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## MODERN DIRECTIONS OF HERPESVIRUS INFECTIONS PHARMACOTHERAPY

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The article presents the data on the etiology, pathogenesis, clinical course, features of an immune response to human herpesvirus infections. Modern approaches to the causal treatment and principles of treatment phasing in these patients category are discussed.

**KEY WORDS:** Herpesvirus infection, etiology, clinical manifestations, immune response, therapy

## СУЧАСНІ НАПРЯМКИ МЕДИКАМЕНТОЗНОЇ ТЕРАПІЇ ГЕРПЕСВІРУСНИХ ІНФЕКЦІЙ

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У статті представлені дані щодо етіології, патогенезу, клінічного перебігу, особливостей імунної відповіді на герпесвірусні інфекції людини. Розглянуто сучасні підходи до етіотропної терапії та принципи етапності лікування у даній категорії хворих.

**КЛЮЧОВІ СЛОВА:** герпесвірусна інфекція, етіологія, клінічні прояви, імунна відповідь, терапія

## СОВРЕМЕННЫЕ НАПРАВЛЕНИЯ МЕДИКАМЕНТОЗНОЙ ТЕРАПИИ ГЕРПЕСВИРУСНЫХ ИНФЕКЦИЙ

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В статье представлены данные об этиологии, патогенезе, клиническом течении, особенностях иммунного ответа на герпесвирусные инфекции человека. Рассмотрены современные подходы к этиотропной терапии и принципы этапности лечения у данной категории больных.

**КЛЮЧЕВЫЕ СЛОВА:** герпесвирусная инфекция, этиология, клинические проявления, иммунный ответ, терапия

Current importance of herpesvirus infections (HVI) is stipulated for practically universal spreading, availability of wide spectrum of clinical manifestations and high degree of contagiousness, duration and hard consequences in case of complicated forms of the disease as well as significant material costs on antivirus and pathogenic therapy. This category of infection is the sphere of clinical medicine being on the joint of interests of various specialties physicians: infectionists, neuropathologists, dermatovenerologists, therapists, gynecologists, immunologists, ophthalmologists, dentists, hematologists, oncologists. According to the data of WHO mortality as the result of diseases, stipulated for herpesvirus infection in the structure of infection pathology takes the second place after gripe [1, 2, 3].

Steady growth of HVI both in adults and in infants, high perinatal losses and birth of children with hard drain deprivations, deprivations of parenchyma organs and lungs stipulate for necessity of thorough study of HVI and elaboration of prophylaxis and treatment effective methods [1, 2, 3].

Course of HVI is often asymptomatic, which is the evidence of virus replication active control possibility outside the host immune system in spite of multiple ways of its deviation from immune response. Though further HVI can occur as recurrent or chronic with clinics specific for each virus and even be accompanied by threatening life conditions. In general both generalized form of the disease or absolute lack of clinic manifestations are most characteristic features for the whole group of herpesviruses. Among life-threatening states inflammatory CNS diseases take a special

place and particularly demyelinating encephalomyelitis which can be caused by viruses of the herpes group - CMV, HSV, EBV. Deviations in the system of virus-host interconnection stipulated for individual congenital peculiarities of host defense reactions are in the basis of unfavorable course of persistent HVI [4, 5].

Universal spreading of herpesviruses is connected with their universality, unique abilities to transform into latent state, integrate into host genome taking a qualitatively new form. Herpesviruses can migrate along the organism implicating various organs and

systems into infection process and causing both light and deadly dangerous diseases with various symptomatologies [4, 6].

More than 100 representatives of herpesvirus family (*Herpesviridae*) are known by now, 8 of which are pathogenic for people. All 8 types are represented by DNC-containing viruses with unique morphology which is not differentiated by electronic microscopy. HVI pathogenesis is interconnected with clinics and epidemiology (tab. 1). Getting into the human organism herpes simplex virus (HSV) lifelong persists in it causing periodic relapses of various severities [5, 6].

