Virus Adaptation and Treatment

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REVIEW

The management of herpes simplex virus infections in HIV infected patients: current issues and the role of cidofovir

This article was published in the following Dove Press journal:
Virus Adaptation and Treatment
22 June 2011
Number of times this article has been viewed

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Abstract: Herpes simplex virus (HSV) type 1 and 2 are among the most common transmitted viral infections causing a spectrum of mucocutaneous and other syndromes. Treatment of these infections has primarily been with acyclovir (ACV) and prodrugs valacyclovir and famcyclovir. Immunocompromised hosts either due to human immunodeficiency virus (HIV) or other factors have given rise to an increase in ACV resistant viruses most commonly due to a mutation in the cellular thymidine kinase enzyme. This review focuses on the spectrum of disease caused by HSV 1 and 2, the emergence of ACV resistant disease, and the role of alternative agents including cidofovir in the treatment of ACV resistant disease.

Keywords: herpes simplex virus, HIV, resistance, cidofovir

Introduction

Herpes simplex virus (HSV) and human immunodeficiency virus (HIV) are closely related sexually transmitted infections, both characterized with persistence and lack of a cure. Interactions between these two viruses show that they have synergistic effects. Infection with HSV causes increased plasma and genital HIV RNA levels due to stimulation of the HIV replication and increased number of immune cells susceptible to HIV. In turn, HIV increases the episodes of HSV reactivation and severe forms of the infection due to suppression of immunity.[1] Treatment for HSV for many decades has been acyclovir (ACV) and its related compounds, however with the era of HIV there is increasing resistance to these drugs.[2] In this review we discuss the use of cidofovir (CDV) as an alternative to drug resistant HSV.

Herpes simplex infection: description of the causative agent

There are eight human herpes viruses under the family of herpes viridae and three subfamilies: alphaherpesvirinae, betaherpesvirinae, and gammaherpesvirinae. HSV belongs to alphaherpesvirinae, and there are two subtypes: HSV-1 and HSV-2. The genome of these viruses is made up of double-stranded DNA surrounded by a capsid of icosahedron symmetry and the virion is enveloped. The genetic homology between HSV-1 and HSV-2 is about 50% and the protein variations between these viruses determine the immune response and can be distinguished serologically.[3]

Epidemiology

Herpes simplex virus infections are common in both immunocompetent and immunocompromised individuals. The sero-prevalence varies from age and countries, but

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http://dx.doi.org/10.2147/VAAT.S12984

generally HSV-1 is more prevalent and acquired early in life with sero-prevalence rates up to 90% in the general adult population and as high as 98% in HIV infected patients and in high-risk individuals. In contrast to HSV-1, HSV-2 antibodies have been reported to appear generally after sexual debut. HSV-2 is more common in sexually active individuals with a prevalence of about 22% in the general adult population and prevalence rates among HIV-positive persons ranging from 70%–90%.[4,5]

Transmission and pathogenesis

Transmission of virus occurs through contact with a person shedding the virus at a peripheral site, most commonly in the genital tract or oral mucosa. Infection is transmitted through secretions or vesicular fluid containing the virus through inoculation of the virus onto a susceptible mucosal surface. Transmission can occur during periods of asymptomatic shedding which is common and may represent an important mode of transmission.[6] HSV-1 infections are common in oral and perioral areas and HSV-2 in the anogenital region, although infection can occur at any site with either virus because autoinoculation from one area to another is not uncommon.[7,8]

Initial HSV infection following exposure to mucosal surfaces is usually asymptomatic with no clinical lesions. Adequate replication of the virus leads to invasion of the sensory and autonomic nerve endings where the virus establishes a latency phase.[9] The common neural sites following primary HSV-1 are the trigeminal nerve, although infection can spread to the inferior and cervical nerve ganglia, the vagus ganglion, and brain tissue.[10,11] The sacral ganglia are the most common site of latency in the case of genital infection.[12] Recent research shows recurrences of keratitis independent of trigeminal viral reactivation proving that latency in non-neural tissues such as the cornea is possible.[13]

