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UPDATE

ANTIVIRAL DRUG REVIEW: A GUIDE TO CLINICIANS

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ABSTRACT

Over the past forty years, there has been a great advance in antiviral infections treatment. The discovery of acyclovir in 1977 paved the way to new antiviral drugs. Other nucleoside analogues such as valacyclovir, penciclovir, famciclovir, ganciclovir, valganciclovir, cidofovir and foscarnet were made available, as well as neuraminidase inhibitors. Also, drugs for the treatment of viral hepatitis and patients with HIV/AIDS have not only increased life quality and expectancy, but also decreased the incidence of some viral infections. Antiviral drugs are important tools to the clinician, especially when treating patients with impaired immunological and clinical condition. Aiming to restore health and prevent further adverse events, the clinician must be aware of the best antiviral drug available, its proper route of administration and dosage. The aim of this review is to present the antiviral drugs currently available, focusing on treatment of common viral infections in clinical practice. A brief description of the mechanisms of action and prescription of antiviral drugs is presented, using the data available from evidence-based medicine.

KEY WORDS: Antiviral agents; herpes simplex virus; influenza virus; cytomegalovirus; varicella zoster virus.

INTRODUCTION

Despite the impact of viral infections on human health, there is still a mismatch when the development of antiviral drugs is compared to other antimicrobial agents, a fact that can be observed by the restricted options of antiviral drugs available for use. Knowing that the goal of an antiviral chemotherapy is the use of antiviral agents that specifically inhibit viral multiplication without affecting normal cell division, the choice of an optimal drug must also rely on patients' age and their immunological and clinical status. People with chronic medical conditions (including obesity), children younger than 2 years old, patients with 65 years old or older, and pregnant women may be at an increased risk for complications of viral infections.

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This manuscript provides information on antiviral treatment for herpes simplex (HSV), varicella zoster (VZV), influenza and cytomegalovirus (CMV) infections.

This information will help clinicians prescribe antiviral drugs to the viral infections described here. The purpose of this review is to present an update on antiviral drugs currently available, focusing on treatment of common viral infections in clinical practice, presenting a brief description of antiviral mechanisms of action in order to guide drug prescription, using the data available from evidence-based medicine.

Seeking not to be repetitive, and especially not incurring in contradictory information to official guidelines available for the treatment of HIV, hepatitis B and C infections, we chose not to address this issue by providing in the list of references the links to access these therapeutic protocols provided by the Brazilian Ministry of Health (Brasil, 2013; Brasil, 2015).

ANTIVIRAL DRUGS

Nucleoside Analogues

In 1977, Gertrude Elion and colleagues discovered acyclovir (ACV), a synthetic drug that was a turning point in antiviral therapy (Elion et al., 1977). ACV (9-[-2-hydroxymethyl]guanine) is a synthetic purine analogue that is obtained by molecular simplification or through the opening of the guanosine ring (Figure 1). It is an effective drug against herpes simplex virus types 1 and 2 (HSV-1, HSV-2) and varicella zoster virus (VZV), with an excellent safety profile. Other nucleoside analogues were subsequently discovered such as valacyclovir (VACV), penciclovir (PCV), famciclovir (FCV), ganciclovir (GCV) and valganciclovir (VGCV) (Figure 1).

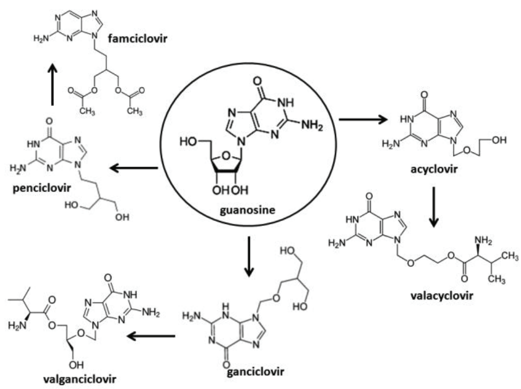

Figure 1. Guanosine nucleoside analogues antiviral drugs.

Acyclovir and Valacyclovir

After intracellular uptake, virally encoded thymidine kinase (TK) converts ACV to acyclovir monophosphate (ACV-MP), which is subsequently converted to acyclovir triphosphate by cell enzymes (ACV-TP) (Figure 2A).

Once ACV-TP is a deoxyguanosine triphosphate analogue (dGTP), it competitively inhibits viral DNA polymerase. Incorporation of ACV-TP molecule into DNA results in chain termination since the absence of a 3'hydroxyl group prevents the attachment of additional nucleosides (Figure 2A). The ACV-TP molecule has a much higher affinity for viral DNA polymerase than for its cell homologue, yielding a high therapeutic ratio (Whitley & Gnann, 1992).

Valacyclovir (VCV) is the L-valyl ester and a pro-drug of the antiviral drug acyclovir. It is converted, in vivo, to ACV, which is then phosphorylated to ACV-TP and irreversibly binds to viral DNA polymerase, effectively inactivating the enzyme (Pier et al., 2004; Field & Vere Hodge, 2013; Zachary, 2014a; Glaxo Wellcome Inc, 2015) (Figure 2B).

