weeks. After completion of treatment, lesions healed with postinflammatory hypopigmentation and hyperpigmentation. Surrounding perilesional skin appeared to be unaffected by treatment. No systemic side effects were noted. The patients achieved complete remission without clinical and histologic evidence of remaining disease 3 months following treatment. All individuals achieved complete remission without clinical and histologic evidence of remaining disease 18 months after discontinuation of therapy. It is unlikely that concomitant highly active antiretroviral therapy (HAART) therapy contributed to the regression of SSC in situ in these men because all patients initially developed lesions while receiving HAART for more than 6 months. In addition, there was no apparent difference in absolute CD4+ T cell counts and viral loads before and after topical therapy with 3% **cidofovir**. Furthermore, none of the antiretroviral agents that target HIV has known or predicted antiviral activity against HPV or any known anticancer activity. Current

therapeutic modalities for SCC in situ such as cryosurgery and 5-fluorouracil might be suboptimal because patients commonly experience multiple recurrences. In addition, anogenital SCC in situ is commonly multifocal, involving a large surface area, making complete surgical excision difficult. Thus, effective topical treatment of anogenital SSC in situ with antiviral medications might represent a significant therapeutic advance.

As mentioned above, HIV+ homosexual and bisexual men are at increased risk for persistent HPV infection, ASIL (including SCC in situ), and invasive anal SCC [17] [18] [19] [20]. Recently, it was shown that screening for anal ASIL in homosexual and bisexual men at all stages of HIV infection is cost effective [26]. The natural history of perianal ASIL is uncertain; however, recent studies of the natural history of anal disease have shown that the early stage of ASIL can progress to high-grade lesions in a short time period and that regression of high-grade ASIL is rare. Although HAART can suppress HIV replication for at least 2 years [27] [28], the long-term impact of potent combination antiretroviral therapy on the incidence of new anal and perianal neoplasia and regression is unknown. It is possible that the risk of ASIL, SCC in situ, and SCC might increase because of the longer life expectancy of HIV-infected individuals with sustained viral suppression [27]; therefore, early eradication of these lesions might significantly decrease morbidity and mortality of HPV-associated disease. In this regard, safe, effective, nonsurgical treatment modalities for HPV-associated anogenital lesions are needed. The prompt and dramatic response to topical **cidofovir** in the treatment of SSC in situ suggests that anogenital SCC in situ might be (in some cases) virally induced. Further studies on the use of topical **cidofovir** in benign and malignant HPV-associated mucocutaneous diseases are needed.

### ***Vulvar intraepithelial neoplasias***

Vulvar intraepithelial neoplasia is difficult to eradicate completely without extensive surgical intervention. Koonsaeng et al [29] reported that **cidofovir** might have a therapeutic role in this disease. She reported that topical **cidofovir** 1% in Beeler base (cetylic alcohol, 15 g; white wax, 1 g; propylene glycol, 10 g; sodium lauryl sulfate, 2 g; and water, 72 g) completely eradicated extensive vulvar intraepithelial neoplasia III in a 43-year-old woman with a 20-year history of genital warts who refused surgical resection. Human papillomavirus (HPV) has been clearly associated with such lesions in the female genital tract. Recently, Snoeck et al [30] reported on the use of **cidofovir** as a novel treatment of cervical intraepidermal neoplasia. **Cidofovir** 1% in gel was applied three times every other day on the cervix under colposcopic examination by a gynecologist. Within 1 month after the start of treatment, the cervix was removed surgically. Histology and Polymerase Chain Reaction (PCR) for HPV DNA were performed on surgical specimens. In seven of the 15 patients there was complete histologic response; four of these seven also has no evidence of HPV DNA by PCR. Thus, this report documented that **cidofovir** 1% gel partially or completely inhibited cervical dysplasia lesions after only three applications, and the drug effects were specific to dysplastic epithelium.

### ***Bowenoid papulosis***

Bowenoid papulosis is another tumor strongly associated with HPV infection that is difficult to differentiate clinically and pathologically from SSC in situ. Treatment alternatives include surgical excision, laser therapy, cryotherapy, or 5-fluorouracil. Snoeck et al [31] reported on a 38-year-old homosexual man with AIDS who presented with a fibrotic lesion of the penis that microscopically showed Bowenoid papulosis. Initially, the patient was treated with 1% topical **cidofovir** reformulated in Beeler base (see preceding section) once a daily for 5 days. At 2 weeks, the patient was treated for another cycle of once daily application for 5 days with improvement of the lesion. One month after beginning **cidofovir** therapy, significant improvement was noted and a third application course (5 days)

was initiated. Two months later, the lesion appeared to be completely healed, and at almost 4 years after therapy there was no evidence of recurrence.