Spectrum of disease

Primary infection is the first manifestation of HSV disease and is characterized by a lack of serum antibodies in acute phase serum. It is accompanied by systemic signs such as fever and malaise in addition to the local lesions and complications are more likely.[9] The second form of infection is the latent infection in which the virus evades the immune response and may continue replicating at low grades in certain tissues or may remain in a nonreplicating stage.[9–11] Upon reactivation of the virus from the latency state, a third form of infection known as reactivated infection arises. The frequency of reactivation is determined by both the host and the viral factors, ie, the anatomical site and virus subtype. HSV-1 is more frequently reactivated compared to HSV-2. Oral/perioral HSV-1 infection recurs more frequently than HSV-2 oral/perioral infection.[14,15]

Infection in immunocompetent individuals is usually mild and self-limiting; however in immunocompromised patients, e.g. HIV patients and organ transplant patients, there are higher chances of reactivation and hence recurrences in these individuals, than any other group of persons. Dissemination to other organs is also common among immunocompromised individuals who also suffer more severe forms of disease, eg, herpetic encephalitis. Atypical presentation is common and lesions may be extensive and appear in regions where they are unexpected.[16,17] Although HSV-1 tends to cause oral disease and HSV-2 genital ulcer disease, considerable overlap exists in the clinical presentations of the two agents,[16] and we have attempted to describe the diseases associated commonly with the different subtypes below.

HSV-1

Orofacial herpes simplex virus infections

Pharyngitis and gingivostomatitis are the most common manifestations of initial HSV-1 infection particularly among children and young adults. As a result of primary infection, lesions may occur on the tongue, hard palate, gingiva, tongue and lips, posterior pharynx, and the tonsillar area. Recurrent infection is characterized by ulcerations on the vermilion border of the lip or external facial skin and at times may be associated with asymptomatic shedding. Furthermore, reactivation of HSV-1 is associated with Bell's palsy.[18–20]

HSV encephalitis

HSV is the leading cause of sporadic fatal encephalitis.[21] Although this clinical manifestation is rare, mortality is as high as 70% in the untreated cases. Encephalitis is thought to arise from primary HSV infection that is exogenously acquired and reaches the central nervous system (CNS) via neural spread commonly through the olfactory nerve or trigeminal nerve. The other mechanism of pathogenesis is hematogenous spread concurrent with mucocutaneous disease. The other cause could be due to reactivation of in situ HSV latent in the CNS without primary infection resulting in CNS infection.[22] Clinical features include fever, headache, hemiparesis, dysphasia, aphasia, ataxia, focal seizures, and altered level of consciousness.[23]

Eye infections

HSV usually affects the anterior of the eye, clinically characterized by recurrent keratitis. If untreated, HSV is one of

the leading causes of corneal blindness, following healing by scarring.[24] When the retina is involved this may lead to necrosis: there are two forms of retinal necrosis: acute retinal necrosis and posterior outer retinal necrosis (PORN). PORN occurs in immunocompromised individuals especially end-stage HIV patients. Clinically there is early involvement of the macular area with minimal anterior chamber inflammation. Vasculitis and hemorrhages are rare and the outer retina is primarily involved. PORN has a poor prognosis because it is usually associated with retinal detachment and antiviral therapy may not play a role at this point.[25]

Visceral infections

Esophageal HSV infection may not be easily distinguished from esophageal candidiasis: both have similar clinical features including fever and dysphagia.[26] Although HSV pneumonitis is rare, it may occur among the severely immunocompromised individuals as a result of spread of infection from the trachea to the lung tissue which results in focal necrotizing pneumonitis or through hematogenous spread leading to bilateral interstitial pneumonitis. Superimposed infections are common and mortality in these patients is high.[27]

HSV-2

Genital ulcer disease

There are various causes of genital ulcer disease besides HSV, e.g. *Trepanoma pallidum* and *Hemophilus ducrei*. HSV however is the most common cause of genital ulcers among all the above agents especially among HIV patients. This is explained by increased frequency of reactivation and frequent coinfection among HIV patients with HSV-2. Ulcers are usually large and persistent.[28]

Herpetic whitlow

This is an infection that occurs as a result of inoculation of virus on broken skin, and commonly occurs among medical and dental practitioners or may occur as a complication of herpetic infection. The main causative agent is HSV-2, although prior to the era of universal use of gloves, the main causative agent was HSV-1. The main anatomic location of the lesion is on the finger and involves one digit. Clinically it is characterized with abrupt erythema and localized tenderness.[29,30]