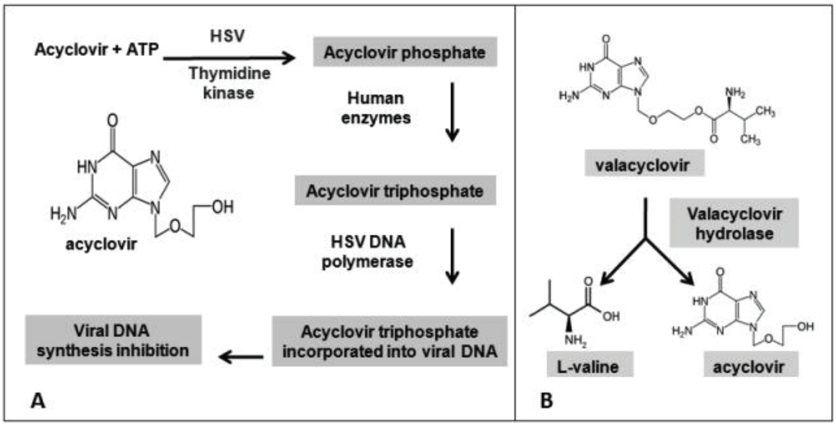

Figure 2. Mechanism of action of antivirals acyclovir (A) and valacyclovir (B).

In decreasing order of susceptibility, ACV and VCV are active against HSV types 1 and 2 (HSV-1, HSV-2), VZV and Epstein-Barr (EBV) viruses (Whitley & Gnann, 1992). ACV is inactive against cytomegalovirus (CMV), which does not encode thymidine kinase (TK). The ACV activity against HSV types 6, 7 and 8 is not well defined (Zachary, 2015a). Although active against EBV, VCV is not usually clinically recommended for EBV infections (Zachary, 2015a).

Mechanisms of resistance to ACV and VCV are rarely reported in immunocompetent patients and occur by (i) reduced or absent thymidine kinase, (ii) altered thymidine kinase activity resulting in decreased ACV phosphorylation or (iii) altered viral DNA polymerase with decreased affinity for ACV-TP (Perrier et al., 2016).

Usually, ACV resistance is linked to mutations in viral TK, while mutations in viral DNA polymerase are rare. In most cases, altered viral TK does not present enzymatic activity and the HSV responsible for the infection is referred to as TK-negative phenotype. TK-negative types also present cross-resistance to famciclovir (FCV) and, although being capable of latency, they are deficient to reactivate. It is suggested that recurrences are most often associated with a drug-sensitive strain. Sometimes, ACV resistance is due to a TK with altered substrate specificity, which can or cannot show resistance to FCV (Boyd et al., 1993).

However, it is noteworthy that the resistance phenomenon is rare in immunocompetent hosts and that therapy failure is usually a result of the delay in initiating antiviral therapy, reduced drug absorption or lack of adherence to treatment. Even in immunocompromised hosts, HSV resistance to nucleoside analogues is lower than 1%, and it is mainly observed in those patients under prolonged therapy (Piret & Boivin, 2011). Confirmation of HSV resistance to ACV or VCV requires genotypic and phenotypic tests and the treatment for ACV-resistant infections is usually done with foscarnet, a pyrophosphate analogue, or with cidofovir, an acyclic analogue of cytosine (Erlich et al., 1989; Hardy, 1992; Zachary, 2015a).

ACV oral bioavailability is about 15 to 30%, which decreases at higher doses. Since intravenous administration yields higher plasma concentrations than oral doses, it should be used for serious infections such as disseminated varicella in immunocompromised hosts (Zachary, 2015a).

VCV has three- to five-fold greater oral bioavailability than ACV and food does not affect its absorption (Zachary, 2014a). Intravenous ACV generates higher peak levels than oral VCV. However, it may also increase the risk of renal toxicity due to precipitation of ACV crystals in renal tubules (Perry & Faulds, 1996; Zachary, 2014a). On the other hand, the safety of high-dose oral VCV remains controversial, especially in immunocompromised patients (Zachary, 2014a).

The management of pregnant women with symptomatic genital herpes should be done in consultation with infectious diseases/sexual health and obstetric specialists simultaneously. ACV and VCV have been assigned to Pregnancy Category B, and ACV has been used in late pregnancy to reduce neonatal transmission. Once ACV has been detected in breast milk, caution is advised when using it in nursing mothers (Sawleshwarkar & Dwyer, 2015).

Penciclovir and Famciclovir

After intracellular uptake, 9-[4-hydroxy-3-(hydroxymethyl)butyl] guanine, known as penciclovir (PCV), is monophosphorylated by virally encoded TK and, subsequently, converted to penciclovir-triphosphate (PCV-TP) by cell enzymes, being then able to act as a viral DNA polymerase inhibitor. At clinical relevant levels, PCV-TP has no substantial effect upon cell DNA polymerase, thereby minimizing side effects to the host (Perry & Wagstaff, 1996).

The PCV mechanism of action is similar to that described for ACV and, although PCV exhibits lower affinity for viral DNA polymerase, it has a longer intracellular half-life than ACV (Perry & Wagstaff, 1996).

Famciclovir, known as 2-[2-(2-amino-9H-purin-9-yl)ethyl]-1,3-propanediol dictate, is an orally administered pro-drug of the antiviral agent PCV, and it is converted, in vivo, to PCV (SmithKline Beecham, 1997). PCV is subsequently phosphorylated to PCV-TP, thus inhibiting the DNA polymerase of susceptible virus (Zachary, 2015b).

PCV and FCV are active against HSV virus types 1 and 2 (HSV-1, HSV-2) and VZV. In vitro, PCV also presents activity against Epstein-Barr virus (EBV) (Perry & Wagstaff, 1996). Mechanisms of resistance to PCV are similar to those described for ACV (Zachary, 2015b).

The bioavailability of orally administered FCV is of 77%, indicating that FCV is well absorbed (Vere Hodge & Field, 2013). Prompt first-pass metabolism in the intestine and liver results in conversion to PCV. Food intake has no clinically important effect on PCV plasma levels (Perry & Wagstaff, 1996). Once it has a prolonged intracellular half-life, PCV-TP requires less frequent dosing when compared to ACV (Perry & Wagstaff, 1996; Zachary, 2015b).