### *Condylomata acuminata*

Anogenital condylomata acuminata are the most frequent clinical manifestation of genital HPV infection. Concomitant infection of HIV and HPV is frequent (26–60% in men). Snoeck et al <sup>[31]</sup> first reported on the use of topical **cidofovir** for relapsing anogenital condylomata in three individuals with AIDS. A 44-year-old homosexual man with recurrent penile lesions that were resistant to podofilox and curettage was treated with 1% topical **cidofovir** once daily for 5 days. On day 7, the patient developed small ulcerations at the sites of previous lesions. The lesions cleared and he remained free of disease 1 year later. Similarly, a 20-year-old man with recurrent genital condylomata that was resistant to electrodesiccation was treated with 1% topical **cidofovir**. After 11 days, verrucous lesions were replaced with erosions that healed in 7 days. Six months later, no recurrence was evident. A 34-year-old woman with recurrent condyloma acuminata of the vulva and surrounding skin was clear after treatment with 1% topical **cidofovir** gel applied once daily for 5 weeks. She remained disease-free for 6 months following discontinuation of therapy.

Snoeck et al <sup>[32]</sup> conducted the first double-blind, placebo-controlled study of the use of topical **cidofovir** for the treatment of genital HPV infections in immunocompetent Belgian patients. Thirty patients were enrolled in the study; 19 received **cidofovir** and 11 received placebo. The median number of warts and the median baseline wart area were comparable for both groups. Nine of 19 (47%) patients in the **cidofovir** group had a complete response, compared with none of the patients in the placebo group ( $P = 0.006$ ). None of the patients in the **cidofovir** group experienced disease progression, compared with five (45%) of 11 patients in the placebo group. Side effects observed in both groups were comparable.

Treatment options for anogenital warts in patients infected with HIV are unsatisfactory because they fail to eradicate latent HPV. Matteelli et al <sup>[33]</sup> conducted a study to determine the efficacy of topical 1% **cidofovir** cream for the treatment of external anogenital warts in HIV-infected patients. They conducted a randomized, placebo-controlled, single-blind, crossover pilot study of either 1% **cidofovir** cream or placebo applied once daily, 5 days a week for 2 weeks followed by 2 weeks of observation. Six patients were randomized to 1% **cidofovir** cream and six to placebo. The placebo patients eventually received 1% **cidofovir** cream. Thus, 12 treatment rounds of **cidofovir** were compared with six rounds of placebo. A reduction of more than 50% in the total wart area was achieved by seven **cidofovir** treatments (58%), compared with no reductions in patients treated with placebo ( $P = 0.02$ ). Local erosion at the site of application occurred in 10 of the 12 patients treated with **cidofovir**, as compared with none of the six subjects in the placebo group ( $P < 0.001$ ). These investigators found that 1% **cidofovir** cream was significantly more effective than vehicle cream in the eradication of anogenital warts, even in HIV-infected patients.

### *Verruca vulgaris*

Verrucae represent a therapeutic challenge in immunocompetent and immunocompromised individuals. Zabawski et al <sup>[4]</sup> reported on two cases of verruca vulgaris refractory to conventional therapy that responded to treatment with topical **cidofovir**. A 7-year-old girl with hundreds of verrucae on both legs was treated with topical 3% **cidofovir** cream twice daily for 10 days. She developed local inflammation followed by postinflammatory hyperpigmentation and subsequently complete clearing of the lesions. She remained completely free of warts for more than 40 weeks. Similarly, a 13-year-old girl who presented with verrucae of the distal fingers of both hands that were resistant to laser destruction was

treated with **cidofovir** 3% cream base once daily for 10 weeks. She developed minor local irritation acutely, but she was free of lesions at the end of therapy and 12 months following treatment.