Visceral infections

Viremia coupled with a compromised immune system facilitates spread of the virus to various organs. The liver, esophagus, and lungs are the organs involved with visceral HSV. The liver is the major target organ of disseminated HSV infection, and is characterized by fulminant hepatic necrosis and other manifestations resulting from severe hepatic dysfunction.[31]

HIV patient focused perspectives for management of HSV

Slow progression to AIDS

At the time of HIV discovery, before the era of antiretroviral therapy, the morbidity and mortality due to HIV/AIDS and related illnesses was high. However this has reduced with the introduction of highly active antiretroviral treatment (HAART).[32] Treatment with ART is lifelong and expensive, and there is necessity for vigorous follow-up to monitor resistance and toxicity.[33] There is a need to devise other cheaper means to slow the progression to AIDS and to alter the prognosis in addition to the use of HAART. Coinfections in HIV play a role in compromising the immunity and augmenting HIV replication, and studies have shown that treatment of coinfections of HIV leads to decreased HIV viral load.[33,34] Therefore treatment of HSV as a coinfection could delay initiation of HAART and reduce the cost of monitoring. One study from subsaharan Africa has shown the suppressive ACV (400 mg twice daily) among HIV infected ART naive individuals may delay HIV disease progression and need for ART by 17%.[34]

Decrease in transmission

Strong epidemiological evidence shows that transmission and acquisition of HIV increases with HSV-2 infection. The biological explanation as discussed earlier in this paper is due to increased plasma and genital HIV viral load, increased number of susceptible immune cells and compromised immunity.[35,36] This strong association between HSV and HIV has led to research to investigate the benefit of HSV treatment as a prevention strategy to acquiring HIV.[37] In a randomized control trial conducted in Tanzania, high-risk HIV-negative women were enrolled and treated with ACV and followed for a minimum of 12 months. However, at the end of the study, results showed no difference in rates of transmission between the study arms.[38] Other studies conducted in Peru and USA among men who have sex with men and women in South Africa, Zambia, and Zimbabwe also failed to show any impact on the risk of acquisition.[39]

Despite strong epidemiologic associations between HSV-2 and HIV transmission risk, clinical trials of suppressive HSV-2 infection have not proven to be efficacious in reducing HIV acquisition and transmission.[38,39] More studies conducted in HIV discordant couples who were coinfected

with HSV compared participants on HSV antiviral therapy and those on placebo and there was no change in the risk of transmission, further challenging this fact.[40,41] The negative findings in all these studies could be explained by a study where punch biopsies were taken at different time intervals from ulcerative lesions of individuals of culture proven HSV. The conclusion was made that there is persistence of CD8 and CD4 cells up to 8 weeks post-healing from HSV infection. Additional in vitro experiments using cells isolated from biopsies of healed lesions were infected with HIV and they contained more copies of HIV DNA following infection compared with the control samples.[42] This shows that there is still a need to understand the immunobiology and interaction of these two viruses.

Treatment of herpes simplex virus in HIV patients

Treatment of HSV infections has similarities with that of HIV. HSV becomes latent in the neural systems and is constantly reactivated depending on the immunity of the individual and is therefore a chronic infection similar to HIV. In addition, there is no curative therapy in both infections and rationale of therapy is mainly focused on suppression of viral replication. There are several drugs used for the management of HSV infections.

Acyclovir

For over two decades, ACV has been the drug of choice for the management of the various forms of HSV infections. Acyclovir is administered orally in a dosage of 200 mg five times for 5 days although in HIV infected persons, especially those with severe infections, dosage is up to 400 mg and can be prolonged to 7 days or is given intravenously in severe cases. It is the most common drug of choice for treatment, prophylaxis, and suppressive therapy of recurrent episodes of HSV and other related herpes infections.

In order for ACV to be active it is phosphorylated by viral encoded thymidine kinase (TK) and subsequently to acyclovir triphosphate, which is the active form by host-cell enzymes. Incorporation of this nucleoside analog by the viral DNA polymerase into the replicating DNA leads to chain termination since it lacks a hydroxyl group to which other true nucleosides can bind. This leads to inhibition of the viral replication through competition with true nucleosides and obligate chain termination on incorporation.[43]

Valacyclovir (VCV) is a prodrug that is converted into the active form of ACV in the small intestines after oral administration; its advantage over ACV is higher bioavailability. It is given as 1000 mg twice daily for 5 days.