FCV excretion is primarily renal and dose reduction is recommended in patients with impaired renal function (creatinine clearance < 60 mL/min) (Perry & Wagstaff, 1996; SmithKline Beecham, 1997).

Ganciclovir and Valganciclovir

Ganciclovir (GCV) was the first antiviral drug approved for treating cytomegalovirus (CMV) infection and it is widely used in immunocompromised patients with CMV disease, particularly those with HIV/AIDS and recipients of solid organ or hematopoietic stem cell transplantation (HSCT). Valganciclovir (VGCV) is an oral pro-drug that is rapidly hydrolyzed to GCV (Roche, 2009; Zachary, 2014b).

Ganciclovir (9-[(1,3,-dihydroxy-2-propoxy)methyl] guanine, or DHPG) is an acyclic analogue of the nucleoside guanosine. During infection, a viral kinase encoded by CMV gene UL97 converts intracellular ganciclovir

(GCV) to ganciclovir 5'-monophosphate (GCV-MP). After that, cell kinases convert GCV-MP to ganciclovir triphosphate (GCV-TP), which will inhibit viral DNA polymerase (Crumpacker, 1996; Faulds & Heel, 1990).

GCV and VGCV are used in treating CMV infections. GCV resistance is rare (around 1%), but it can occur in HIV/AIDS patients with CMV retinitis (Roche, 2016). The main mechanism of resistance to GCV is the lower ability of the viral kinase to form active triphosphate molecules, due to an UL97 gene mutation. Mutations in the viral DNA polymerase have also been reported as being responsible for CMV resistance to GCV, and these virus types can also be resistant to other anti-CMV drugs (Roche, 2016; Tatti et al., 1998; Zachary, 2014b).

GCV distribution volume is correlated to body weight and to distribution volumes observed in steady states. GCV is excreted, unmodified, in the urine after glomerular filtration (Roche, 2016).

VGC, a GCV pro-drug, is well absorbed after oral administration, rapidly hydrolyses to GCV in the intestinal wall and liver, and has a bioavailability of approximately 60 per cent (10 times > than GCV) (Roche, 2016).

Cidofovir

Cidofovir (HPMPC) [(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine] is an acyclic cytosine phosphate analogue. It is an antiviral drug that needs two phosphorylation steps to be converted to its active metabolite, cidofovir-biphosphate. Cidofovir conversion to cidofovir-monophosphate is not dependent on phosphorylation by viral TK and the biphosphate form competes with the deoxycitidine incorporation on viral DNA. This action causes a delay on DNA chain elongation during its synthesis. The incorporation of two molecules of cidofovir-biphosphate to the DNA chain breaks the DNA synthesis (De Clercq, 2003; Xiong et al., 1997).

Cidofovir has shown effectiveness and is used off-label against many DNA virus infections, such as HSV, VZV, CMV, human papillomavirus (HPV), poxvirus, adenovirus and polyomavirus (Geerinck et al., 2001; Snoeck et al., 2001).

CMV isolates resistant to ganciclovir can be susceptible to cidofovir. Cross-resistance between ganciclovir and cidofovir, caused by selective mutations in DNA polymerase gene, as observed after in vitro selection of ganciclovir-resistant CMV isolates. However, this type of resistance was not seen when viral DNA polymerase UL97 gene mutation is present. CMV mutant isolates, selected by foscarnet, did not show cross-resistance with cidofovir (Gilead Sciences, 2010).

Cidofovir has poor oral bioavailability and the drug excretion is renal. Once it has a long intracellular half-life, cidofovir offers a more prolonged antiviral response when compared to its acyclic analogues, such as acyclovir, which shows an antiviral response within a few hours, allowing less frequent dosing (Neyts et al., 1991).

Pyrophosphate analogue

Foscarnet

Foscarnet (trisodium phosphonoformate) is a pyrophosphate analogue and binds reversibly near the pyrophosphate-binding site of the DNA polymerase (or reverse transcriptase), blocking the cleavage of the pyrophosphate moiety from deoxynucleotide triphosphates, halting DNA chain elongation (Wagstaff & Bryson, 1994). A 100-fold greater foscarnet concentration is required to obtain the inhibition of human DNA polymerase (Wagstaff & Bryson, 1994).

Foscarnet has antiviral activity against HSV, VZV, CMV and it also inhibits HIV reverse transcriptase (RT). It is used almost exclusively to treat CMV infections (particularly when ganciclovir cannot be employed) in HIV/ AIDS patients or those recipients of solid organ and hematopoietic stem cell transplantation (HSCT) (Biron, 2006).

Foscarnet resistance is mainly due to point mutations in viral UL54 pol gene and it is considered a second choice therapy in cases of ganciclovir resistance (Stewart, 2010).

Foscarnet has poor oral bioavailability and is excreted solely by the kidney. Caution is required when treating patients with impaired renal function due to foscarnet toxicity to renal tubules. Patients require adequate hydration and frequent monitoring of creatinine levels (Biron, 2006; Stewart, 2010).

Neuraminidase inhibitors (NI)

Two drugs of this group are approved for treating influenza virus infection: the oral drug oseltamivir, and the inhalation drug zanamivir.

Oseltamivir and zanamivir

Oseltamivir is commercially available as Tamiflu®, and since 1999 it has been used to treat infections of influenza A and B viruses (Beigel & Bray, 2008).

Zanamivir was discovered in 1989 and is effective against influenza A and B viruses in children (aged 7 years and over) and adults (Burls et al., 2002).