Table 1

Types of herpes viruses

Name	Abbreviation (English)	Synonym	Most prominent clinical manifestation
<b>Herpes simplex Type 1</b>	HSV-1, HHV-1 ( $\alpha$ -Herpesviridae)	Simple herpes, Bidwill zoster	Oral-facial deprivation, aphthous-ulcerous stomatitis, labial herpes, herpetic dermatitis, herpetiform eczema, keratitis, conjunctivitis,
<b>Herpes simplex Type 2</b>	HSV-2, HHV-2 ( $\alpha$ -Herpesviridae)	Herpes genitalis	Genital mucosal deprivation, meningitis
<b>Varicella Zoster virus, Human herpes virus Type 3</b>	VZV, HZV, HHV-3 ( $\alpha$ -Herpesviridae)	Herpes Zoster	Pox, shingles deprivation along sensitive nerve endings, pre- and perinatal infection
<b>Epstein-Barr virus, Human herpes virus Type 4</b>	EBV, HHV-4 ( $\gamma$ -Herpesviridae)	Virus of infection mononucleosis	Infection mononucleosis, Berkitt lymphoma, nasopharyngeal carcinoma, lymphoepithelioma of salivary gland (thymoma), hepatitis
<b>Cytomegalovirus, Human herpes virus Type 5</b>	CMV, HHV-5 ( $\beta$ -Herpesviridae)	Cytomegalovirus	Pre- и perinatal infection, teratogenic effect, immunodeficit, lever, kidneys, lungs, eyes, lymphatic nets, CNS deprivation. Inclination to infection generalization
<b>Human herpes virus Type 6</b>	HHV-6 ( $\beta$ -Herpesviridae)	Human B lymphotropic virus	Abrupt exanthesis of infants, mononucleosis-like syndrome, syndrome of chronic defatigation, encephalomyelitis, co-factor of VID- infection, oral and cervical carcinoma
<b>Human herpes virus Type 7</b>	HHV-7 ( $\beta$ -Herpesviridae)		Abrupt eczema of infants, syndrome of chronic defatigation
<b>Kaposi's sarcoma associated herpesvirus, Human herpes virus Type 8</b>	KSHV, HHV-8 ( $\gamma$ -Herpesviridae)	Human B lymphotropic virus	Kaposi's sarcoma, initial disseminated lymphoma

Distinctive feature of persistent virus infections essentially predicamenting antivirus chemical therapy conduction is an availability of latent form in them, i.e. virus, being incorporated in cell chromosomes is not only preserved for a long time but is also

transformed into filial cells. Besides decrease of specific and non-specific factors of immune reactivity and sensibilization of the organism are marked in persisting virus infections. That is why the treatment of persistent virus infections accompanied by immune system

deprivation remains of current importance and demands complex approach – due consideration of both etiological factor and pathogenic peculiarities of the whole organism [1, 4].

Despite variability of remedies used for HVI treatment there are no medical preparations providing full treatment from herpes. This infection is considered a hardly controlled disease which is connected, first of all, with the variety of clinical deprivations, development of virus resistance to medications, existence of molecular mimicry in herpesviruses. That is why it is necessary to choose adequate antivirus preparation for successful treatment of HVI, its doze and duration of treatment, use the combination of various remedies. It is also necessary to include immune biological preparations into the therapy schemes which promote correction of immune status as well as pathogenic remedies improving the patient condition [5, 7].

Only patients with manifest forms of HVI are subjected to treatment. The question about reasonability of the treatment prescription moreover in clinics is defined by many factors, namely, clinical form of the disease, severity course, household conditions and character of work of a sick person. In cases when hospitalization is necessary (generalized herpes, severe herpetic gingivostomatitis or

vaginal herpes) patients should be put into separate hospital ward, considering easiness of infection spreading [8, 9].

### ETIOTROPIC THERAPY

At present main antivirus preparations used for various forms of HVI treatment are *aciclovir*, *valaciclovir*, *famciclovir* (tab. 2).

These remedies mechanism of activity is connected with virus DNA synthesis suppression and viruses replication by the way of competitor inhibition of virus DNA-polymerase.