Other drugs that have a similar mechanism of action to ACV include pencyclovir (PCV), which acts by terminating chain elongation also known as a short chain terminator. PCV is poorly absorbed and there are no oral formulations available. Famcyclovir was developed to improve on the bioavailability of PCV; it is given orally and readily absorbed to be converted to PCV in the liver.[44] Another nucleoside analog that has antiviral effects on HSV is brivudin, which acts selectively against HSV-1.[45]

Resistance

Resistance to ACV presents a big challenge among the immunocompromised (eg, HIV patients). Prevalence rates range from 3.5% to 7% and as high as 10% in bone marrow transplant patients compared to the immunocompetent patients where prevalence of resistance ranges from 0.3%– 0.7%.[2,17,46] The difference in the prevalence of resistance between these two populations is due to the fact that if the immune system is impaired there is continuous viral replication leading to persistence and failure to clear mutant viral populations that would otherwise not be pathogenic in an immunocompetent individual.[47]

There are multiple reasons that bring about poor sustained response to antiviral agents including poor adherence, drug toxicities, and drug interactions.[17] The molecular mechanisms of resistance to ACV and its derivatives are due to mutations in the UL23 gene that encodes for phosphorylation of the TK enzyme and in the UL30 gene which encodes for the viral DNA polymerase enzyme. The different phenotypic manifestations of TK mutations include: TK negative mutants that have no activity, TK lower producer mutants with reduced activity, and TK altered substrate mutants that alter the substrate specificity of the thymidine kinase, which strictly phosphorylates thymidine and not ACV.[47] Another mechanism is caused by mutations in the DNA polymerase gene enabling the virus to continue replicating despite the presence of ACV.[48–50] Resistance to ACV can be detected using phenotypic and genotypic methods. The phenotypic methods are plaque reduction assays, fluorography, and thymidine kinase assay. However the limitation with these methods is that the number of infectious particles may be too low to be isolated from the cell culture. Genotypic methods where sequential gene analysis of isolates that are more rapid could be used in conjunction with phenotypic tests.[51,52]

Management of resistant HSV

Foscarnet

Foscarnet not only has antiviral properties against HSV, it inhibits HIV as well. It acts by reversibly inhibiting viral

DNA polymerase. There are no oral formulations and it must be given intravenously. It is used as an alternative therapy to HSV or varicella-zoster virus ACV resistant infection and also used for the treatment of cytomegalovirus (CMV) as a second-line alternative in incidences of neutropenia or resistance to ganciclovir.[16]

Vidarabine

Vidarabine is an analog of adenine deoxyriboside. Following phosphorylation to a triphosphate by cellular enzymes, the drug acts by competitively inhibiting HSV DNA polymerase and acting as a viral DNA chain terminator. It is administered by slow infusion and this requires large amounts of fluid and therefore limits usage in patients with congestive heart failure and in cases where renal function is impaired. Side effects include weakness, fatigue, diffuse myalgias, granulocytopenia, tremor, ataxia, and prerenal azotemia. Studies comparing the use of foscarnet and vidarabine showed that foscarnet has better efficacy and fewer side effects.[16] Because of the toxic side effects, vidarabine cannot be recommended for systemic treatment of HSV infections. The previous systemic use of vidarabine has been superseded by ACV, although topical formulations commonly used in ophthalmic infections are available.

Trifluorothymidine

Trifluorothymidine (TFT), a fluorinated pyrimidine nucleoside, inhibits viral thymidylate synthetase by thymidine substitution during replication. It is available in 1% TFT topical formulations and used in mucocutaneous lesions, however there is limited data available for the usage of TFT. Evidence shows increased efficacy once combined with interferon-α.[5,53]

Thymidine kinase inhibitors

The compound L-653180, a selective inhibitor of HSV, has no antiviral factors in cell cultures; however, it reduces reactivation from latency thereby reducing recurrences. In animal models, recurrent HSV infections over a 10-week observation trial were decreased when compared with controls, however, mammalian administration is limited by the compound's poor water solubility and the fact that the compound is not in clinical use.[53] The greatest disadvantage with this compound is that HSV can replicate without this enzyme; since mutant virus produces less TK compared to wild-type. Therefore, this can lead to selection of strains of virus in which TK is an irrelevant enzyme.[16,53]