Neuraminidase inhibitors (NI) act on the viral neuraminidase protein, blocking the release of viruses from infected host cells and prevents the infection of new host cells. These antiviral agents inhibit all subtypes of neuraminidase enzymes; therefore they are effective against influenza (FLU) viruses A and B. Although the genetic composition of the virus is under constant mutation, the amino acid sequence at the enzyme active site is highly conserved, offering an optimal region for antiviral therapy (Burls et al., 2002; Beigel & Bray, 2008).

Oseltamivir (ethyl (3R,4R,5S)-4-acetamido-5-amino-3-pentan-3-yloxycyclohexene-1-carboxylate) is a cyclohexene analogue of silica acid (Ferraris et al., 2010).

Zanamivir (2R,3R,4S)-3-acetamido-4-(diaminomethylideneamino)-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid) is a guanido-neuraminic acid (Burls et al., 2002).

NIs are drugs effective against influenza A and B infections.

Oseltamivir resistance was considered rare until 2006-2007. However, by December 2008, almost all seasonal FLU A (H1N1) cases showed resistance to oseltamivir, as a consequence of neuraminidase mutations (Baek et el., 2015; Gupta & Padhy, 2010; L'Huillier et al., 2015; Pontoriero et al., 2016; Trebbien et al., 2017).

After oral administration, oseltamivir is rapidly absorbed and metabolized by esterase enzymes present in the gastrointestinal tract, liver and blood. Absorption is slightly affected by food intake but the general bioavailability is not altered (Wattanagoon et al., 2009).

Zanamivir has a short plasma half-life, but it can be detected in lungs over 24 hours after single dose inhalation. It should not be used in patients with respiratory diseases (asthma or chronic obstructive pulmonary disease) due to the risk of bronchospasm and impairment of pulmonary function (He et al., 1999; Burls et al., 2002; Beigel & Bray, 2008; Wattanagoon et al., 2009; Ferraris et al., 2010; Gupta & Padhy, 2010).

Oseltamivir requires a dose adjustment in those patients with low creatinine clearance (< 30 mL/min). Gastrointestinal intolerance (usually less than 1 day) occurs in 5 to 15% of patients treated with oseltamivir, but it rarely (<2%) requires drug interruption (He et al., 1999).

Table 1 lists the most common viral infections in clinical practice with their recommended treatments (Hirsch et al., 1980; Spruance et al., 2002; Spruance et al., 2003; Pier et al., 2004; Mandell et al., 2005; Spruance et al., 2006; Modi et al., 2008; Gershon & Gershon, 2013; Zachary, 2014a; Albrecht, 2015; Almeida et al., 2015; Centers for Disease Control and Prevention [CDC], 2015; Zachary, 2015a; Zachary, 2015b).

Table 1. Treatment Protocol for Viral Infections in Adults and Children

Site of Infection	Infection	Agent	Antiviral Dosage Regimen			Duration of treatment
			First choice	Alternative	Alternative	
Orolabial Infection	First episode	Herpes simplex virus	Recommended drugs and doses for genital Herpes			-
	Recurrence[A]	Herpes simplex virus	Acyclovir 5% cream[a] 6 times/day	Penciclovir 1% cream[a] 12 times/day	-	a = 4 days See observation[1]
			Topic treatment only in recurrent episodes. Start therapy in the first 24h symptoms.			
			Acyclovir orally 200mg[a] 5 times/day or 400mg[a] 3 times/day	Valacyclovir[b] orally 2g twice a day	Famciclovir[c] orally 1500mg	a= 5 days b= 1 day c= single dose See observation[2]
	Suppression therapy	Herpes simplex virus	Acyclovir orally 400mg[a] twice a day or 200mg 3 times/day	-	-	a= up to 1 year See observation[3]

	First episode	Herpes simplex virus	Acyclovir orally 200mg[a] 5 times/day or 400mg[a] 3 times/day or intravenous[a] 5-10mg/kg 3times/days	Valacyclovir[a] orally 1g twice a day	Famciclovir[a] orally 250mg 3 times/day	a= 7 to 10 days*
			* The treatment may be extended if there is no complete cure after 10 days.			
	Recurrence in immunocompetent	Herpes simplex virus	Acyclovir orally 200mg[a] 5 times/day or 400mg[a] 3 times/day	Valacyclovir orally 1g[a] once a day	Famciclovir orally 1000mg[b] twice a day	a= 5 days b = 1 day
Genital Tract Infection	Recurrence in HIV+	Herpes simplex virus	Acyclovir intravenous 5-10mg/kg[a] 3 times/days or 400mg[a] 5 times/day orally	Valacyclovir 1g[a] once a day orally	Famciclovir 500mg[a] once a day orally	a= 7 to 14 days
	Recurrence in Pregnancy**	Herpes simplex virus	Acyclovir orally 400mg[a] 3 times/day	Valacyclovir orally 500mg[a] twice a day	-	a= 5 days
			**Treatment should start at 36 weeks of pregnancy.			