Two ways of antivirus chemical preparations use are defined: episodic prescription (under HVI exacerbation if necessary) and suppressive or preventive therapy. In the first case preparation is prescribed in a short course of treatment (5-10 days), in the second – every day receiving of the preparation for some months, sometimes even years calls rate not as much cut short the relapse as prevent the development of the relapses in general. It is necessary to remember that etiotropic therapy efficacy will be maximal when the treatment is prescribed in the harbinger period or initial manifestations (in prodromal period) of the disease, during first 48 hours of virus reactivation [7, 9, 10, 11, 12].

Table 2

#### Antiherpetic remedies

Remedy name	Indications	Usage and dozing
<b>Chemical preparations (abnormal nucleosides)</b>		
<b>Aciclovir (zovirax, heviran)</b>	Herpetic deprivations of skin and mucosa caused by HSV, HSV relapse prophylaxis	Internally, in HSV –200 mg 5 times a day for 5-10 days; in relapse – during 5 days
<b>Vilaciclovir (valtrex, valavir)</b>	Herpetic deprivations of skin and mucosa caused by HSV, HSV relapse prophylaxis, infection mononucleosis	Internally, in shingles herpes –1000 mg 3 times a day (7 days), in HSV –500 mg 2 times a day; in relapse –5 days course
<b>Penciclovir (vectavir)</b>	Herpetic vesicular lips dermatitis	Externally. Adults and infants older than 16 years old – apply on rash every 2 hours in the daytime for 4 days
<b>Famciclovir (famvir)</b>	Acute and relapsing infections caused by Herpes zoster, Herpes simplex I and II	In first appeared HSV-1, HSV-2 or relapse – 250 mg 3 times a day for 5 days, for treatment of repeat episode of relapse herpes–125 mg 2 times a day for 5 days; long suppressive therapy for clinically distinct and latent relapses of herpes infection prophylaxis –250 mg 2 times a day

New and perspective antiherpetic chemical preparations are cidofovir and brivudin. These remedies have higher efficacy in comparison with aciclovir and ganciclovir, though are worse endured which limits their wide clinical use. They should be used in severe life-threatening forms of herpesvirus infections in condition of known and expected resistance to aciclovir and ganciclovir [12, 13, 16].

Antiherpetic preparations comprise about 80% of all existing antivirus preparations. Antivirus preparation existing at present cannot eliminate virus latency. As a result one and the same man can be infected, then re-infected and super-infected; autoinoculation of the virus into a new place can also occur. Early prescription of acyclic nucleosides (particularly, valtrex or famvir) can cause decrease of virus latency degree which cannot be neglected. The available remedies give good results in initial phase of the disease and relapses cutting short [14, 16].

### **IMMUNOTHERAPY**

Individual parameters of immune status should be considered on all stages of the treatment, peculiarities of HVI clinical course, psychological sentiment and character of the patient including willingness to the treatment (compliance). In accordance with this choice and execution of immune therapy should be done, considering severity of HVI course, data of antivirus defense – interferon status, lymphocytes sub-populations as well as cytokine profile, clinical index of therapy, severity course index and concomitant diseases [8, 12, 15].

Necessary for immunotherapy: inter-ferons inductors; interferons; thymic factors; dialysed leukocytic extracts and transfer-factor preparations; vaccines; 6) immune modulators with polyvalent activity, for example: polyoxidonium, licopid, galavit, mielopid, imidazol derivatives, panavir, cagocel; substances and preparations, exerting predominant influence on non-specific (natural) resistance of the organism: adaptogenes, lizocim, vitamins, microelements, etc.

Most often the following preparations from the group of *interferons inductors* are used: amixin, neovir, cycloferon [8].

Prescription of *immunomodulators* is reasonable to those patients who are in proliferative phase of antiherpetic immune

response, i.e. not earlier than the 21-st day in acute and the 14-th day in relapse process. Alpizarin, imunofan, likopid, cagocel, polyoxidonium, galavit are the most effective. Influence of immunomodulators on specific immune response in other phases of infection process is incomparably tiny in comparison with direct immunomodulating effect of herpesviruses themselves and emission of natural cytokines into hemocirculation concomitant to any virus infection. That is why hope to success should be connected with specific antiherpes preparations application which is proved by successful treatment of acute and relapse HVI forms and the use of immunomodulators is reasonable to limit by intercurrent and reparative phases of these unusual persistent diseases.