Topical **cidofovir** has also been found to be effective in the treatment of verruca in HIV-infected individuals. Davis et al <sup>[34]</sup> reported on a 37-year-old HIV+ woman who presented with a large verrucous plaque involving her right foot. HPV-66 was identified in the lesional skin biopsy sample. The wart responded rapidly to topical **cidofovir** therapy. Recently, Calista et al <sup>[35]</sup> reported on a case of a 45-year-old man with AIDS and multiple warts on his gingival mucosa that were recalcitrant to conventional therapies but were successfully treated with **cidofovir** 1% cream. This represents the first case in which topical **cidofovir** has been reported to be effective for the treatment of a HPV infection of the oral mucosa.

Calista <sup>[36]</sup> treated 14 HIV+ individuals with 1% **cidofovir** cream, 10 of whom had extensive HPV lesions and four of whom had molluscum contagiosum (MCV); all patients were reportedly unresponsive to conventional therapies. The subjects had been on treatment with HAART for almost on 1 year before applying **cidofovir** cream. Thirteen of the 14 patients (92.8%) completed the therapy; one dropped out. All 13 patients eventually responded. In nine individuals, the lesions regressed 2 weeks from the end of the first cycle of therapy. Three patients needed two cycles and the last three consecutive courses of topical therapy before the lesions healed. No recurrence was observed in nine patients over an average follow-up period of 24.1 months (range 12–30 months). Four patients had isolated relapses that were successfully treated with simple curettage. All patients experienced local side effects, including inflammation, erosions, and burning sensations. Postinflammatory hyperpigmentation was observed in six cases, whereas two patients developed local transient alopecia on the beard area. No systemic side effects were noted.

### ***Molluscum contagiosum***

MCV commonly affects children and individuals who are immunocompromised. The prevalence of MCV infection among HIV-infected individuals ranges from 5% to 18%. Children with AIDS who exhibit extensive and recalcitrant MCV suffer from increased morbidity and disfigurement. Recalcitrant MCV in these patients represents a therapeutic challenge.

In 1999 Meadows et al <sup>[5]</sup> reported that **cidofovir** induced clearing of MCV in three HIV+ adults who presented with extensive MCV lesions that were unresponsive to various treatments. Two patients received IV **cidofovir** and the third was treated with topical **cidofovir**. One patient demonstrated dramatic clearing of MCV lesions when IV **cidofovir** therapy was started for his treatment for coexisting CMV retinitis. In the second patient, IV **cidofovir** therapy was started for CMV retinitis and extensive facial MCV involvement. One month following treatment, all clinical evidence of MCV had resolved. Both patients remained clear of MCV while receiving maintenance IV **cidofovir** at the time of the report. A third individual, 37-year-old man with extensive MCV facial lesions, was treated with **cidofovir** compounded as a 3% cream in Dermovan once daily, 5 days a week, for a total of 2 weeks. This patient experienced moderate inflammation during therapy and complete resolution of lesions 1 month later.

Topical **cidofovir** has also been found to be efficacious for the treatment of MCV in HIV-immunocompromised individuals. Davies et al <sup>[37]</sup> reported that topical **cidofovir** was effective in the treatment of MCV in a 12-year-old boy with Wiskott-Aldrich syndrome. More than 75% of the patient's body surface was covered with MC lesions. Within 2 to 3 weeks, the lesions treated with **cidofovir** showed acute inflammation followed by complete resolution.

Recently, the authors reported the successful use of topical 3% **cidofovir** in Dermovan in the treatment of recalcitrant facial and generalized MCV in two children with AIDS [6]. These children suffered from severe social isolation because of their facial disfigurement. Their MCV lesions were refractory to numerous therapeutic modalities, including liquid nitrogen, cantharidin, and 0.05% tretinoin gel. Both children had MCV lesions, elevated viral loads, and low CD4 T cell counts despite HAART for a median of 24 months. The patients exhibited hundreds of MC lesions that were disseminated over the entire body, including the face and perineal area. The authors found that topical **cidofovir** was effective in the treatment of generalized and recalcitrant MC in children with AIDS. The authors' two patients had refractory MCV despite extensive treatment with HAART. Most nucleoside analogs are relatively specific for HIV except lamivudine, which has also shown activity against hepadena viruses [38]. None of the agents that target HIV has known predicted antiviral activity against MCV. Although these patients received concomitant HAART during topical **cidofovir** therapy, there was suboptimal control of HIV replication. It is therefore unlikely that HAART was responsible for the resolution of the MCV lesions. Topical **cidofovir** is a nonsurgical method that avoids the potential significant renal toxicity associated with systemic therapy. The authors' findings suggest that topical 3% **cidofovir** is a safe and potentially effective treatment in recalcitrant MCV in children. Double-blind control trials of topical **cidofovir** in Dermovan for MCV in HIV-infected children will confirm the authors' preliminary results.