	Suppression therapy	Herpes simplex virus	Acyclovir orally 400mg^{a} twice a day	Valacyclovir orally 500mg^{a} once a day or 1g^{a} once a day (>10 episodes /year)***	Famciclovir orally 250mg^{a} twice a day	a= up to 1 year
	Suppression therapy in HIV+	Herpes simplex virus	Acyclovir orally 400mg^{a} 3 times/day or 800mg^{a} twice a day	Valacyclovir orally 500mg^{a} twice a day	Famciclovir orally 500mg^{a} twice a day	a= up to 1 year
			***Valacyclovir 500mg once a day may be less effective than other dose regimens in patients with 10 or more episodes/year.			
	Severe disease or complications that demand hospitalization (generalized infection, pneumonia, hepatitis)	Herpes simplex virus	Acyclovir intravenous 10-15mg/kg^{a} 3 times/day followed by Acyclovir orally 400mg^{b} 3 times/day	-	-	a= 2 to 7 days* b= until complete 10 days of total therapy
			* Or until clinical improvement is observed.			
	Episodic treatment in resistance^{B} to Acyclovir, Valacyclovir and Famciclovir	Herpes simplex virus	Foscarnet intravenous 40-80mg/kg^{a} 3 times/day	Cidofovir intravenous 5mg/kg^{a} once a week or Gel 1%^{b} once a day	Imiquimod Cream 5%^{b} once a day	a= until clinic remission b= 5 days

	Varicella patients> 40Kg	Varicella zoster virus	Acyclovir orally 20mg/kg[a] (≤800mg) 4 times/day	-	-	a= 5 days See observation [4]
			Treatment should start within the first 24 hours of the onset of the lesions.			
Other Skin and Mucous Infections	Varicella in immunocompromised patient or disseminated disease (pneumonia, encephalitis) in adults or infants	Varicella zoster virus	Acyclovir intravenous 10mg/kg[a] 3 times/day	-	-	a= 7 to 10 days
	Herpes Zoster	Varicella zoster virus	Acyclovir orally 800mg[a] 5 times/day	Valacyclovir orally 1g[a] 3 times/day	Famciclovir orally 500mg[a] 3 times/day	a= 7 to 10 days
	Herpes Zoster in Immunocompromised patient	Varicella zoster virus	Acyclovir intravenous 10mg/kg[a] 3 times/day	-	-	a= 7 to10 days
Central Nervous System	Encephalitis	Herpes simplex virus	Acyclovir 10-15mg/kg[a] 3 times/day intravenous	-	-	a= 14 to 21 days

Infections	Disseminated disease in newborn	Herpes simplex virus	Acyclovir intravenous 10-20mg/kg[a] 3 times/day	-	-	a= 14 to 21 days
	Cytomegalovirus neurologic disease in transplant and HIV/AIDS patients	Cytomega-lovirus	Initial: Ganciclovir intravenous 5mg/kg[a] twice a day 1h infusion. Maintenance: Ganciclovir intravenous 5mg/kg[b] once a day or intravenous 6mg/kg[b] 5 times/week or Valganciclovir orally 900mg once a day[b]	Initial: Foscarnet intravenous 60mg/Kg[a] 3 times/day or 90mg/Kg[a] twice a day intravenous, 1- 2h infusion Maintenance: 90-120mg/Kg once a day intravenous	Initial: Cidofovir intravenous 5mg/Kg/ week[c] Maintenance: intravenous 5mg/Kg[c] every 15 days	a= 14 to 21 days b= Recommended for HIV+ patients with CD4+ counts <100 cells/mm3. For transplant hosts, see maintenance protocol c= 2 weeks
Eye Infections★	Keratoconjunctivits	Herpes simplex virus	Acyclovir ophthalmic ointment 3%[a] 5 times/day	-	-	a= 7 to10 days

	AIDS-related cytomegalovirus retinitis and transplant patients cytomegalovirus retinitis	Cytomega-lovirus	Ganciclovir intravenous Initial: 5mg/kg[a] twice a day Maintenance: intravenous 5mg/kg[b] once a day or intravenous 6mg/kg[b] 5 times/week or Valganciclovir orally Initial: 900mg[a] twice a day Maintenance: 900mg once a day[b]	Foscarnet intravenous Initial: 60mg/Kg[a] 3 times/day or intravenous 90mg/Kg[a] twice a day Maintenance: intravenous 90-120mg/Kg[b] once a day	Cidofovir intravenous Initial: 5mg/Kg/ week[c] Maintenance: intravenous 5mg/Kg[c] every 15 days✚	21 days b= Recommended for HIV+ patients with CD4+ counts <100 cells / mm3. For transplant hosts, see maintenance protocol c= 2 weeks
			□Associate with hydration with saline before and after therapy, and probenecid orally 2g 3h prior to dosing, followed by orally 1g 2h and 8h after dose (total 4g). This regimen should be avoided in patients who are allergic to sulpha due to cross hypersensitivity with probenecid. ★Drug choice, as well as the route of administration, must be made in conjunction with the ophthalmologist. The anatomic location of the retinal lesion, vision in the contralateral eye, immunological and virological status of the patient and the response to antiretroviral therapy (ART) should be considered.			

Digestive Tract Infections	Esophagitis or colitis in transplant hosts and AIDS patients	Cytomega-lovirus	Ganciclovir intravenous 5mg/kg[a], twice a day	Valganciclovir orally 900mg[a] twice a day✤	-	a= 21 to 42 days or until symptoms remission
			☐ As soon as the patient tolerates orally therapy.			
Respiratory Tract Infection	Pneumonia in transplant and AIDS patients	Cytomega-lovirus	Initial: Ganciclovir intravenous 5mg/kg[a] twice a day Maintenance: Ganciclovir intravenous 5mg/kg[b] once a day or intravenous 6mg/kg[b] 5 times/week or Valganciclovir orally 900mg once a day[b]	Foscarnet intravenous Initial: 60mg/Kg[a] 3 times/day or intravenous 90mg/Kg[a] twice a day Maintenance: Intravenous 90-120mg/Kg[b] once a day	Cidofovir intravenous Initial: 5mg/Kg/week[c] Maintenance: 5mg/Kg[c] intravenous every 15 days	21 days b= Recommended for HIV+ patients with CD4+ counts <100 cells / mm3. For transplant hosts, see maintenance protocol c= 2 weeks
	Influenza in Adults	Influenza virus	Oseltamivir orally phosphate 75mg[a] twice a day	Zanamivir* 10mg: two inhalations[a] twice a day	-	a= 5 days