Cidofovir: pharmacology, mode of action, and pharmacokinetics

Cidofovir is a cyclic nucleotide analog of cytosine as well as adenine or guanosine: [S-HPMPC (S)-1-(3-hydroxy-2-phosphonymethoxypropyl) cytocysine or S-HPMPA (S)-9-(3-hydroxy-2-phosphonylmetoxypropyl)adenine, 9-[(2-hydroxyethoxy)methyl]guanine]. In vivo and in vitro antiviral effects of CDV on other DNA viruses besides HSV, for example CMV and pox viruses, have been demonstrated.[54–56] Although CDV is not yet licensed as a second-line agent for the management of herpes infections, many studies have demonstrated clinical benefits of administration of CDV.[55,57–59] Considering the possibility of increased levels of resistance to ACV, CDV is another option that could be used for certain cases.[46]

Mechanism of action

Cidofovir is a phosphoryl derivative and therefore needs a two-step activation to its active form by cellular kinases differing from other nucleoside analogs (eg, ACV) that require a three-step phosphorylation with the initial step provided by the viral thymidine kinase. Cidofovir is phosphorylated by pyrimidine nucleoside monophosphate (PNMP) kinase and further by cellular nucleoside diphosphate (NDP) kinase, pyruvate kinase, or creatine kinase to CDV diphosphate (HPMPCpp), which is the active metabolite.[58] The active metabolite acts by actively competing with 2′-deoxyribonucleoside 5′triphosphate for incorporation by the viral DNA polymerase and once incorporated, leads to chain termination (Figure 1).[59,60] The affinity for the viral DNA polymerase is higher than that of cellular polymerase, and therefore selectivity is achieved by this mechanism.[61]

Cidofovir use in acyclovir resistant HSV

In a study that compared susceptibility of the wild-type and the TK mutant viruses, an increase in susceptibility to CDV with the mutant viruses was reported. This is explained by the fact that there are lower pools of dCTP in mutant viruses because of inadequate phosphorylation by the thymidine kinase, thereby reducing the pool of nucleoside triphosphates with which CDV has to compete with and thus making mutant viruses more susceptible to it.[62] Furthermore, CDV is very potent and has a long in vitro and in vivo antiviral effect since the drug has a long intracellular half-life in the absence of extracellular drug, which is most likely attributed to the accumulation of the metabolite cidofovir monophosphate-choline, which may act as a reservoir for cidofovir diphosphate. Clinically it has been shown by the immediate and more

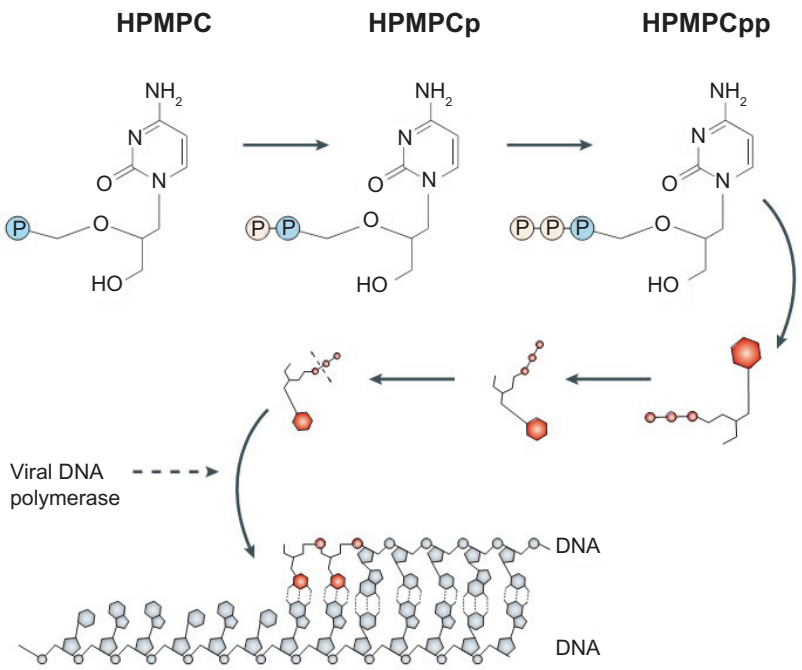

Figure 1 Mechanism of action of cidofovir.
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frequent cessation of viral shedding in patients receiving CDV compared to those receiving placebo.[62–64]