Sodium nucleate, pentoxil, metiluracil, vitamins of B group, adaptogenes of vegetable origin can be used as immunomodulating remedies (eleutherococcus, panax ginseng, yarrow).

Consequently, effective HVI treatment nowadays can be provided only in connected application of means of etiotropic and immunocorrection pathogenic therapy [8].

One more way to change the immune response to herpesviruses antigens is a *vaccinotherapy*. Principal ability of a specific antigene material to cause imperatively formation of valuable specific multicomponent and long-term immunity in organism of immunocompetent people in all cases serves a pathogenic validation of vaccinotherapy repeatedly experimentally and clinically proved under various bacterial and virus diseases. That is why vaccinotherapy is formally prescribed in severe acute HVI treatment as well as relapse processes or in prophylactics of these diseases. Thus vaccinotherapy is the only candidate on the role of populational method of HVI prophylactics and treatment [8, 14].

Nowadays the scientists efforts are directed to elaboration of 6 types of vaccines against simple herpes: killed integral virion vaccine; subisolated vaccine: henetically attenuated live vaccine; live vaccine with limited ability to replication; vaccine, containing non-pathogenic replicated vector, expressing HSV antigen; DNA-vaccines on the basis of plasmids.

Course of vaccinotherapy stipulates intradermal injection of inactivated herpetic vaccine into palm surface of the arm – 0,2 ml

of standard solution once with 3-4 days interval. It is repeated twice (in 2 weeks and 6 months).

A program of treatment and prophylactics of herpetic infection was proposed by

St. Petersburg group of scientists virologists and infectionists headed by V.A. Isakov (1993) (tab. 3).

Table 3

#### Principles of HVI treatment and prophylactics stages

<b>I stage:</b> treatment in acute period of the disease(relapse)	<ul style="list-style-type: none"> <li>• Antiherpetic remedies (intravenously, perorally, locally),</li> <li>• ncrease of the doses of chemical preparations and course and prophylactics duration in persons with immune deficit,</li> <li>• Natural antioxidants (vitamins E and C), course 10-14 days,</li> <li>• In case of pronounced exudative component prostaglan-dines inhibitors are prescribed (indometacin, etc.), course 10-14 days,</li> <li>• Immune-biological remedies: preparations of interferon or its inductors, immunomodulators.</li> </ul>
<b>II stage:</b> therapy in the stage of remission, early convalescence	<p>Main aim is preparation of the patient to vaccinotherapy Immune modulators,</p> <ul style="list-style-type: none"> <li>• Adaptogenes of vegetable origin,</li> <li>• In pronounced immune suppression – thymic hormones (timalin and others) in short course.</li> </ul>
<b>III stage:</b> specific prophylactics of HVI relapses	<p>Vaccination with the aim of cell immunity activation, its immune correction and specific desensibilization of the organism, Herpetic vaccines are used (inactivated, recombined.</p>
<b>IV stage:</b> sanitarium observation and rehabilitation	<p>Clinic-laboratory examination of convalescents every 3-6 months.</p>

It was demonstrated that exactly complex approach to HVI treatment decreases probability of herpesvirus stable strains appearance, leads to immune-correcting effect achievement and shortens the acute period duration of the disease.

#### CONCLUSION

HVI therapy must be complex and prolonged. It is necessary to take into account various types of viruses differences in sensitivity to various preparations as well as peculiarities of immune status of the patient.

The main aim of HVI therapy must be in suppressing virus reproduction with establishing proper control over them from the side of immune system of the patient. That is why immune therapy together with antivirus preparations is the main component of modern therapeutic schemes. Physicians of all specialties must be able to diagnose correctly and treat adequately reactivated herpesvirus infections. General scientifically reasonable principles of therapy implementation in practice will allow reaching progress in control over HVI outbreaks in human population.

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