	Influenza in children < 1 year	< 3 months	Influenza virus	Oseltamivir orally phosphate 12mg[a] twice a day	-	-	a= 5 days
		3 to 5 months	Influenza virus	Oseltamivir orally phosphate 20mg[a] twice a day	-	-	a= 5 days
		6 to 11 months	Influenza virus	Oseltamivir orally phosphate 25mg[a] twice a day	-	-	a= 5 days
	Influenza in children > 1 year	< 15 kg	Influenza virus	Oseltamivir orally phosphate 30mg[a] twice a day	-	-	a= 5 days
		> 15 kg to 23 kg	Influenza virus	Oseltamivir orally phosphate 45mg[a] twice a day	-	-	a= 5 days
		> 23 kg to 40 kg	Influenza virus	Oseltamivir orally phosphate 60mg[a] twice a day	-	-	a= 5 days
		> 40 kg	Influenza virus	Oseltamivir orally phosphate 75mg[a] twice a day	-	-	a= 5 days
	Influenza Chemoprophylaxis in children and adults		Influenza virus	For chemoprophylaxis use the same dosages recommended for treatment, but only ONCE a day.			a= 10 days
				*Zanamivir cannot be used in patients on mechanical ventilation because this medication can block the fan circuit and is not recommended for children under seven years of age.			

[A] The margin of safety and tolerability of three drugs is excellent.

[B] All Acyclovir (ACV) resistant Herpes simplex viruses (HSV) are also resistant to Valacyclovir and most of them are also resistant to Famciclovir (FCV).

Observations:

1) Clinical studies have shown that topical agents are effective; however there is a great difficulty of obtaining patient compliance due to the frequent dosing required for good results, making oral medication the most convenient.

2) Although there are no clinical trials comparing conventional treatment for orolabial herpes with ACV for 5 days with Famciclovir (FCV) or oral Valacyclovir (VACV) single dose, studies showed similar reduction in duration and symptoms remission. After analysis of studies by Spruance et al. (2006), the Food and Drug Administration (FDA) approved the use of a single dose of Famciclovir (FCV) for the treatment of recurrent orolabial herpes in immunocompetent patients.

3) Suppressive therapy is not a common practice in the management of recurrent herpes orolabial, and the episode therapy remains the most recommended.

4) Early intravenous therapy should be instituted for patients infected with Varicella zoster virus (VZV) at high risk of development serious infection, as those with leukemia, transplant recipients, HIV and other causes of immunosuppression.

Drugs for the treatment of viral hepatitis

Viral hepatitis is a systemic infection caused by virus, with a liver inflammatory response-based physiopathology and that, despite the important scientific advances, continues among the most common causes of acute and chronic liver disease and may progress over time to fibrosis (scarring of the liver) and cirrhosis (chronic liver failure), which increases the risk of developing hepatocellular carcinoma (Pawlotsky et al., 2015).

Seeking to increase life expectancy and improve the patient's quality of life, as well as reduce the incidence of infection by hepatitis C virus (HCV), eradicating-virus therapy should be established according to the Clinical Protocol and Therapeutic Guidelines to Hepatitis C and Coinfection[1], available online at http://www.aids.gov.br/sites/default/files/anexos/publicacao/2015/58192/pcdt_capa_miolo_09_2015_baixa_pdf_31917.pdf.

Drugs for the treatment of HIV/AIDS patients

Antiretroviral drugs emerged in the 80's and are of extreme importance for treatment and prevention of HIV infection.

They are grouped into six drug classes

I) Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

II) Nucleoside reverse transcriptase inhibitors (NRTIs)

III) Protease inhibitors (PIs)

IV) Fusion inhibitors

V) CCR5 antagonists (CCR5s) (also called entry inhibitors)

VI) Integrase strand transfer inhibitors (INSTIs)

The Clinical Protocol and Therapeutic Guidelines for HIV/AIDS Patients (Brasil, 2013) present the recommended HIV regimens and are available online at: http://www.aids.gov.br/sites/default/files/anexos/publicacao/2013/55308/protocolofinal_31_7_2015_pdf_31327.pdf

REFERENCES

1. Albrecht MA. *Treatment of herpes zoster in the immunocompetent host.* In: UpToDate, Post TW (Ed) UpToDate, Waltham, MA. Available at: <http//uptodate.com>. Accessed at 07/10/2015.
2. Almeida FJ, Berezin EN, Farhat CK, Cintra OA, Stein RT, Burns DAR, Arns CC, Lomar AV, Neto JT, Medeiros R. *Consenso para o tratamento e profilaxia da FLU (Gripe) no Brasil. In:* Sociedade brasileira de pediatria. Available at: http://www.sbp.com.br/PDFs/conseso_FLU.pdf. Accessed at 23/10/2015.