There are disadvantages for the use of CDV as a first-line drug choice in the management of HSV infections due to dose-dependent nephrotoxicity,[63] bone marrow suppression, and low oral bioavailability therefore requiring intravenous administration. Experiments in animals have shown teratogenic effects although no evidence is available from human studies, and use in pregnant women is not documented. Intralesional administration of the drug is an alternative to reduce the side effects and has been successful in one case report.[65] Studies have been performed on topical applications but mainly in animal models in which bioavailability ranges from 0.2%–2% in intact skin and up to 41% in nonintact skin without compromising renal functions.[65–67] Despite the side effects, there are cases where CDV has been used to successfully treat ACV-resistant HSV.

In a randomized, double-blind, placebo-controlled trial carried out among 30 AIDS patients with ACV unresponsive mucocutaneous infections, Lalezari et al reported on 20 patients who received CDV gel. Nine were treated with 1% CDV gel, eleven with 0.3% gel, and ten were on placebo. Fifty percent showed improvement and 30% of patients treated with CDV gel had complete healing compared to none on placebo. Negative viral cultures were reported in 87% of patients receiving CDV and no patient on placebo reported negative viral cultures (median time of obtaining negative cultures being 2 days) showing the rapid viral suppression despite lack of complete healing in some cases.[64]

Another randomized Phase I/II clinical trial enrolled 96 immunocompetent patients with recurrent genital herpes infections. Gel preparations were applied locally at varied concentrations of 1, 3, and 5% CDV and a placebo. All patients receiving CDV showed a shorter duration for symptoms and cessation of viral shedding proven by negative cultures compared to those on placebo.[68]

Snoeck et al has demonstrated clinical use of CDV in two immunocompromised cases. One was an AIDS patient with perianal lesions due to HSV-2 infection. The second patient was immunocompromised following bone marrow transplant and had oral facial lesions due to HSV-1 infections. Both patients were nonresponsive to ACV and foscarnet and were managed with two consecutive courses of 1% topical HPMPC.[69]

Studies of cross resistance between ACV, PCV, and ganciclovir have been found due to the similar mechanisms in which these drugs are phosphorylated (ie, initial step).[57] Therefore there are limited alternatives in case of ACV resistant HSV; foscarnet being the only licensed option, this drug bypasses the viral activation by thymidine kinases, which is similar to CDV. However, its use has limitations, for example, the necessity for parental administration

with nephrotoxicity and resistance being reported.[62,67] The advantage of using CDV is HSV resistance to CDV but is rare, since mutations that confer resistance have to occur in the DNA polymerase.[69] These mutations occur at a low frequency and they have to be at particular sites in order to bring about phenotypic changes. To date, resistance of HSV developed against CDV in vivo has been described only in one case.[70] Cidofovir should be considered for management of HSV resistant infections in HIV infected persons and for prophylaxis against recurrences.[71] However, adequate information should be provided to patients considering there is limited research and information about clinical use, and patients should be made aware before they consent to treatment.

Besides use for treatment of HSV infections, CDV has been used to treat other infections, eg, CMV retinitis among HIV patients. In addition, there is potential for prevention of mucosal transmission of HIV according to a report by Srinivas et al. In vivo experiments showed that, despite the lack of anti HIV effects in CD4+ cells, HPMPC inhibited HIV-1 replication in nonlymphocytic cells.[72]

Conclusion

Herpes simplex virus type 1 and 2 continue to pose clinical challenges particularly in the setting of HIV and other immunocompromised hosts. Although treatment with ACV has remained the mainstay of therapy, the emergence of ACV resistant infections has resulted in the need for alternative treatment options. The importance of HSV-2 coinfection globally in the setting of the HIV pandemic has created other populations who may benefit from antiviral therapy either to prevent HIV transmission or delay HIV progression. Cidofovir is a potential alternative for practitioners faced with ACV resistant disease with the advantage being its potency, long half-life, and activity against ACV resistant strains. However, the delivery (intravenous) and nephrotoxicity of the current formulation of CDV remain challenges to the treating physician.

Disclosure

No conflicts of interest were declared in relation to this paper.

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