### ***Kaposi's sarcoma***

**Cidofovir** has been shown to have marked activity against Kaposi's sarcoma (KS)-associated herpes virus (KSHV; HHV-8) in vitro. Few studies have been performed to investigate the efficacy of **cidofovir** on KSHV in vitro, KSHV viremia, and KS lesions [38] [39] [40] [41]. Kedes and Ganem evaluated the anti-KSHV activity of various antiviral agents (including **cidofovir**) in vitro [42]. They found that **cidofovir** was a more potent inhibitor of KSHV than acyclovir, **cidofovir**, foscarnet, and ganciclovir. Similarly, Medveczky et al [43] showed that **cidofovir** strongly inhibited KSHV DNA synthesis and virus secretion in vitro.

Mazzi et al [44] described the effect of **cidofovir** treatment on cutaneous lesions and KSHV viremia in two AIDS patients with KS. The patients had developed multiple cutaneous KS lesions despite long-term, efficient HAART and treatment with multiple-agent cytotoxic chemotherapy (vinblastine, vincristine, and interferon- $\alpha$ ). **Cidofovir** was administered at a dose of 5 milligrams per kilogram IV at 1-week intervals for the first two administrations and every 2 weeks thereafter. The overall **cidofovir** treatment period was 10 months for one patient and 12 months for the second patient. Regression of all cutaneous KS lesions was observed after 3 months of treatment. KSHV viremia also became undetectable. No adverse reactions occurred during therapy with **cidofovir**. Treatment was stopped after a 6- and 8-month period in which patients were period free of KS. Both patients experienced reactivation of old lesions or new KS lesions at 6 and 15 months after the end of treatment, respectively. These results, although promising, should be interpreted with caution. Unpublished results from the National Cancer Institute trial suggest that **cidofovir** is not effective for KS.

### ***Herpes simplex virus infection***

Various reports suggest that **cidofovir** is efficacious in the treatment of HSV infection. Saint-Leger et al [45] reported on a case of an AIDS patient who presented with a history of recurrent scrotal ulcerations secondary to HSV type II (HSV-II). After several hospitalizations and treatment with acyclovir, valacyclovir, and foscarnet, IV **cidofovir** was initiated and complete healing was obtained. This particular viral strain of HPV-II was found to be resistant to acyclovir, valacyclovir, and foscarnet. Similarly, Lateef et al [46] reported on the use of topical **cidofovir** 1% in the treatment of a 4-year-old

boy with AIDS and a facial HSV ulcer. Initially, the patient was treated with oral and IV acyclovir with only partial response. The patient then developed an aggressive recurrence and cultures demonstrated acyclovir-resistant HSV. Although foscarnet and fluorothymidine were added, the patient developed a 10 cm ulcer extending across the cheeks bilaterally. Prior treatment was stopped and 1% **cidofovir** cream every day was started. Several weeks later, the ulcer was healing well, with granulation tissue at the ulcer base. The authors comment that this is the first report that demonstrates the effectiveness and safety of topical **cidofovir** as an alternate treatment of multi-drug-resistant HSV in an immunocompromised patient.

Snoeck et al <sup>[47]</sup> reported on the use of topical **cidofovir** in persistent mucocutaneous HSV infections in two individuals. The first patient had AIDS and a chronic perineal HSV-II ulceration that was unresponsive to acyclovir. The patient did not tolerate foscarnet, so daily topical **cidofovir** 3% gel was instituted. After 3 days of treatment, the lesions completely resolved; however, the lesions recurred 3 weeks later. Subsequent repeat treatment with daily application of **cidofovir** gel for 3 days again led to complete resolution of the lesion. A second recurrence 7 weeks later was also successfully treated with topical **cidofovir**. The second patient reported by Snoeck was a bone marrow transplant recipient who experienced severe oral HSV type I infection that was resistant to acyclovir and foscarnet. Two courses of topical **cidofovir** resulted in the emergence of an acyclovir-susceptible strain that then responded to treatment with acyclovir.