3. Baek Y, Song M-S, Lee E-Y, Kim Y, Kim E-H, Park S-J, Park K, Kwon H, Pascua P, Lim G-J, Kim S, Yoon S-W, Kim M, Webby R, Choi Y-K. Profiling and Characterization of Influenza Virus N1 Strains Potentially Resistant to Multiple Neuraminidase Inhibitors. *J Virol 89*: 287-299, 2015.
4. Beigel J, Bray M. Current and future antiviral therapy of severe seasonal and avian influenza. *Antiviral Res 78*: 91-102, 2008
5. Biron KK. Antiviral drugs for cytomegalovirus diseases. *Antiviral Res 71*: 154-163, 2006.
6. Boyd MR, Safrin S, Kern ER. Penciclovir: A review of its spectrum of activity, selectivity, and cross-resistance pattern. *Antivi Chem Chemother 4*: 67-84, 1993.
7. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, AIDS e Hepatites Virais. *Protocolo clínico e diretrizes terapêuticas para hepatite viral C e coinfecções*. Clinical protocol and therapeutic guidelines for viral hepatitis C and coinfections. A Normas e Manuais Técnicos. 2015. Available at: http://www.aids.gov.br/sites/default/files/anexos/publicacao/2015/58192/pcdt_capa_miolo_09_2015_baixa_pdf_31917.pdf. Accessed at 11/11/2015.
8. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, AIDS e Hepatites Virais. *Protocolo Clínico e Diretrizes Terapêuticas para Adultos Vivendo com HIV/AIDS*. Clinical protocol and therapeutic guidelines for HIV/AIDS Patients. A Normas e Manuais Técnicos. 2013. Available at: http://www.aids.gov.br/sites/default/files/anexos/publicacao/2013/55308/protocolofinal_31_7_2015_pdf_31327.pdf. Accessed at 11/11/2015.
9. Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, Fry-Smith A. Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation. *Health Technol Assess 6*: 1-87, 2002.
10. Centers for Disease Control and Prevention (CDC). 2015. *Genital HSV Infections - 2015 STD Treatment Guidelines*. Available at: http://www.cdc.gov/std/tg2015/herpes.htm. Accessed at 16/10/2015.
11. Crumpacker CS. Ganciclovir. *N Engl J Med 335*: 721-729, 1996.
12. De Clercq E. Clinical potential of the acyclic nucleoside phosphonates cidofovir, adefovir, and tenofovir in treatment of DNA virus and retrovirus infections. *Clin Microbiol Rev 16:* 569-596, 2003.
13. Elion GB, Furman PA, Fyfe JA, de Miranda P, Beauchamp L, Schaeffer HJ. Selectivity of action of an antiherpetic agent, 9-(2-hydroxyethoxymethyl) guanine. *Proc Natl Acad Sci USA 74*: 5716-5720, 1977.
14. Erlich KS, Mills J, Chatis P, Mertz GJ, Busch DF, Follansbee SE, Grant RM, Crumpacker CS. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. *N Engl J Med 320*: 293-296, 1989.
15. Faulds D, Heel RC. Ganciclovir: A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in cytomegalovirus infections. *Drugs 39*: 597-638, 1990.
16. Ferraris O, Escuret V, Bouscambert-Duchamp M, Lina B, Morfin F. Intérêts des inhibiteurs de la neuraminidase dans la prise en charge des infections dues aux virus influenza. *Pathologie Biologie 58*: e69-e78, 2010.
17. Field HJ, Vere Hodge RA. Recent developments in anti-herpesvirus drugs. *Br Med Bull 106:* 213-249, 2013.
18. Geerinck K, Lukito G, Snoeck R, De Vos R, De Clercq E, Vanrenterghem Y, Degreef H, Maes B. A case of human orf in an immunocompromised patient treated successfully with cidofovir cream. *J Med Virol 64*: 543-549, 2001.
19. Gershon A, Gershon M. Pathogenesis and Current Approaches to Control of Varicella-Zoster Virus Infections. *Clin Microbiol Rev 26*: 728-743, 2013.

20. Gilead Sciences. 2010. *Vistide (cidofovir) product monograph*. 2010 Sep. Available at: www.gilead.com/~/media/files/.../vistide/vistide.pdf. Accessed at 11/11/2015.

21. Glaxo Wellcome Inc. 2015. *Valtrex (valacyclovir hydrochloride) product monograph*. 2015. Available at: http://www.gsk.ca/english/docs-pdf/product-monographs/Valtrex.pdf. Accessed at 11/11/2015.

22. Gupta YK, Padhy BM. Issues in pharmacotherapy of 2009 H1N1 influenza infection. *J Postgrad Med 56:* 321-327, 2010.

23. Hardy WD. Foscarnet treatment of acyclovir-resistant herpes simplex virus infection in patients with acquired immunodeficiency syndrome: preliminary results of a controlled, randomized, regimen-comparative trial. *Am J Med 92*: 30S-35S, 1992.

24. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet 37*: 471-484, 1999.

25. Hirsch MS, Swartz MN. Drug therapy: antiviral agents (first of two parts). *N Engl J Med 302*: 903, 1980.

26. L'Huillier A, Abed Y, Petty T, Cordey S, Thomas Y, Bouhy X, Schibler M, Simon A, Chalandon Y, Delden C, Zdobnov E, Boquete-Suter P, Boivin G, Kaiser L. E119D Neuraminidase Mutation Conferring Pan-Resistance to Neuraminidase Inhibitors in an A(H1N1)pdm09 Isolate From a Stem-Cell Transplant Recipient. *J Infect Dis 212*: 1726-1734, 2015.

27. Mandell G, Bennett J, Dolin R. 2005. *Principles and practices of infectious diseases* 7th ed. Philadelphia, PA: Elsevier Inc., 2010.

28. Modi S, Van L, Gewirtzman A, Mendoza N, Bartlett B, Tremaine AM, Trying S. Single-day treatment for orolabial and genital herpes: a brief review of pathogenesis and pharmacology. *Ther Clin Risk Manag 4*: 409-417, 2008.

29. Neyts J, Snoeck R, Balzarini J, De Clercq E. Particular characteristics of the anti-human cytomegalovirus activity of (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (HPMPC) in vitro. *Antiviral Res 16*: 41-52, 1991.

30. Pawlotsky J-M, Aghemo A, Back D. EASL recommendations on treatment of hepatitis C. *J Hepatol 63*: 199-236, 2015.

31. Perrier M, Désiré N, Deback C, Agut H, Boutolleau D, Burrel S. Complementary assays for monitoring susceptibility of varicella-zoster virus resistance to antivirals. *J Virol Methods 233:* 10-14, 2016.

32. Perry CM, Faulds D. Valaciclovir. A review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. *Drugs 52*: 754-772, 1996.

33. Perry CM, Wagstaff AJ. Famciclovir. A review of its pharmacological properties and therapeutic efficacy in herpesvirus infections. *Drugs 50*: 396-415, 1995.

34. Pier G, Lyczak J, Wetzler L. *Immunology, Infection, and Immunity*. American Society for Microbiology Washington, DC: ASM Press, 2004.

35. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother 55*: 459-472, 2011.

36. Pontoriero A, Avaro M, Benedetti E, Russo M, Czech A, Periolo N, Campos A, Zamora A, Baumeister E. Surveillance of antiviral resistance markers in Argentina: detection of E119V neuraminidase mutation in a post-treatment immunocompromised patient. *Mem Inst Oswaldo Cruz 11*: 745-749, 2016.

37. Roche. *Cymevene (ganciclovir sodium) product monograph*. 2016 Aug. Available at:

< https://www.old.health.gov.il/units/pharmacy/trufot/.../4132.pdf>.

38. Roche. *Valcyte (valganciclovir hydrocloride) product monograph*. 2009 Aug. Available at: <http://www.rochecanada.com/en/products/pharmaceuticals/consumer_information/valcyte.html>.

39. Sawleshwarkar S, Dwyer DE. Antivirals for herpes simplex viruses. *BMJ 351*: h3350, 2015.
40. SmithKline Beecham. Famvir (famciclovir) product monograph. 1997 Jul. Available at: https://www.drugs.com/monograph/famvir.html>.
41. Snoeck R, Bossens M, Parent D, Delaere B, Degreef H, Van Ranst M, Noël JC, Wulfsohn MS, Rooney JF, Jaffe HS, De Clercq E. Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis 33:* 597-602,2001.
42. Spruance S, Bodsworth N, Resnick H, Conant M, Oeuvray C, Gao J, Hamed K. Single-dose, patient-initiated famciclovir: A randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. *J Am Acad Dermatol 55*: 47-53, 2006.
43. Spruance SL, Jones TM, Blatter MM, Vargas-Cortes M, Barber J, Hill J, Goldstein D, Schultz M. High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. *Antimicrob Agents Chemother 47*:1072–1080, 2003.
44. Spruance SL, Nett R, Marbury T, Wolff R, Johnson J, Spaulding T. Acyclovir cream for treatment of herpes simplex labialis: results of two randomized, double-blind, vehicle-controlled, multicenter clinical trials. *Antimicrob Agents Chemother 46*: 2238-2243, 2002.
45. Stewart MW. Optimal management of cytomegalovirus retinitis in patients with AIDS. *Clin Ophthalmol 4*: 285-299, 2010.
46. Tatti KM, Smith IL, Schinazi RF. Mutations in human cytomegalovirus (HCMV) DNA polymerase associated with antiviral resistance. *Intern Antiviral News 6:* 6-9, 1998.
47. Trebbien R, Pedersen S, Vorborg K, Franck K, Fischer T. Development of oseltamivir and zanamivir resistance in influenza A(H1N1)pdm09 virus, Denmark, 2014. *Euro Surveill 22:* 30445, 2017.
48. Vere Hodge RA, Field HJ. Antiviral agents for herpes simplex virus. *Adv Pharmacol 67*: 1-38, 2013.
49. Wagstaff AJ, Bryson HM. Foscarnet. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections. *Drugs 48:*199-226, 1994.
50. Wattanagoon Y, Stepniewska K, Lindegårdh N, Pukrittayakamee S, Silachamroon U, Piyaphanee W, Singtoroj T, Hanpithakpong W, Davies G, Tarning J, Pongtavornpinyo W, Fukuda C, Singhasivanon P, Day NP, White NJ. Pharmacokinetics of high-dose oseltamivir in healthy volunteers. *Antimicrob Agents Chemother 53*: 945-952, 2009.
51. Whitley RJ, Gnann JW. Acyclovir: a decade later. *N Engl J Med 327*: 782-789, 1992.
52. Xiong X, Smith JL, Chen MS. Effect of incorporation of cidofovir into DNA by human cytomegalovirus DNA polymerase on DNA elongation. *Antimicrob Agents Chemother 41*: 594-599, 1997.
53. Zachary, KC. (2014a) *Valacyclovir: an overview. In*: UpToDate, Post TW (Ed) UpToDate, Waltham, MA. Available at: <http//uptodate.com> Accessed on October 07, 2015
54. Zachary, KC. (2014b). *Ganciclovir and valganciclovir: an overview*. *In*: UpToDate, Post TW (Ed) UpToDate, Waltham, MA.. Available at: <http//uptodate.com> Accessed on October 07, 2015
55. Zachary, KC. (2015a) *Famciclovir: an overview. In*: UpToDate, Post TW (Ed) UpToDate, Waltham, MA. Available at: <http//uptodate.com>. Accessed on October 07, 2015
56. Zachary, KC. (2015a). *Acyclovir: an overview. In*: UpToDate, Post TW (Ed) UpToDate, Waltham, MA. Available at: <http//uptodate.com> Accessed on October 07, 2015