Lalezari et al <sup>[48]</sup> conducted a randomized, double-blind, multicenter trial to evaluate the safety and efficacy of **cidofovir** gel for treatment of acyclovir-resistant HSV infections in 30 AIDS patients. Eleven patients received 0.3% gel, nine patients received 1.0% gel, and 10 patients were treated with a placebo gel once daily for 5 days. Half of the cidofovir-treated patients and none of the 10 placebo-treated patients demonstrated complete healing or greater than 50% improvement of the infection. One third of cidofovir-treated patients had complete healing in contrast with none of the placebo-treated patients. Viral shedding ceased in 87% of 15 cidofovir-treated patients and in none of the placebo-treated patients. Application site reactions occurred in 25% of cidofovir-treated patients and 20% of placebo-treated patients. Cidofovir-treated patients showed a median of 21 days to achieve a complete or good response and a median of 2 days to have a negative HSV culture.

### **Smallpox**

Smallpox is caused by infection with the variola virus, a member of the *Orthropoxvirus* genus. Vaccination against smallpox is performed by inoculation with the vaccinia virus, a related *Orthropoxvirus*. Because of widespread vaccination programs, smallpox was officially eradicated from the world in December 1979; however, rare stocks of virus were preserved in restricted laboratories. Because of its potential use in bioterrorism, the identification of drugs with antiviral activity against the variola virus has become important. Furthermore, vaccination for smallpox with vaccinia virus can cause severe infections in immunocompromised individuals <sup>[49]</sup>, and drugs are needed for this disease as well.

Smee et al <sup>[50]</sup> reviewed the literature and reported on the characterization of wild-type (WT) and cidofovir-resistant (CDV-R) isolates of monkeypox and vaccinia viruses. CDV-R cytomegaloviruses have been isolated from treated patients <sup>[51]</sup> or derived by cell culture passage of WT viruses under drug pressure <sup>[52]</sup>. Mutations were found in the viral DNA polymerase gene that conferred drug resistance <sup>[53]</sup> <sup>[54]</sup>. Resistance to **cidofovir** results in cross-resistance to other antiviral drugs. The most serious clinical consequence of infection with drug-resistant viruses is the inability to treat the disease effectively with the specific medication and sometimes with other similar-acting drugs. It will be difficult to prove that **cidofovir** works against smallpox, because the disease was declared to be eradicated. It is therefore

important to identify an appropriate animal model to study smallpox before the remaining stocks of variola are destroyed.

In this regard, **cidofovir** has been used to control infection in mice inoculated with the vaccinia virus [55] [56] [57]. Recently, Smee and colleagues have shown that **cidofovir** is active against 31 different strains of variola virus in vitro. They also showed that **cidofovir** can protect monkeys exposed to monkeypox virus. This is an important finding because monkeypox virus infections have recently been reported in humans living in the Democratic Republic of the Congo (leading to death of some) [58].

Of all drugs approved by the FDA, **cidofovir** is the most effective anti-*Orthopoxvirus* agent. In cases of smallpox threats or outbreaks, **cidofovir** could be used in conjunction with vaccination to treat and prevent infections; however, some experts doubt that any antiviral drug would prove effective against symptomatic smallpox. **Cidofovir** therapy might play a role during the window of time between initial infection and onset of disease [55]. Regardless, **cidofovir** should be useful as therapy for immunocompromised individuals who have disseminated infection following vaccination with the vaccinia virus.

Promising results have been reported of a development of oral form of a related drug to **cidofovir**, hexadecyloxy propyl-cidofovir (HDP-cidofovir), by Hosterler and colleagues at the Fifteenth International Conference of Antiviral Research in Prague [59]. Unlike **cidofovir**, HDP-cidofovir is 93% orally available in mice. In addition, it is 100 to 1000 fold more active than **cidofovir** against herpesvirus and cytomegalovirus in vitro. These researchers also found that HDP-cidofovir was 100 to 200 fold more active against **cidofovir** against poxviruses, including small pox.

## Summary

**Cidofovir** is a new antiviral drug that has a broad spectrum of activity against several DNA viruses. Many of the disorders caused by these viruses do not have satisfactory therapy, and given the efficacy of this agent in treating many of these conditions, it holds great promise. It is hoped that ongoing studies will confirm the initial anecdotal reports regarding its therapeutic efficacy and lack of systemic side effects. It is also hoped that the cost to formulate and use **cidofovir** topically will eventually decrease to a level that will allow more widespread use of this drug.

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